ORAL SESSION

ORAL SESSION 1A
GENETICS, GENOMICS, PROTEOMICS, METABOLOMICS

1A.01 MUTATIONS AFFECTING THE CONSERVED ACIDIC MOTIF OF WNK1 CAUSE INHERITED NORMOTENSIVE HYPERKALEMIC ACIDOSIS

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Objective: Mutations in the WNK1 and WNK4 genes have been shown to cause Familial Hyperkalemic Hypertension (FHHt, OMIM #145260), an inherited disorder combining arterial hypertension and hyperkalemia with metabolic acidosis. More recently, mutations in the KLHL3-CUL3 E3 ubiquitin ligase complex have shed light on the importance of the With-No-Lysine kinases (WNKs) cellular degradation on ion transport.

Design and method: Here we identified a new form of autosomal dominant hyperkalemic tubular acidosis with normal blood pressure caused by missense mutations in the WNK1 gene. Using full exome sequencing in a four-generation family and then targeted sequencing in 26 other FHHt cases, we identified six charge-changing substitutions in nine pedigrees.

Results: All of them were clustered in a short acidic conserved motif, homolog to that found mutated in the WNK4 protein in FHHt patients. Affected subjects had an early-onset disease and a marked biological phenotype, but surprisingly normal blood pressure values. Comparison with subjects with WNK1 intron 1 deletion or WNK4 mutations showed significant blood pressure differences.

Conclusions: In conclusion, we have identified a new type of WNK1 mutations leading to distal tubular hyperkalemic acidosis without tendency for arterial hypertension.

1A.02 MICRORNA-208A AND ITS HOST GENE CARDIAC MYOSIN HEAVY CHAIN MYH6 ARE INVOLVED IN HYPERTROPHIC HEART DYSFUNCTION

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Objective: Circulating microRNAs may be markers of cardiac damage or dysfunction. miR-208a has heart-specific expression since its host gene – myosin heavy chain MYH6, dominant cardiac myosin motor is also heart-specific and its expression maintains proper cardiac output. Our aim was to evaluate miR-208a and MYH6 as key contributing factors involved in hypertrophic heart dysfunction.

Design and method: 18–20 weeks old male Wistar rats were treated for 8 days with isoproterenol (ISO; N=12; 5 mg/kg intraperitoneally) or vehicle (CON; N=12). Relative expressions of cardiac myosin heavy chains (MYH6, MYH7, MYH7B), markers of cardiac damage (natriuretic peptides ANP, BNP) and heart-related microRNAs miR-1, miR-133a, miR-208a, miR-499 were analyzed using quantitative real-time PCR in samples from left ventricle, microRNAs also in venous blood. Cardiac hypertrophy and dysfunction was quantified with heart gravimetry and left heart catheterization, respectively.

Results: Treatment with isoproterenol induced cardiac hypertrophy (heart mass increased by +36% vs. CON ($P<0.01$) and 53% mortality associated with cardiovascular dysfunction characterized by a deteriorated peak left ventricular pressure and rate of isovolumetric pressure change during contraction (+dP/dt) compared to CON (−8% and −27% resp., $P < 0.01$). Gene expression of cardiac myosin heavy chain MYH6 in left ventricles was decreased by −61% indicating myosin switching in contractile apparatus. Cardiac dysfunction was further confirmed by 10-fold increase of atrial natriuretic peptide (ANP; $P<0.01$). Cardiac levels of microRNAs miR-1, miR-133a, miR-208a, miR-499 were strongly decreased (−71%, −65%, −59%, −75% resp., $P < 0.01$). Plasma levels of the same microRNAs were unchanged except for the cardio-specific miR-208a that showed a significant, 56-fold increase ($P<0.01$). ROC curve for detection of cardiac hypertrophy based on plasma miR-208a had a corresponding AUC = 98.8% (95% confidence interval, 85.3% – 100%).

Conclusions: Cardiac hypertrophy was associated with a decrease of several heart-related gene-regulatory microRNAs expression in the heart. Increased miR-208a in plasma is a strong predictor of cardiac hypertrophy. Isoproterenol induced heart damage also involves decrease in expression of dominant cardiac myosin motor MYH6 which is the host gene of miR-208a. In summary, miR-208a and myosin heavy chain MYH6 are key factors in hypertrophic heart dysfunction.

1A.03 TRANSCRIPTIONAL NETWORK ASSOCIATED WITH THE CONTRACTILE PHENOTYPE OF SMOOTH MUSCLE CELLS IN HUMAN CAROTID ATHEROSCLEROSIS

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Objective: During atherogenesis, vascular smooth muscle cells (VSMCs) undergo a phenotypic modulation leading to migration and loss of contractility. Here we propose a gene regulatory network specific of the contractile phenotype of the carotid VSMCs from transcriptomic data.

Design and method: Human carotid atheroma plaque (ATH, Stary>4) and nearby macroscopically intact tissue (MIT, Stary<3) of 32 patients were analysed by microarrays (Affymetrix HuGene-1.0ST). Histological analysis ensured the large predominance of VSMCs in MIT. Vascular smooth muscle contraction (VSMcontr) involved 119 genes (KEGG database). Transcriptional regulators (TRs) were obtained from Genomatix© and KEGG. Co-expression of TRs and VSMcontr genes was assessed by significant pairwise correlations ($p < 10–3$) between expression levels across the 32 patients. For each TR, its connecting index (CI) with VSMcontr was obtained from its connectivity, number of its significant ($p < 0.001$) correlations with the VSMcontr genes, weighted by its expression centile rank.

Results: Forty VSMcontr genes were under-expressed (localFDR< 5%) in ATH vs MIT: 11 genes encoding contractile proteins and their kinases/phosphatases, 11 genes encoding receptors and Ca2+/K+ channels, and 18 genes involved in Ca2+ or G-protein signalling. They were taken as the core-VSMcontr gene set. TRs showing the highest CI with core-VSMcontr in MIT that strongly decreased in ATH were taken as representative of the contractile phenotype of VSMCs. Conversely, TRs whose CI with core-VSMContr strongly increased reaching the highest levels in ATH were taken as representative of the synthetic phenotype of VSMCs in ATH. Ninety-one TRs had high positive (CI+) or negative (CI-) connecting index with core-VSMcontr specifically in MIT or ATH: 49 TRs with high CI+ (including NRF1, SRF and THRA) and 16 with high CI- (including HIF1A and STAT1) were MIT-specific, whereas 17 (including ERCC6, PRRX1 and ARID5B) and 9 (including RNF4 and USF1) other TRs had respectively high CI+ and high CI- and were ATH-specific.

Conclusions: The regulatory network around core-VSMcontr genes showed clear changes in ATH compared to MIT by reducing the involvement of TRs related to cell contractility and energy metabolism, and increasing that of TRs related to cell dedifferentiation, proliferation and migration or with yet unknown function.

1A.04 CORRELATES OF PERIPHERAL BLOOD MITOCHONDRIAL DNA COPY NUMBER IN A GENERAL POPULATION

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Objective: Mitochondrial DNA (mtDNA) molecules are highly susceptible to oxidative stress. Accumulation of mtDNA mutations leads to alterations of mitochondrial biogenesis and function that might result in decrease of mtDNA content within cells. This implies a possible role of mtDNA content as a potential biomarker in processes associated with oxidative stress and inflammation. However, data on correlates of the mtDNA content in a general population are sparse. Therefore, the objectives of the present study were to describe in a randomly recruited population sample the distribution and determinants of the peripheral blood mtDNA content.

Design and method: We examined 689 individuals (50.4% women, mean age, 54.4 years), randomly selected from a Flemish population. Relative mtDNA copy number compared to nuclear DNA was measured by quantitative real-time PCR in peripheral blood.

Results: There was a curvilinear relationship between the relative mtDNA copy number and age. Indeed, mtDNA content increased until the fifth decade of life and declined in older subjects (P age2 = 0.0005). Moreover, the mtDNA content significantly and independently increased with female sex (P = 0.0078) and platelet count (P < 0.0001), whereas it decreased with white blood cell count (WBC) (P < 0.0001). We also observed a slightly decrease in mtDNA content in women using oestroprogestogens (P = 0.044).

Conclusions: In conclusion, we demonstrated in a general population that peripheral blood mtDNA content is significantly associated with sex and age. In addition, blood mtDNA content is influenced by platelet and WBC counts and intake of oestroprogestogens. Further studies are required to clarify the impact of inflammation and hormone therapy on mitochondrial function.

1A.05 COMPARISON OF THE WHOLE GENOME SEQUENCE REVEALED GENETICALLY DISTINCT LOCI BETWEEN SHR/IZM AND SHRSP/IZM

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Objective: SHR and SHRSP are well-established model rats for studying not only hypertension and/or stoke but also several other adult-onset diseases. These two strains have a significant difference in the stroke susceptibility, which is resulted from the genetic difference. However, difference in the genomic architecture has not been elucidated enough between them. In this study, we therefore performed the comparison of the whole genome sequence of SHR/Izm and SHRSP/Izm, in addition to their control strain, WKY/Izm.

Design and method: Genomic DNA of each strain was extracted from the liver. Libraries were prepared from genomic DNA using the EZ Bead system. Sequencing was performed on the SOLiD 4 system. Both paired-end and fragment analyses were performed and read 85 and 50 bases/run, respectively. Five million reads were obtained for the genome of each strain, which covered approximately 20 times of the rat genome. The sequence reads were mapped to the Rattus norvegicus genome assembly (rn6) with the bowtie software. SNPs (Single Nucleotide Polymorphisms) against the rn6 genome sequence were called using SAMtools software.

Results: The analysis identified 684,759 and 999,114 SNPs in SHR/Izm and SHRSP/Izm, respectively, when the rn6 was used as a reference, SHRSP and SHR shared approximately 64.1% or 63.2% of SNPs with those observed in WKY, respectively. To identify fragments showing obvious difference in the genomic architecture between SHR and SHRSP, the number of SNPs shared with WKY in every 1 kbp bin were compared throughout the genome of SHR or SHRSP. We identified several genomic regions where the number of the shared SNPs were statistically different between SHR and SHRSP. Those loci in SHR and SHRSP were considered to carry a distinct genomic architecture, and might contribute to the phenotypical difference between the two strains. Functional classification of SNPs identified 21 and 18 strain-specific nonsense mutations in the whole genome of SHR and SHRSP, respectively.

Conclusions: These results would contribute to identify genomic loci which are responsible for phonotypical differences between SHR and SHRSP.

1A.06 MITOCHONDRIAL DNA HAPLOGROUP H IS ASSOCIATED WITH SUBCLINICAL CAROTID ATHEROSCLEROSIS IN RUSSIAN POPULATION

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Objective: It is known that type of mitochondrial haplogroup, based on the combination of inherited mtDNA mutations, may influence the progression of various multifactorial diseases. For example, belonging to haplogroup H is associated with early myocardial infarction in the population of Asturias (northern Spain). Aim of this study was to identify the relationship between the type of mitochondrial haplogroup and presence of subclinical atherosclerosis and hypertension in Russian population.

Design and method: A total of 80 persons from Moscow region (Russia) were included in the study. 45 study participants without CHD or myocardial infarction had ultrasonographically detected atherosclerotic lesions of the carotid arteries, others were controls without atherosclerosis. 32 patients had arterial hypertension. DNA was isolated from blood and the enrichment of mitochondrial DNA was performed. Detection of mtDNA haplogroups was made on the basis of Phylotree and MITOMAP databases and using Mitotool software on the data of mtDNA full sequences obtained by high-throughput sequencing of the mitochondrial genome using Roche 454 technology with GS Junior Titanium system. Statistical analysis was performed using IBM SPSS Statistics v.21.0 software.

Results: Mitochondrial haplogroups H, U, T and J were the most common in the observed sample (85.7% of cases), what corresponds to the general Russian population data. It was found that belonging to haplogroup H is associated with an increased risk of atherosclerosis (x2 = 3.97, p = 0.046; OR = 2.76, 95 % CI 1.01–7.58). 2706A and 7028C variants, that are markers of mitochondrial haplogroup H, were more common in atherosclerotic patients (p < 0.05), which proofs the role of this haplogroup as a marker for suspectability to atherosclerotic-related diseases. There were no statistically significant evidence that any other haplogroups are associated with atherosclerosis and hypertension in the observed sample.

Conclusions: Results of our study based on NGS data showed that haplogroup H is associated with carotid subclinical atherosclerosis and not associated with hypertension in Russian population.

1A.07 GENOME-WIDE PROFILING OF LONG NONCODING RNA EXPRESSION PATTERNS IN THORACIC AORTA FROM SPONTANEOUSLY HYPERTENSIVE RATS

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Objective: Numerous studies have indicated that long non-coding RNAs (lncRNAs) are involved in the cardiovascular development, as well as pathology, such as heart failure and coronary arterial disease. However, the roles of lncRNAs in essential hypertension remain unclear. Here we investigated the genome-wide lncRNA expression profiles in the aorta of spontaneously hypertensive rats (SHR), a rodent model of essential hypertension.

Design and method: LncRNA and mRNA expression profile were analyzed with GeneChip® Rat Gene 2.0 ST Array. Quantitative real-time PCR was used to validate 9 candidate lncRNAs. Bioinformatics analysis including Gene Ontology (GO) analysis, pathway analysis, and lncRNA-mRNA co-expression network analysis were carried out for further investigation.

Results: Microarray data showed that 29 lncRNAs as well as 1159 mRNAs, were differentially expressed. GO analysis showed that “ion transport” were most significant in both up- and down-regulated genes. Pathway analysis indicated that “metabolic pathway” may be especially important in the pathogenesis of hypertension.

Conclusions: These findings revealed differentially expressed lncRNAs in the artery of SHR, which may provide novel insight into the roles of lncRNAs in the pathogenesis of essential hypertension.

1A.08 GENETIC MARKERS IN CARDIAC RESYNCHRONIZATION THERAPY TREATMENT SUCCESS

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Objective: Cardiac resynchronization therapy (CRT) can improve ventricular size, shape and mass and reduce mitral regurgitation by reverse remodelling of the failing ventricle. CRT combines right atrial and ventricular pacing with pacing of the left ventricular free wall by a third lead to resynchronize contraction between and within ventricles. About 30% of patients do not respond to this therapy for unknown reasons. In the present study, we aimed at the identification and classification of CRT responder by the use of genetic variants and clinical parameters.

Design and method: Out of 1,421 CRT patients, 207 subjects were consecutively selected and CRT responder and non-responder were matched for their baseline parameters before CRT. Treatment success was defined as decrease in left ventricular end systolic volume (LVESV) >15% at follow-up echocardiography compared to baseline LVESV. An association study was performed to identify genetic variants associated with CRT success. For the classification of CRT patients into responder and non-responder, machine learning algorithms were applied using combinations of clinical parameters and the identified genetic variants.

Results: Significant differences, resulting from the defined remodelling phenotypes, were found between CRT responder and non-responder for volume ($p < 0.001$) and function ($p < 0.001$) changes. In CRT responder patients, LVEDV decreased by 22 ml [-37 to -16 ml] and LVEF improved by 11% [6 to 16%], whereas changes in LV volume (deltaLVEDV 2 ml [-4 to +10 ml]) and LVEF (deltaLVEF 2.5% [-2 to +5%]) were slight in CRT non-responders. We identified 4 genetic variants to be associated with the CRT responder phenotype at the allelic ($p < 0.035$) and genotypic ($p < 0.031$) level: rs3766031 (ATPIB1), rs5443 (GNB3), rs5522 (NR3C2) and rs7325635 (TNFSF11). By application of the classifiers "Clinical & Genotypes" and "Clinical & Alleles" in the machine learning process, the rule-based methods C4.5 and PART were identified to exceed 82.5% accuracy.

Conclusions: We demonstrate that rule induction algorithms can successfully be applied for the classification of heart failure patients in CRT responder and non-responder status using clinical and genetic parameters. Our analysis included information on alleles and genotypes of 4 genetic loci, pathophysiologically associated with remodelling of the failing ventricle.

1A.09 DISTINCT GENETIC ARCHITECTURE OF RENAL IMPAIRMENT COMPONENTS IN TYPE 2 DIABETES WITHIN CAUCASIAN POPULATIONS OF CELTO-GERMANIC AND SLAVIC ORIGINS

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Objective: The genetic architecture of type 2 diabetes (T2D) has been reported to be different between Asian and Caucasian populations (BBRC 2014;452:213–220). It is also well recognized that renal complications of T2D start earlier and are more severe in Asian subjects. Our objective was to determine whether such heterogeneity exists within the Caucasian population with respect to phenotypic and genomic determinants of renal complications in T2D.

Design and method: We analyzed two major aspects of renal impairment: increase of albuminuria as UACR and decline of estimated glomerular filtration rate as log(eGFR) in Caucasian patients during the 5 year period of the ADVANCE trial (NEJM 2014;371:1392–406). Celto-Germanic and Slavic origins of 3449 genotyped subjects were determined by principal component analysis with Eigenstrat software. The first principal component separated the 3449 individuals along a geographical gradient from East/West Europe: 1133 T2D patients were Slavic and 2316 were Celto-Germanic. Phenotypic analyses and Genome Wide Association Studies (GWAS) were performed in the two groups separately.

Results: The prevalence of hypertension was significantly higher ($p = 1.7x10–32$) in ADVANCE Slavic subjects. The prevalence of albuminuria and UACR levels were significantly higher ($p = 10–4$ and $9.5x10–5$, respectively) at baseline and its progression over the 5-year period was steeper ($p = 6.2x10–4$) in patients of Slavic origin, contrasting with a more significant decline of eGFR in Celto-Germanic subjects ($p = 4.9x10–21$). Other T2D outcomes (myocardial infarction and stroke) did not exhibit such a difference between East and West Europe. GWAS analyses of eGFR decline did not reveal any associated SNPs (threshold p-value of $< 10–3$) in common between the two geo-ethnic groups and only 6% of associated genes were shared. Similarly, GWAS of UACR progression showed that only 0.1% of SNPs were common and 7% of genes were shared between the two groups. This was very different for stroke: 25% of SNPs and more than 50% of genes were common.

Conclusions: Genetic analyses have to consider geo-ethnic characteristics even within Caucasians, demonstrated here for cardinal features of renal impairment in T2D. Our data suggest that distinct understanding of genomic architectures is important to ascertain clinical utility.

1A.10 ASSOCIATION BETWEEN GENE POLYMORPHISMS AND RISK OF CARDIOVASCULAR EVENTS IN PATIENTS WITH CORONARY HEART DISEASE

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Objective: Coronary heart disease (CHD) development is associated to a combination of lifestyle and genetic factors. A number of lifestyle risk factors is well defined, while genetic factors have not yet been well determined.

Design and method: To the PROGNOSIS (Prognostic Value of Ambulatory Blood Pressure Monitoring in Patients with Coronary Artery Disease Confirmed by Angiography) study there were included 1345 subjects with CHD. The median follow up period was 8.6 years (interquartile range 6.1 to 11.1 years). There were tested 19 SNPs for association with Major Advanced Cardiovascular Events (MACE), Acute Coronary syndromes (ACS) and Revascularizations. The Logistic Regression Model was used to estimate the association of genetic risk related to SNPs with MACE, ACS and Revasularisations.

Results: During 11 264 person-years of follow-up, 245 participants died (21.7 per 1000 person-years), 114 of cardiovascular cause (10.1 per 1000 person-years). A fatal or nonfatal cardiovascular event occurred in 882 participants (78.3 per 1000 person-years) including 214 ACS (19.0 per 1000 person-years), 578 revascularizations (51.3 per 1000 person-years) and 90 strokes (8.0 per 1000 person-years). The significant relationships between SNPs and MACE, ACS, and revascularization is shown in the table.

Conclusions: The PROGNOSIS study revealed relationship between SNPs: CXCL12, LPA, MRAS and PPAP2B and risk of MACE, MIA3 and risk of ACS and CXCL12, PHACTR1 and risk of revascularizations in patients with CHD.

1A.11 ASSOCIATION OF KIF6 AND HMGCR LOCI WITH CARDIOMETABOLIC PHENOTYPES AND RESPONSE TO STATIN THERAPY IN THE BRISIGHELLA COHORT

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Objective: Cardiovascular disease (CVD) represents the most common and lethal chronic disease worldwide. Lipids levels are the strongest risk factors for CVD and this is demonstrated by the fact that lipid-lowering statin therapy is largely used to prevent CVD. The role of the KIF6 gene in response to the statin therapy is controversial, and the biological mechanism through which it may act is still unknown.
We investigated the role of KIF6 locus variants alone and their interaction with the well-established lipid locus at HMGCR in the variability of metabolic traits and in response to statin therapy in an Italian sample.

Design and method: We genotyped two intronic rs20455, rs9462535 and a coding rs9471077 within the KIF6 gene, as well as two non-coding rs3761740 and rs3846662 at HMGCR. We tested the association of these SNPs with 19 cardiometabolic phenotypes and lipid-lowering therapy response in a sample of 1645 individuals from the Brisighella cohort (BC).

Results: Established rs3846662 (Willer et al, Nat Gen 2013) at HMGCR is associated (P=8.5x10-4) with LDL cholesterol (LDL-C) in BC. We did not find any significant association of KIF6 variants with response to statin therapy. We observe a locus-wide significant association at KIF6 between rs9471077 and APOB levels and rs20455 and HDL-C (P less than 0.001). rs3761740 at HMGCR showed an effect on systolic and diastolic blood pressure (SBP/DBP, P less than 0.007), which however wasn't significant after multiple testing correction.

Conclusions: This is the first genetic study reported for Brisighella cohort, which confirms association with LDL-C at HMGCR locus. We noticed an effect of KIF6 variants on APOB and HDL-C, while we don't observe any effect on statin therapy. The study sample is relatively small to discover a common variant effect and might still be due to chance; therefore, we are seeking for replication in additional cohorts. These findings, if confirmed, might contribute to development of approaches for stratified patient care.

1A.12 GENETIC BACKGROUND OF FEMORAL ATHEROSCLEROTIC PLAQUE FORMATION

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Objective: Femoral atherosclerosis, a major cause of peripheral artery disease, has been associated with higher cardiovascular risk in lower extremity peripheral arterial disease patients. The purpose of our study was to assess the effects of the heritable components of atherosclerotic plaque formation in the femoral artery.

Design and method: 161 Hungarian and Italian twin pairs (n = 322, 75 Hungarian and 86 Italian pairs from Padua, Perugia and Terni; 83 monozygotic /MZ/, 78 dizygotic /DZ/; mean age 50 ± 13 years) recruited from the Hungarian and Italian Twin Registries underwent B-mode sonography of bilateral common and superficial femoral arteries (CFA, SFA). Concordance rates between members of the MZ and DZ pairs were calculated, and compared by Chi-square test. Rough heritability was analysed by Falconer formula.

Results: Plaques were identified in 24% and 6% of patients in CFA and SFA, respectively. Significantly higher concordance rate was found in MZ twins compared to DZ pairs regarding the presence of plaques in CFA (rMZ = 0.869 vs. rDZ = 0.696) and SFA (rMZ = 0.622 vs. rDZ = 0.403) on left or right side, which indicated a 34% and 44% rough heritability, respectively.

Conclusions: Femoral atherosclerotic plaque formation in CFA and SFA is moderately genetically determined. Further studies should elucidate whether offsprings of families at high risk for femoral atherosclerosis may benefit from early ultrasound screening.

ORAL SESSION

ORAL SESSION 1B
BLOOD PRESSURE MEASUREMENT

1B.01 24 HOUR MODULATION OF PERIPHERAL AND CENTRAL BLOOD PRESSURE, HEART RATE AND ARTERIAL STIFFNESS IN HEART TRANSPLANT HYPERTENSIVE INDIVIDUALS

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Objective: After transplantation heart is denervated, resulting in increased resting heart rate (HR) and altered physiologic response to exercise. In heart transplant (HTX) recipients, absence of blood pressure (BP) dipping phenomenon has been reported, but information on central blood pressure, pulse wave velocity (PWV) and Augmentation Index (Aix) is scanty. Aim of our study was to investigate 24 h modulation not only of brachial BP but also of central-aortic BP (CABPM), HR, PWV and Aix in hypertensive HTX patients.

Design and method: We enrolled 24 hypertensive patients, 12 HTX recipients (Ht-HTX), at a mean time after HTX of 10,4 years, and 12 matched controls (Ht-C). All the patients were clinically stable and had normal LV systolic function. Ambulatory brachial BP, CABPM, PWV and Aix were recorded over 24 hours by Mobilograph device.

Results: Baseline brachial and central BP were similar in Ht-HTX vs Ht-C, as were 24 h brachial (128/78 mmHg ± 11/8Vs124/79mmHg ± 14/2) and central BP (119/81 mmHg ± 12/8 vs114/79 mmHg ± 13/7), HR (74.5 ± 11 vs 69 ± 10 bpm), PWV (8.15 ± 1.8 vs 8.2 ± 1.3 m/s) and Aix (23.6 ± 7.5 vs 22.8 ± 5.8%). PWV showed a dipping phenomenon in Ht-C (daily 8.3 ± 1.2, night 7.9 ± 1.4 m/s), $p < 0.001$) but not in Ht-HTX (daily 8.15 ± 1.8, night 8.15 ± 1.8). This was the case also for HR. Central systolic BP remained unchanged from day to night in Ht-HTX (118 ± 12 vs 119 ± 16 mmHg) but not in Ht-C (117 ± 15 vs 95 ± 33 mmHg), with night central systolic BP being higher in Ht-HTX vs Ht-C ($p < 0.05$). An index of 24 h variability (standard deviation) of BP and HR was lower in Ht-HTX than in Ht-C, reaching statistical significance only for 24h-HR (4.3 ± 1.7 vs 6.7 ± 2.3, p: 0.01).

Conclusions: Our study shows for the first time that in Ht-HTX there is no nocturnal dipping not only of brachial BP and HR but also of CABPM, and PWV up to 10 years after HTX, probably due to persistent cardiac denervation and/or interference by immunosuppressant drugs. Altered autonomic cardiovascular modulation could play a role in the development of restrictive physiology and possibly also of graft vasculopathy.

1B.02 CENTRAL VERSUS PERIPHERAL BLOOD PRESSURE IN PREDICTING TARGET-ORGAN DAMAGE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: There is evidence suggesting that central (aortic) blood pressure (BP) is a more accurate index of the hemodynamic stress on target-organs (heart, brain, aorta and kidneys) than peripheral (brachial) BP. A systematic review and meta-analysis of the evidence on the relationship of central versus peripheral BP with target-organ damage was performed.

Design and method: A PubMed search (1913–2014) was performed to identify studies reporting comparative data of central versus peripheral BP in terms of their association with several indices of target-organ damage. Correlation coefficients were pooled by random-effects model meta-analysis.

Results: Twelve studies assessing echocardiographic left ventricular mass index (n = 6431, pooled age 56.8 [95% CI 51.4, 62.2] years, 50% males, 51% hypertensives, 25% diabetics) showed stronger correlations with central (pooled correlation coefficient r = 0.30; 95% CI 0.23, 0.37; carotid or radial applanation tonometry) versus peripheral systolic BP (r = 0.26; 95% CI 0.19, 0.33; $p < 0.01$ for coefficients' comparison; z-statistic). Six studies assessing carotid intima-media thickness (n = 3798, pooled age 52.5 [95% CI 49.5, 55.5] years, 54% males, 50% hypertensives, 18% diabetics) showed stronger correlation with central (r = 0.32; 95% CI 0.26, 0.38; carotid or radial applanation tonometry) versus peripheral pulse pressure (r = 0.25; 95% CI 0.21, 0.29; $p < 0.01$ for coefficients' comparison). Fourteen studies assessing pulse wave velocity (n = 3701, pooled age 55.8 [95% CI 50.7, 60.8] years, 50% males, 53% hypertensives, 29% diabetics, 11% chronic renal insufficiency) revealed slightly stronger correlations with central (pooled correlation coefficient r = 0.42; 95% CI 0.37, 0.48) versus peripheral systolic BP (r = 0.39; 95% CI 0.33, 0.45; $p < 0.01$ for coefficients' comparison). Four studies assessing urine albumin excretion (n = 3718, pooled age 55.9 [95% CI 49.7, 62] years, 56% males, 69% hypertensives, 40% diabetics, 58% chronic renal insufficiency) reported similar correlations with central (r = 0.22; 95% CI 0.14, 0.29) versus peripheral systolic BP (r = 0.22; 95% CI 0.12, 0.32; p = NS for coefficients' comparison).

Conclusions: The available evidence suggests that central BP is slightly but consistently superior to the peripheral BP in predicting preclinical organ damage except for albuminuria.

1B.03 WHITE-COAT AND MASKED HYPERTENSION AS RISK FACTORS FOR PROGRESSION TO SUSTAINED HYPERTENSION: THE FINN-HOME STUDY

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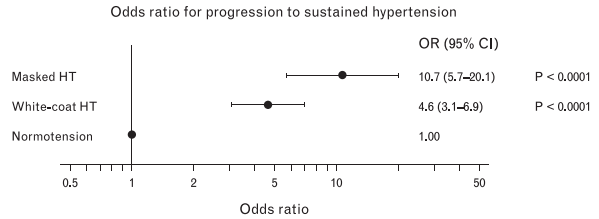
Objective: To assess the risk of progression from white-coat hypertension (WCHT) and masked (MHT) to sustained hypertension (SHT) in a nationwide unselected population sample.

Design and method: Both office and home blood pressure (BP) were measured in all participants in the years 2000 and 2011. We compared the risk of progression to SHT (office BP >=140/90 mmHg and home BP >=135/85 mmHg or start of treatment with antihypertensive medication) between 528 participants with normotension (NT, office BP <140/90 mmHg and home BP <135/85 mmHg), 142 participants with WCHT (office BP >=140/90 mmHg and home BP <135/85 mmHg), and 63 participants with MHT (office BP <140/90 mmHg and home BP >=135/85 mmHg) with no antihypertensive drug treatment at baseline. Office BP was measured twice by a nurse on a single occasion and home BP was measured twice every morning and evening for one week with a validated, oscillometric device. We used the chi-square and Mantel-Haenszel tests to compare differences and trends in categorical variables. A multivariable-adjusted logistic regression model (adjusted for age, gender, body mass index, diabetes, hypercholesterolemia and smoking) was used to evaluate the association between baseline BP categories and incident SHT.



Results: Over an 11-year follow-up, the rate of progression to SHT increased from NT (18%) to WCHT (52%) and MHT (73%), $P < 0.0001$. Progression to SHT became more likely with an increasing baseline home BP (P for trend <0.0001). During follow-up, 2.4%, 10.4% and 16.4% of participants with NT, WCHT and MHT ($P < 0.0001$), respectively, suffered a major adverse cardiovascular event (a composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for

heart failure and coronary intervention). The multivariable-adjusted odds ratios (95% confidence interval) for developing SHT, as compared with NT, were 4.6 (3.1–7.0, P < 0.0001) for WCHT and 10.7 (5.7–20.1, P < 0.0001) for MHT (Figure). The other covariates did not reach statistical significance.

Conclusions: Neither WCHT, nor MHT can be considered a harmless benign phenomenon. Persons in these categories have a several-fold risk of developing SHT than those with NT and could benefit from active follow-up and lifestyle counselling.

1B.04 WHITE COAT PHENOMENON CRUCIALLY AFFECTS CENTRAL BLOOD PRESSURE VALUES

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Objective: Although blood pressure measured over the brachial artery is a powerful predictor of cardiovascular morbidity and mortality, recent studies suggest that central blood pressure is more closely associated with cardiovascular events and target organ damage than brachial blood pressure. The present study was designed to investigate effects of white coat phenomenon on central blood pressure.

Design and method: Outpatients with essential hypertension who were under antihypertensive medication with a stable blood pressure control at least for the last 6 months (n = 50, 70 ± 14 years) were recruited. They were instructed to measure blood pressure by themselves in the morning at home (home blood pressure). At medical examination, brachial blood pressure (oscillometer) and radial artery pressure waveforms (tonometer) were recorded using an automated device, and central blood pressure was estimated using systolic pressure corresponding to the second systolic peak of radial pressure waveforms (HEM-9000AI, Omron Healthcare, Kyoto). White coat phenomenon was quantified by the following formula: [(office blood pressure) – (home blood pressure)]/ (home blood pressure).

Results: Estimated central blood pressure correlated with both office blood pressure (r = 0.86, p < 0.001) and home blood pressure (r = 0.53, p < 0.01), but the relationship of central blood pressure with office blood pressure was somewhat closer as compared to that with home blood pressure. A correlation was observed between central blood pressure and white coat phenomenon (r = 0.44, p < 0.05). In multiple regression analysis, white coat phenomenon was an independent predictor of central blood pressure.

Conclusions: Office blood pressure may have greater impact on central blood pressure than self-measured home blood pressure. Although central blood pressure may be a good marker of cardiovascular events and target organ damage, possible effects of white coat phenomenon should be considered when interpreting central blood pressure values.

1B.05 IN HYPERTENSION THE CHANGE FROM A NON-DIPPER TO A DIPPER PATTERN IS ASSOCIATED WITH A BETTER CARDIOVASCULAR PROGNOSIS THAN THE PERSISTENCE WITHIN THE NON-DIPPER PATTERN

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Objective: It is known that the non dipping pattern of systolic blood pressure (ND) circadian rhythm determined by ambulatory blood pressure monitoring (ABPM) is a predictor of cardiovascular (CV) events. However it is not known if changing to a dipper pattern changes the CV prognosis.

Methods: Retrospective observational analysis of hypertensive outpatients who repeated ABPM during the period of 1994 until 2013. Follow-up was defined from first appointment to 31st of December 2014 or cardiovascular event (CV) (acute coronary syndrome, stroke, heart failure or arrhythmia and sudden death).

Design and method: 226 patients were included, 181 female (48,9%), mean age 56,4+/− 16,4 years. Each patient had at least 2 ABPM in a total of 634 ABPM. During a mean follow-up of 4,7 +/−1.37 years, 28 patients (7,6%) had CV event and there were 16 deaths (37,5% cardiovascular). When comparing patients with vs. without events, patients with events were older (69,0+/−13,4 vs. 55,4 +/− 16,2 years p < 0,01), had higher 24 h SBP (136,8+/− 15,6 vs. 129,8+/− 12,4 mmHg; p 0,005) and casual diastolic blood pressure (DBP) (82,6+/− 17,2 vs. 89,0+/−13,6 mmHg: p 0,02) but lower 24 h DBP (71,3+/− 11,0 vs. 75,5+/− 9,8 mmHg; p 0,03). Nocturnal fall of SBP was less pronounced in patients with events (5,9+/− 9,4 vs. 10,5+/− 7,5 mmHg; p 0,03). Analyzing the SBP pattern of nocturnal fall, in 52,7% of ABPM the pattern remained the same. When we selected only patients with a ND pattern in the initial ABMP, the Kaplan Meier free of events survival curves showed that, comparing those who stayed ND with those who changed to dipper (D) and to reverted dipper (RD), those who changed to D had significantly less CV events then those who remained ND and those who changed to RD (log rank 6,2 p < 0,05).

Conclusion: In our study the modification from ND to D vs the persistence of ND is associated with less CV events. These results suggest that SBP nocturnal dipping is not only a static marker of CV risk but can undergo therapeutic intervention to improve prognosis.

1B.06 MASKED HYPERTENSION PREVALENCE AND ITS MARKERS IN ORGANIZED COHORT

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Objective: The masked hypertension (MH) is the actual problem of medicine due to association with high risk of cardiovascular complications. The aim of study was assess MH prevalence and markers in organized cohort (employees with antihypertensive treatment [masked noneffective therapy; MNT] or without it [MH]).

Design and method: Cross-sectional cohort study of employees (n = 477) of large industrial enterprise with office blood pressure (OBP)<140/90 mm Hg. The ambulatory BP monitoring (ABPM), ECG, echocardiography, anthropometry, blood chemistry were performed. The selection criterion for ABPM records was the quality adequate for sophisticated analyses: duration> = 24 hours, absence of data gaps>1 hour. The criterion for MH and MNT were OBP<140/90 mm Hg and mean BP in working hours (08:00–17:00, [WBP])>134 and/or 84 mm Hg. We defined MH and MNT markers as patient characteristics significantly associated with the ratio of OBP and WBP.

Results: The total number of employees with normal OBP was 185, mean age 53.2 ± 5.5, males – 38.4%. The MH prevalence was 10.8%, MNT – 34.6% (45.4% of employees with normal OBP). The main differences included: between MH group and normotensive persons – higher left ventricular (LV) mass index (129.0 ± 21.2 vs. 109.5 ± 28.8 g/m2 in males, 105.2 ± 43.2 vs. 82.4 ± 25.3 g/m2 in females, p < 0.05) and weight (85.4 ± 13.3 vs. 81.3 ± 10.1 kg, p = 0.05); between MNT group and employees with effective antihypertensive treatment (normal OBP and WBP) – weight (89.4 ± 16.1 vs. 85.4 ± 15.8 kg, p < 0.05), triglycerides (1.56 ± 0.95 vs. 1.23 ± 0.55 mmol/l, p < 0.01) and uric acid (388.5 ± 89.5 vs. 357.2 ± 84.5 mmol/l, p < 0.05), LV hypertrophy signs (the interventricular septum thickness 1.34 ± 0.19 vs. 1.26 ± 0.19 mm, the LV posterior wall thickness 1.27 ± 0.13 vs. 1.21 ± 0.16, p < 0.05), incidence of coronary heart disease (n = 3 vs. n = 15, p < 0.05) and the higher number of patients with angiotensin converting enzyme inhibitors intake (64.1% vs. 46.9%, p < 0.05). In this study the professional factors were not associated with MH and MNT.

Conclusions: MH and MNT in organized cohort were diagnosed in approximately 50% employees. The MH and MNT markers of this group include traditional risk factors. High MH and MNT prevalence makes it necessary to detect these hypertension phenotypes carefully.

1B.07 EVALUATION OF CENTRAL BLOOD PRESSURE DURING A VERY LONG DISTANCE WALKING

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Objective: To evaluate the behavior of central blood pressure (BP) variables in male athletes before and during a very long distance walking - 310Km route in five days.

Design and method: Longitudinal study with 25 participants. This walking nominated as 'Ecological Walk' happens in Brazil every july since 1991. Its main goals are environmental preservation awareness, health lifestyle incitement as well as exercise practice incitement. The participants traveled the 310 Km during five days alternating walking and light running, a 72 Km/day average. First data collection occurred one month before the walking (V0) and the others, during the second (V2), third (V3) and fourth walking day (V4); just after the athletes finished the daily route. Mobil O Graph was the device used to get central BP variables: pulse wave velocity (PWV), augmentation index (AIx), peripheral vascular resistance (PVR), central pulse pressure (PPc) and amplified pulse pressure (PPA).

Results: Sample composition was 25 males, regular physical activity practitioners, mean age 45,3 ± 9,1 years old. Brachial systolic (SBP) and diastolic blood pressure (DBP) had the same response during the route, reduction from V0 to V2, and a slight increase from V2 to V3 and V4. PPc decreased from V0 (33,5mmHg) to V2 (28,7mmHg); p = 0,05 and increased from V2 (28,7mmHg) to V4 (32,9mmHg); p = 0,01. Brachial PP decreased from V0 (49,2mmHg) compared with all the others evaluated days (38,2mmHg; 42,7mmHg; 41,2mmHg), respectively. PPA increased

from V0 to V2, and decreased from V0 to V3 and from V0 to V4. PVR increased from V3 (1,07s*mmHg/ml) to V4 (1,13 s*mmHg/ml); p = 0,046. PWV decreased from V0 (7,0m/sec) to V2 (6,6m/sec) and from V0 (7,0m/sec) to V3 (6,5m/sec). Pulse wave velocity showed strong correlation with age during all the measurements.

Conclusions: These datas indicate that central blood pressure changes are sharpest in the first days, after this it seems that an exercise physiological accommodation occurred. There was a strong correlation between age and pulse wave velocity in this sample.

1B.08 USEFULNESS OF 24-HOUR AMBULATORY BLOOD PRESSURE MONITORING IN PEOPLE LIVING WITH HIV

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Objective: This study aimed to determine the utility of 24-hour ambulatory blood pressure monitoring (ABPM) in a priori normotensive and known hypertensive people living with HIV by quantifying new hypertension (HTN), masked hypertension, uncontrolled BP, and white coat effect.

Design and method: Data analysed was from the Register of cardiovascular Complications among people living with HIV (RECOVIH), including 263 HIV+ individuals with 1 or more CV risk factors who underwent 24-h ABPM in our cardiac centre.
Diagnostic criteria:
Elevated clinic BP: at or above 140/90 mmHg
Elevated mean 24-h ABPM: at or above 130/80 mmHg, systolic and/or diastolic
New hypertension: elevated clinic BP and/or elevated mean 24-h ABPM
Masked hypertension: normal clinic BP and elevated mean 24-h ABPM
Uncontrolled BP: elevated clinic BP and/or elevated mean 24 h ABPM, in known HTN
White coat effect: elevated clinic BP and normal mean 24-h ABPM, in a priori normotensives.

Results: The cohort had a mean age of 50.3 ± 7.7 years, was predominantly male (91%), had a long median HIV duration (15.3 years), and included 150 (57%) known HTN.
In RECOVIH the prevalence of new HTN was 22% (n = 25), of which 50% masked hypertension diagnosed by 24-h ABPM solely. Uncontrolled HTN prevalence was 45% using clinic BP alone and 32% using 24-h ABPM alone. 24-h ABPM revealed that this masked uncontrolled HTN was frequently due to poor nocturnal BP control.
White coat effect prevalence was not significantly different between the 2 groups (6.3% a priori normotensives vs. 9.3% known HTN, p = 0.37).
HTN subjects were older, had higher BMI, and more frequently had a history of diabetes, coronary heart disease, and heart failure as compared to normotensives.

Conclusions: Masked hypertension prevalence is high in RECOVIH, particularly among a priori normotensives. Suboptimal BP control is frequent among patients with treated and well-controlled clinic BP. Clinic BP monitoring alone is inadequate to diagnose HTN and assess true BP control because elevated nocturnal BP was frequent.
These findings suggest ABPM should be more routinely used to diagnose HTN and confirm BP control in people living with HIV.

1B.09 ACCURACY OF HOME VERSUS AMBULATORY BLOOD PRESSURE MONITORING IN THE DIAGNOSIS OF WHITE-COAT AND MASKED HYPERTENSION

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Objective: We investigated accuracy of home blood pressure (BP) monitoring in the diagnosis of white-coat and masked hypertension in comparison with ambulatory BP monitoring.

Design and method: Our study subjects were enrolled in the ongoing China Ambulatory and Home Blood Pressure Registry and underwent clinic, home and 24-hour ambulatory blood pressure measurements. The blood pressure threshold for hypertension diagnostic was 140mmHg and/or 90mmHg (systolic/diastolic) for clinic blood pressure, 130mmHg and/or 80mmHg for 24-hour ambulatory blood pressure and 135mmHg and/or 85mmHg for home blood pressure. We defined white-coat hypertension as an elevated clinic systolic/diastolic pressure and a normal 24-hour ambulatory or home systolic/diastolic pressure and masked hypertension as a normal clinic systolic/diastolic pressure and an elevated 24-hour ambulatory or home systolic/diastolic pressure.

Results: In untreated subjects (n = 573), the prevalence of white-coat hypertension (13.1% vs. 19.9%), masked hypertension (17.8% vs. 13.1%) and sustained hypertension (46.4% vs. 39.6%) significantly (P < 0.02) differed between 24-hour ambulatory and home BP monitoring. In treated subjects (n = 1201), only the prevalence of masked hypertension differed significantly (18.7% vs.14.5%, P = 0.005). Regardless of the treatment status, home compared with 24-hour ambulatory BP had low sensitivity (range, 47%-74%) but high specificity (86%-94%) and accordingly low positive (41%-87%) but high negative predictive values (80%-94%), and had moderate diagnostic agreement (82%-85%) and Kappa statistic (0.41–0.66). In untreated and treated subjects, age advancing was associated with a higher prevalence of white-coat hypertension and a lower prevalence of masked hypertension defined by 24-hour ambulatory (P < 0.04) but not home BP (P > 0.10).

Conclusions: Home BP monitoring has high specificity but low sensitivity in the diagnosis of white-coat and masked hypertension, and may therefore behave as a complementary to, but not a replacement of, ambulatory BP monitoring.

1B.10 DOES THE RIGHT ARM KNOW WHAT THE LEFT ARM IS DOING? ETHNIC VARIATIONS IN CLINICAL INTERARM DIFFERENCE AND RELATIONSHIP TO WHITE COAT EFFECTS

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Objective: Evidence suggests an interarm difference (IAD) of >=10mmHg in blood pressure (BP) is associated with a greater incidence of cardiovascular disease. Effect of ethnicity on the prevalence of this difference has not been reported.

Design and method: The Blood Pressure in Ethnic Groups Study (BP-Eth), based in primary care, investigated the relationship between ethnicity and different methods of BP measurement. Using these data the prevalence of a significant IAD was investigated in 770 people (300 White British, 229 South Asian, 241 African-Caribbean). Repeated BP measurements were obtained simultaneously in the right and left arm using two BP-Tru machines and comparisons made between the first reading, mean of 2nd/3rd readings and mean of 2nd-6th readings for patients with and without known hypertension.

Results: No significant difference was seen in the prevalence of a systolic IAD between ethnicities whichever combinations of BP measurement were used and whether or not an individual was hypertensive. Overall the prevalence of IAD fell as more measurements were used in the comparison: first measurement (n = 161, 22%), mean 2nd/3rd (113, 16%) and mean 2–6th (78, 11%) (first vs clinic and research mean p < 0.001). To investigate whether this change in IAD prevalence with repeated measurement was due to a white coat effect (WCE), the three types of measurement were compared with participants' mean daytime ambulatory readings (ABPM). WCE was defined as Clinic BP >=10mmHg higher than ABPM. Unadjusted results show patients with a WCE were twice as likely to have an IAD on their first BP measurement (OR 2.1, 95% CI 1.4 - 3.1), mean 2nd/3rd (2.1, 95% CI 1.3 - 3.4) and mean 2–6th (2.1, 95% CI 1.2 - 3.9) compared to those without a WCE.

Conclusions: Ethnicity did not affect the prevalence of IAD in people with or without hypertension. However the prevalence of IAD was affected by the number of readings suggesting an element of white coat effect and this was confirmed by comparison with ambulatory monitoring. Therefore ABPM may play an important role in the investigation of those with >=10mmHg interarm blood pressure difference.

1B.11 ACCURACY OF DIFFERENT TYPES OF BLOOD PRESSURE MEASURING DEVICES AT HIGH ALTITUDE. DATA FROM HIGHCARE-ALPS STUDY

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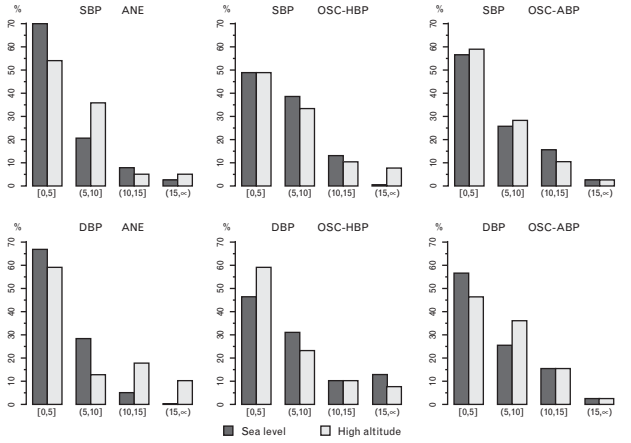
Objective: Blood pressure (BP) measuring devices may become inaccurate at high altitude due to low barometric pressure. Aim of this study was to assess the changes in the accuracy of different types of BP measuring devices between sea level and high altitude, taking auscultatory measurements with mercury sphygmomanometer as reference.

Design and method: In the frame of HIGHCARE-ALPS project, we obtained multiple BP measurements in 39 healthy, normotensive volunteers (age:36.4 ± 8.5y, M/F:21/18), using a mercury (MER, reference), an aneroid (ANE), and two validated oscillometric devices [one for home (OSC-HBP; AND UA-767PC) and one for ambulatory (OSC-ABP; AND TM2430)] BP monitoring, at sea level and during acute exposure to high altitude (4559m, 437–439 Torr). BP measurements with the different devices were performed sequentially on the same arm in random order, consistent under both study conditions.

Results: Mean systolic (S) and diastolic (D)BP were higher at high altitude than at sea level (MER: 117.6/80.3 vs. 110.9/74.1 mmHg, $p < 0.001$) The mean differences in SBP between MER (reference) and the other devices at baseline and high altitude were $1.7 \pm 6.5/0.6 \pm 7.1$ (OSC-ABP), -3.1 ± 5.3*/-3.8 ± 6.3* (ANE) and $-1.2 \pm 7.0/-5.0 \pm 6.7$* (OSC-HBP) respectively. The corresponding differences for DBP were -3.9 ± 5.9*/-4.5 ± 6.5* (OSC-ABP), -2.2 ± 5.1*-5.3 ± 6.7* (ANE) and -4.8 ± 7.6*/-1.8 ± 7.1 (OSC-HBP), (mmHg, *$p < 0.01$ vs. MER). The over or underestimations of BP values by tested devices as compared with MER were consistent and similar at sea level and high altitude, except for a greater underestimation of SBP by OSC-HBP ($p = 0.01$), and of DBP by ANE ($p = 0.03$) at altitude, and for a greater underestimation of DBP by OSC-HBP ($p = 0.02$) at sea level. In spite of the statistical significance, the absolute changes in the size of error between sea level and high altitude never exceeded 4 mmHg. The distribution of mean between-device differences within the group was consistent between sea level and high altitude, with about 50% of subjects displaying between-devices differences always smaller than 5 mmHg (Figure).



Conclusions: BP measuring devices commonly used at sea level remain reasonably accurate at high altitude. We did not find consistent and clinically relevant changes in the accuracy of the tested devices caused by low barometric pressure at altitude.

1B.12 EFFECT OF OVERCUFFING ON THE ACCURACY OF OSCILLOMETRIC BLOOD PRESSURE MEASUREMENTS

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Objective: Overcuffing, or using a blood pressure (BP) cuff that is too large, is known to artificially lower auscultatory BP; however, its effect on oscillometric BP is unclear. The possibility that overcuffing biases oscillometric BP is currently widely disregarded. We performed a two-phase study to confirm that overcuffing lowers auscultatory BP and to assess the effect of overcuffing on oscillometric BP.

Design and method: Community-dwelling adults (aged 18y or older) with arm circumferences within the standard range 25–32 cm were recruited. Using primarily the International Standards Organization (ISO) 2009 protocol, we compared the standard Baum adult (25–35 cm) to the large adult (33–47 cm) cuff. The standard cuff was considered the 'reference standard'. In Phase I (auscultatory assessment performed by two trained observers), 87 subjects were recruited to reach the required 255 paired BP determinations. In Phase 2 (oscillometric assessment), 85 subjects were required. Each study phase was analyzed independently using paired t-tests to calculate p-values and by generating Bland-Altman plots.

Results: The results of Phase I confirmed that, compared to the standard cuff size, overcuffing reduced auscultatory BP by $3.6 \pm 5.1/2.8 \pm 4.0$ (p-values<0.0001 for both). For Phase 2, the mean age was 39.30 ± 18.3 years, mean arm circumference was 28.0 ± 1.9 cm, 79% were female and 22% had a past history of hypertension. Mean BPs were $112.2 \pm 13.1/67.8 \pm 7.3$ mmHg for the large cuff and $117.8 \pm 13.3/71.2 \pm 7.1$ for the standard cuff (difference of $-5.5 \pm 5.9/-3.4 \pm 5.2$; p-values<0.0001).

Conclusions: Overcuffing leads to a clinically important downward bias in oscillometric BP. These findings indicate that upper size limits for oscillometric cuffs should be specified.

ORAL SESSION

ORAL SESSION 1C
CARDIOVASCULAR RISK FACTORS

1C.01 SOLUBLE UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR AS A PROGNOSTIC MARKER OF ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN A BLACK POPULATION

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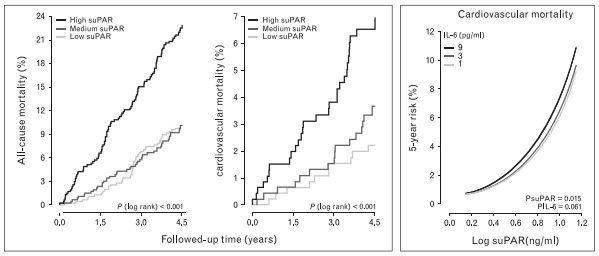
Objective: Elevated inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are well-known risk factors for cardiovascular mortality. The less familiar marker, soluble urokinase plasminogen activator receptor (suPAR), is known to predict cancer, infections and all-cause mortality. We determined whether suPAR, CRP and IL-6 are predictive of both all-cause and cardiovascular mortality in a black population, highly burdened by cardiovascular disease and HIV infection.

Design and method: We included 1 425 black South Africans, of which 208 died within five years after baseline data collection. EDTA plasma biomarker levels were determined, while all-cause and cardiovascular mortality were used as endpoints.

Results: At baseline suPAR, CRP and IL-6 were higher in non-survivors than in survivors (P < 0.001). SuPAR (HR 1.27, 95% CI 1.09–1.48), IL-6 (HR 1.49, 95% CI 1.24–1.78) and CRP (HR 1.39, 95% CI 1.17–1.65) predicted all-cause mortality, while only suPAR (HR 1.40, 95% CI 1.04–1.87) and IL-6 (HR 1.61, 95% CI 1.10–2.35) predicted cardiovascular mortality. The prognostic value of suPAR was independent of IL-6 and CRP (P<=0.015).



Conclusions: SuPAR predicted both all-cause and cardiovascular mortality, independent of traditional risk factors, HIV and other inflammatory markers, underlining the prognostic value of suPAR in a black population.

1C.02 EVIDENCE FOR A PROGNOSTIC ROLE OF ORTHOSTATIC HYPERTENSION ON SURVIVAL IN A VERY OLD INSTITUTIONALIZED POPULATION

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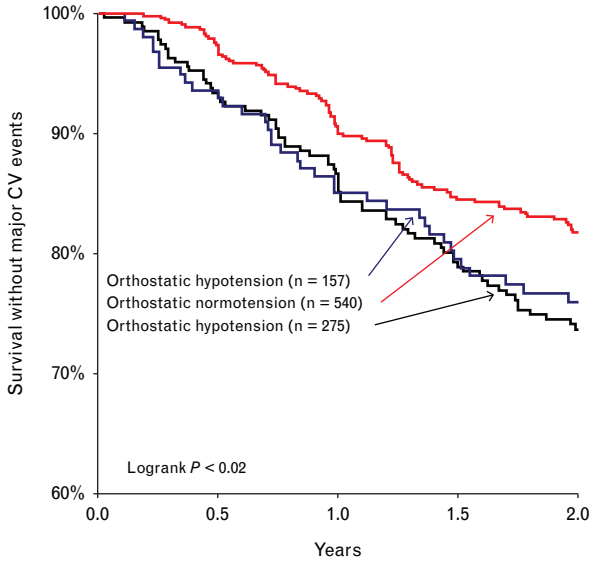
Objective: The prevalence and the prognostic role of orthostatic hypertension (OHyperT) in a very elderly population remain unknown. We aimed to investigate the association of OHyperT with cardiovascular morbidity and mortality in a population of elderly institutionalized patients.

Design and method: A longitudinal study with 2-year follow-up was conducted on 972 very elderly individuals (mean age [SD] 88[5]) living in nursing homes (223 men) that were able to maintain standing position, included in the PARTAGE study. Socio-demographic characteristics, medical history, chronic diseases (cardiovascular, central nervous system and respiratory), history of falls, comorbidity and medication use were collected. In addition, clinical examination of functional status, cognitive function, blood pressure (BP) and aortic stiffness was performed. BP measurements were repeated at 1 and 3 minutes after standing position. OHyperT was defined as an increase in SBP >20mmHg during the 3 first minutes of standing up. Orthostatic hypotension (OH) was defined as a decrease in systolic BP (SBP) >20mmHg and/or in diastolic BP (DBP) >10mmHg. Cardiovascular morbid-mortality included nonfatal cardiovascular events leading to hospitalization or a specific long-term new treatment as well as death from cardiac, cerebrovascular, and other vascular causes.

Results: The population was divided into 3 groups: orthostatic normotension (ONT)(n = 540), OH(n = 157), and OHyperT(n = 275) groups. Mean age was similar and women were 82% in OHyperT versus 69% in OH group. At inclusion, all comorbidities but peripheral arterial disease (11% in OH versus 5% in OHT) were similarly distributed in the three groups. Sitting SBP was higher in OH compared to ONT and OHyperT groups (146[23],136[21],136[20] mmHg respectively, all P < 0.001). OHyperT was associated with an increased risk of cardiovascular morbi-mortality adjusted (age and gender) risk-ratio [95% CL] (1.53[1.12–2.08]) compared to ONT. Adjusted (age and gender) risk-ratio of OH versus ONT was directionally increased (1.40[0.96–2.05]). Kaplan-Mayer curves (figure) for cardiovascular morbi-mortality show that ONT group presented higher survival than both OH (HR 1.44[0.95–2.17], P = 0.057) and OHyperT (HR 1.51[1.09–2.08], P < 0.01).

Conclusions: In a very old frail institutionalized population, increase in SBP by >20mmHg in upright position has a negative prognostic impact on cardiovascular morbi-mortality.



1C.03 GENDER DIFFERENCES IN OFFICE AND HOME BLOOD PRESSURE CONTROL IN UNCOMPLICATED HYPERTENSIVES, WHO OBTAINED STANDARDIZED ALGORITHMIC TREATMENT IN LONGITUDINAL REAL-LIFE STUDY

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Objective: To compare both target office (<140/90mmHg) and normal home (<135/85mmHg) blood pressure (BP) attainment after 6 month (M) standardized

algorithmic treatment and home BP monitoring (HBPM) in men and women <75 years with uncomplicated hypertension (UH).

Design and method: Per protocol cohort of PERFECT-BP prospective observational study (ISRCTN75706523) included 430 newly diagnosed (18.3%) or treated but uncontrolled (BP<200/120mmHg) UH patients (pts) aged 57.6 ± 0.5, 197(45.8%) male, 74(17,2%) diabetics. HBPM was performed by standardized automatic Microlife BP3AG1 device with individually selected cuff. At visit 1, pts were given training and written instructions for HBPM and recording (twice per day for 7 consecutive days before each visit) and were prescribed or switched to perindopril/amlodipine fixed-dose combination (FDC) (doses at discretion of MDs). Step 2 was FDC uptitration, step 3 – indapamide SR„ step 4 – spironolactone, step 5 – moxonidine or doxazosin.

Results: At baseline men differed from women by younger age (56,1 ± 0,7 vs 59,2 ± 0,6 years, p < 0,01), higher glomerular filtration rate (106,4 ± 2,0 vs 88,3 ± 1,6 kg/m2, p < 0,001), lower incidence of obesity (39,1 vs 59,9%, p < 0,01), higher smoking rate (35 vs 6,7% p < 0,001), higher office and home BP (table). Maximal FDC dose (10/10 mg) prescription obtained 48,7% men vs 33,9% women (p < 0,05), triple therapy – 25,4% vs 28,3%, and 4 or more drugs – 11,7% vs 9,5% (all p>0,05). By 6 M, target office BP was attained in 145(73,6%) men vs 206(88,4%) women, normal home BP – in 110(55,8%) vs 179(76,8%), both target office and normal home BP – in 104(52,8%) vs 169(72,5%, all p < 0,01). Masked uncontrolled hypertension at 6 M was identified in 41(20,8%) and 37(15,9%) pts, white coat one – in 6(3%) and 10(4,3%) respectively, (all p > 0,05).

		Office SBP	Office DBP	Home SBP&○	Home DBP&○
Men	Baseline	167,3±1,0*○	98,6±0,7*○	150,6±1,2*○	89,9±0,7*○
	6M	132,0±0,7*#○	80,3±0,5*#○	130,8±0,6**#○	78,9±0,5*#○
Women	Baseline	164,3±0,9○	95,9±0,7○	147,5±1,1○	87,0±0,7○
	6M	129,6±0,6#○	78,4±0,4#○	127,8±0,5#○	77,2±0,5#○

#-p<0,001, compared to baseline; *-p<0,05, compared to women; **-p<0,01, compared to women; &-by day 7.

Conclusions: Standardized algorithmic treatment based on FDC in real life setting provided lower rates of office and home BP control in men compared to women. Sex differences did not affect the incidence of masked uncontrolled and white-coat hypertension.

1C.04 COFFEE CONSUMPTION IS A PREDICTOR OF CARDIOVASCULAR EVENTS IN YOUNG AND MIDDLE AGED HYPERTENSIVE SUBJECTS

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Objective: Controversy still exists about the long-term cardiovascular and metabolic effects of coffee consumption in hypertension. Aim of the study was to assess the predictive capacity of coffee use for cardiovascular events (CVE) and to ascertain whether the coffee-CVE association was mediated by the long-term effects of coffee on blood pressure (BP) and glucose metabolism.

Design and method: The analysis was made in 1201 participants from the HARVEST, a prospective cohort study of non-diabetic subjects aged 18–45 years, screened for stage 1 hypertension. BP was measured with ambulatory monitoring in all.

Results: Among the participants, 26.3% were abstainers, 62.7% were moderate coffee drinkers (1–3 cups/day) and 10.0% were heavy coffee drinkers (>3 cups/day). During a 12.5 year follow-up there were 60 CVE. In multivariable Cox analyses, coffee consumption was a significant predictor of development of hypertension needing treatment with hazard ratios (HR) of 1.5 (CI,1.1–1.9) for heavy drinkers and 1.1 (0.9–1.3) for moderate drinkers compared to abstainers. Also, coffee was a predictor of future prediabetes with HRs of 2.0 (1-3-3.1) and 1.3 (0.9–1.7), in the heavy and moderate drinkers, respectively. In multivariable Cox analyses, including other lifestyle factors, age, sex, parental CVE, BMI, total cholesterol, 24 h ambulatory BP, 24 h ambulatory heart rate and follow-up changes in body weight, both coffee categories were independent predictors of CVE with HRs of 4.3 (1.3–13.9) for heavy coffee drinkers and 2.9 (1.04–8.2) for moderate drinkers. Inclusion of hypertension development in the regression attenuated the strength of the coffee-CVE association with HRs of 3.9 (1.2–12.5) for heavy and of 2.8 (0.99–7.8) for moderate drinkers. When future prediabetes was also incorporated, the relationship was of boderline significance for heavy coffee drinkers (HR, 3.2, 0.94–10.9) and was no longer significant for moderate drinkers (HR, 2.3, 0.8–6.5).

Conclusions: Coffee use is linearly associated with increased risk of CVE in stage 1 hypertension. The effect of coffee on CVE seems to be at least partially mediated by its long-term effects on BP and glucose metabolism. Coffee consumption should be reduced in young-to-middle-age patients with hypertension.

1C.05 MORNING SURGE AND SLEEP-TIME BLOOD PRESSURE AS PROGNOSTIC MARKERS OF CARDIOVASCULAR RISK: THE HYGIA PROJECT

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Objective: The extent of blood pressure (BP) surge upon waking has been associated with increased cardiovascular (CVD) risk in some, but not all, studies. Numerous studies, however, have consistently shown the association between elevated sleep-time BP mean and the rising BP pattern with increased CVD risk, leading to a paradox, as patients with sleep-time hypertension or non-dipper/riser BP pattern have attenuated morning BP surge. We evaluated the comparative prognostic value for CVD events of the morning BP surge and sleep-time BP among the participants in the ongoing Hygia Project.

Design and method: This study involved 11255 subjects, 6028 men/5227 women, 58.9 ± 14.5 years of age, prospectively evaluated throughout a 4.0-year median follow-up. BP was measured at 20-min intervals from 07:00 to 23:00 h and at 30-min intervals at night for 48 h. During monitoring, subjects maintained a diary listing the times of going to bed and awakening.

Results: We documented 1539 total events, including 400 deaths, 176 strokes, 144 myocardial infarctions, 147 coronary revascularizations, and 193 heart failures. A greater prewaking systolic BP surge was associated with significantly lower, not higher, CVD risk in a Cox proportional-hazard model adjusted for the significant influential characteristics of age, sex, diabetes, chronic kidney disease, cigarette smoking, waist perimeter, and history of previous CVD event (hazard ratio [HR] 0.83 [95%CI 0.78–0.88] per each 1-SD increment; P < 0.001). The HR was progressively and significantly higher in the first three than in the last two quintiles of increasing prewaking BP surge. The prognostic value of morning surge markedly decreased after correcting by the asleep BP mean, the single most significant prognostic marked of total CVD events (HR = 1.37 [1.29–1.44], P < 0.001).

Conclusions: Our findings document that, when properly analyzed as a continuous variable, a larger morning BP surge is associated with a significantly lower CVD risk, in line with the markedly greater risk associated with decreasing dipping of the BP pattern, and the most highly significant prognostic value of progressively elevated asleep BP, an independent prognostic marker of CVD risk that has also been prospectively validated as a relevant therapeutic target for CVD risk reduction.

1C.06 AMBULATORY PULSE PRESSURE IS NEGATIVELY ASSOCIATED WITH EXCRETIONS OF URINARY CAFFEINE AND ITS METABOLITES

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Objective: Systolic blood pressure (BP) has been associated with urinary caffeine and its metabolites such as paraxanthine and theophylline. Caffeine and caffeine metabolites could influence arterial pulse pressure (PP) via sympathomimetic effects, smooth muscle relaxation, and phosphodiesterase inhibition. The purpose of this analysis was to explore the association of ambulatory PP with urinary caffeine and its related metabolites in a large population-based sample.

Design and method: Families were randomly selected from the general population of three Swiss cities (2009–2013). Ambulatory BP monitoring was conducted

using validated Diasys Integra devices. PP was defined as the difference between the systolic and diastolic ambulatory BP. Urinary caffeine, paraxanthine, theophylline, and theobromine excretions were measured in 24 h urine using ultra-high performance liquid chromatography tandem mass spectrometry. Urinary excretions were log-transformed to satisfy regression assumptions. We used linear mixed models to explore the associations of urinary caffeine and caffeine metabolite excretions with 24-hour, day- and night-time PP while adjusting for major confounders.

Results: The 836 participants (48.9% men) included in this analysis had mean (±SD) age of 47.8 (±17.5), and mean 24-hour systolic and diastolic BP of 120.1 mmHg (±13.9) and 78.0 (±8.6). Except theobromine, log transformed urinary caffeine and caffeine metabolite excretions were associated negatively with 24-hour, daytime and night-time ambulatory PP. 24-hour, daytime, and night-time ambulatory PP decreased by −0.804 mmHg (SE, 0.209), −0.749 (0.215), and −0.968 (0.243) (all P values <0.005), for each doubling excretion of caffeine. Strong negative associations with night-time ambulatory PP were observed for paraxanthine and theophylline.

		Beta, SE (mmHg)
Caffeine*	PP 24h	-0.804, 0.209
	PP day	-0.749, 0.215
	PP night	-0.968, 0.243
Paraxanthine*	PP 24h	-0.905, 0.241
	PP day	-0.809, 0.248
	PP night	-1.210, 0.279
Theophylline*	PP 24h	-0.881, 0.240
	PP day	-0.833, 0.247
	PP night	-1.046, 0.279
Theobromine*	PP 24h	0.109, 0.241
	PP day	0.110, 0.248
	PP night	0.048, 0.281

Conclusions: The negative associations of PP with caffeine, paraxanthine, and theophylline excretions suggest that caffeine and its metabolites do lower BP, possibly by modifying arterial stiffness.

1C.07 PRONEUROTENSIN INDEPENDENTLY PREDICTS CARDIOVASCULAR DISEASE. THE MALMÖ PREVENTIVE PROJECT

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Objective: Neurotensin is released from the gut after fat intake and has a role in appetite regulations. Proneurotensin is a stable fragment of the neurotensin precursor hormone and fasting plasma proneurotensin levels have shown to be significantly associated with the development of cardiovascular disease in middle aged participants of the Malmö Diet and Cancer Study. Here, we aimed at replicating the initial findings in an independent second cohort and to extend its validity to an older population.

Design and method: Malmö Preventive Project (MPP) is a Swedish population based prospective study which comprised 18240 subjects for reexamination in 2002–2006. Fasting proneurotensin was measured in plasma from a random sample of 4804 participants (Age 69 SD (6,2), 68% Male). Multivariate Cox proportional hazard models adjusted for age, sex, use of antihypertensive medications, systolic blood pressure, BMI, current smoking, high density lipoprotein cholesterol (HDL-C), LDL-C, history of diabetes were used to relate the log transformed levels of fasting proneurotensin to the risk of first fatal or non-fatal cardiovascular event (myocardial infarction or stroke) in the mean follow up time of up to 6.5 years.

Results: There were 456 cardiovascular events observed in the study. Hazard ratios (HR) for CVD were expressed per 1 (SD) increment of log transformed proneurotensin for cardiovascular disease as HR 1,102; 95% CI; 1,006–1,088; P = 0,037. In addition, proneurotensin was divided in to quartiles where quartile 1 defined as (Ref = 1). The risk of CVD was 1,107(0,848–1,444), 1,349 (1,040–1,749), 1,336 (1,016–1,757) in quartile 2–4 when compared with the reference quartile (P for trend = 0.013).

Conclusions: Fasting proneurotensin levels are independently associated with the risk of developing cardiovascular disease which replicates the findings in MDC study.

1C.08 THE INTER-ARM DIFFERENCE IN BLOOD PRESSURE AND MORTALITY: SYSTEMATIC REVIEW AND META-ANALYSIS

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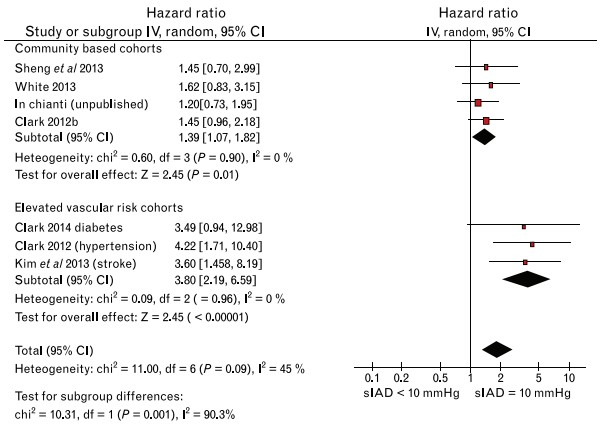
Objective: We previously reported the association of inter-arm differences in blood pressure measurements (IAD) with increased cardiovascular and all-cause mortality. Several new large cohorts have been reported since our 2012 meta-analysis. We have therefore updated our meta-analyses to take account of these new data.

Design and method: Systematic review and meta-analysis: Medline, Embase and CINAHL were searched for studies reporting survival data in association with IAD. Study level hazard ratios (HR) were extracted for systolic IADs >=10mmHg and >=15mmHg, and pooled using generic inverse variance in a random effects model. Statistical heterogeneity was assessed using the I^2 statistic.

Results: Searches to 12th November 2014 identified 3514 unique citations. Eighty full texts were assessed, and 13 studies (reporting data for 14 unique cohorts) contributed to the analyses, Median follow up ranged from 3 to 13 years. Five cohorts employed a simultaneous method of IAD measurement; the remainder used sequential measurements. Ten cohorts were recruited from community populations, including one hypertensive and one diabetic cohort. Four were selected hospital cohorts at increased vascular risk.
Cardiovascular mortality was greater with an IAD >=10mmHg (HR 1.9 (95%CI 1.3 to 2.6; 7 cohorts, 13815 participants; I^2 = 45%) and an IAD >=15mmHg (HR 1.7 (1.2 to 2.4; 9 cohorts; 18241 participants; I^2 = 30%). For all-cause mortality HRs were 1.4 (1.2 to 1.8; 10 cohorts, 17709 participants; I^2 = 62%) for IAD >=10mmHg and 1.4 (1.1 to 1.7; 12 cohorts, 18714 participants; I^2 = 46%) for IAD >=15mmHg. Heterogeneity between studies could be accounted for by stratification according to underlying population cardiovascular risk, with higher HRs seen in populations at elevated risk; cardiovascular mortality with an IAD >=10mmHg: HR 1.4 (1.1 to 1.8; I^2 = 0%) for community based cohorts compared to 3.8 (2.2 to 6.6; I^2 = 0%) for those at elevated cardiovascular risk (p = 0.001; Figure).



Conclusions: New studies confirming the association of an IAD with increased cardiovascular and all-cause mortality are consistent with previously published findings. Risks associated with an IAD rise in association with the underlying vascular risk of the population studied.

1C.09 SERUM RESISTIN AS AN INDEPENDENT BIOMARKER ASSOCIATED WITH ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN ELDERLY HYPERTENSIVE, NON-DIABETIC PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD)

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Objective: Hypertensive patients with CKD present an increased risk for cardiovascular mortality. Among the proteins synthesized and released from adipose tissue, resistin is a cytokine whose physiologic role has been the subject of much research and controversy. We and others have demonstrated that serum resistin levels are higher in patients with CKD and correlate directly with inflammatory markers, including TNF-α and hsCRP. Since inflammation has been consistently linked to atherosclerosis, death, and cardiovascular (CV) events, our goal was to investigate

the interaction between resistin levels and long term all-cause and CV mortality in elderly non-obese and non-diabetic with hypertension.

Design and method: We studied 80 patients (52 men/28 women) 70.9 ± 8.6 years of age with hypertension and CKD. Exclusion criteria was obesity and diabetes mellitus, active infection, acute illness, chronic inflammatory disease or cancer, and immunosuppresive, anti-inflammatory or anti-lipidemic drugs. Demographic data, clinical information and blood samples were collected prospectively. The patients were observed for 5 years.

Results: During the follow-up 28 of 80 (35%) patients died: 16 (57%) deaths due to CV events and 12 (43%) of other causes. Patients who died were older and had higher DBP, compared to survivors, but had no differences in BMI, smoking, SBP and HR. Deceased patients had higher WBC, hsCRP, BUN, creatinine, cystatin C, phosphate, magnesium and potassium levels and lower eGFR, Hct/Hg, T3, T4, total cholesterol, LDL-C, albumin and sodium levels compared to survivors. No significant differences in platelet count, TNF-α, fibrinogen, oxLDL, ADMA, HgA1C and HOMA-index were revealed between the groups. eceased patients had significantly higher resistin levels than survivors at baseline ($p = 0.025$), but adiponectin, visfatin and leptin did not differ between the two groups. Five variables, namely resistin, sodium, cholesterol, T3 and WBC remained significantly associated with survival and were used in the multivariate Cox regression analysis, which revealed that only resisitin, cholesterol and WBC maintained their discriminatory ability, as independent predictors of mortality both by forward and backward stepwise analysis.

Conclusions: Elevated serum resistin was a significant independent biomarker of CV and all-cause mortality in elderly, non-diabetic CKD patients with hypertension.

1C.10 METABOLIC SYNDROME IN A POPULATION OF EMPLOYEES WORKING FOR COMPANIES IN MEXICO

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Objective: In Mexico, cardiovascular diseases represent the second cause of death, after Diabetes. This is the first trial to describe the metabolic syndrome in a population of Mexican urban employees, working for private companies.
To analyze the presence of metabolic syndrome in Mexican employees working for private companies.

Design and method: Study of a consecutive series of evaluated cases between 2010 and 2014. Each participant was subject to the following: comprehensive physical examination, blood pressure, heart rate, height, weight, body mass index, waist/hip index, body fat index, abdominal girth, and lab profile, including lipid profile and glycemia. Publication criteria on harmonization for metabolic syndrome were considered: 3 of the following 5 criteria: presence of central obesity (abdominal girth > 90 cm for men and > 80 cm for women),TA 130/85, Triglycerides > 150 mg%, Glycemia > 100 mg% and HDL < 40 mg% Men, < 50 mg% Women.

Results: 7367 evaluated subjects, average age: 37.4 +/- 9.6 (CI 95% 37.3 - 37.7), 52% male. Table 1 shows metabolic syndrome prevalence by gender, Table 2 presents data by age and gender.

	HOMBRES	MUJERES	P-Value
METABOLIC SYNDROME	33%	15%	0.0001

Table 1: Prevalence of Metabolic Syndrome by Gender

	18-24	25-34	34-44	45-54	44-64	≥ 65
METABOLIC SYNDROME Male	19%	24%	35%	43%	51%	47%
METABOLIC SYNDROME Female	3%	8%	16%	27%	29%	56%
P-Value	<0.05	0.0001	0.0001	0.0001	0.0001	Ns
Total	11%	17%	27%	36%	41%	52%

Table 2: Prevalence of metabolic syndrome by age group and gender

Conclusions: The population of Mexican employees working for private companies analyzed presents a high prevalence of metabolic syndrome, that increases with age, placing it at a high risk for cardiovascular disease. Men present a higher metabolic syndrome prevalence ($p < 0.0001$) compared to women analyzed in the group under 65 years. From 65 years and on, both groups present a high prevalence.

1C.11 CARDIOVASCULAR RISK PROFILE IN WOMEN WITH UTERINE FIBROIDS: THE HELISUR STUDY

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Objective: More women than men die of heart disease each year. A major risk factor for cardiovascular morbidity and mortality is hypertension. Our previous study showed that women with surgically treated fibroids have a greater hypertension risk than control women, independent of age, body mass index, and ethnicity. However, little is known about the complete cardiovascular risk profile of women with fibroids. Therefore, we assessed the total cardiovascular risk profile of women with self-reported uterine fibroids.

Design and method: We analyzed a cross-sectional, random, multiethnic sample of the general population of Suriname of 201 participants, aged 18 to 70 years. The primary outcome was the difference in occurrence of cardiovascular risk factors (including hypertension, obesity, current smoking, diabetes and hypercholesterolemia) between women with uterine fibroids and women without fibroids, with a nested case control analysis to follow, if the data would demand this. Cut off values for risk factors were defined in accord with international guidelines.

Results: Of the 201 women, with a median age and body mass index of respectively 45 (18–70) years and 28.0 (14.1–53.1) kg/m2, we analyzed 50 women with self-reported uterine fibroids and 151 women without fibroids. The women with fibroids were more often obese and of African ancestry, and had a higher prevalence of hypertension, diabetes and hypercholesterolemia than women without fibroids (Table 1). Therefore, we conducted a secondary nested case control analysis, matching for age and African ancestry. In this subanalysis of 61 women, only mean systolic and diastolic blood pressure were significantly higher in the women with fibroids with values of respectively 135.8/87.3 vs 125.6/81.0 mmHg ($p < 0.05$ for both outcomes).

	Women without self-reported fibroids (n=151)	Women with self-reported fibroids (n=50)
Age, years	43 (18-70)	51 (33-70)*
BMI, kg/m^2	27.6 (17.4-53.1)	29.5 (19.8-46.3)
Obesity, %	37.7	46.0
African ancestry, %	18.5	42.0*
Current smoking, %	6.6	2.0
Creatine kinase, U/L	109.0 (49.0-447.0)	112.0 (51.0-433.0)
SBP, mmHg	127.0 (88.5-210.0)	135.0 (106.5-196.0)*
DBP, mmHg	78.5 (60.5-106.5)	82.0 (68.5-128.5)*
Hypertension, %	40.4	64.0*
Fasting glucose, mmol/L	4.9 (3.7-23.1)	5.3 (4.0-16.0)
Diabetes, %	16.6	26.0
Total cholesterol, mmol/L	5.0 (5.9-8.2)	5.2 (3.1-8.6)
Triglycerides, mmol/L	1.0 (0.0-6.8)	1.2 (0.3-4.0)
LDL, mmol/L	3.4 (1.6-6.2)	3.7 (1.7-6.9)
HDL, mmol/L	1.3 (0.7-11.0)	1.3 (0.8-2.3)
Hypercholesterolemia, %	13.2	22.0
Creatinine, umol/L	58.0 (30-177)	66.0 (35-117)*

Legend. Data are median (range) unless specified otherwise. *p < 0.05 compared to controls. BMI, body mass index; SBP/DBP, systolic/diastolic blood pressure.

Conclusions: Women with uterine fibroids seem to have a worse cardiovascular risk profile than controls, in particular concerning hypertension. This study shows that blood pressure is not only increased in women with surgically treated but also with self-reported fibroids. Currently, uterine fibroids are classified as a benign condition. However, these data indicate that more awareness about the cardiovascular health of women with fibroids is warranted.

1C.12 DIETARY SALT INTAKE AND ALDOSTERONE-RELATED ORGAN DAMAGE IN HYPERTENSION

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Objective: Chronic exposure to elevated aldosterone levels results in cardiac and renal tissue injury with mechanisms that are independent of blood pressure levels. Although the interaction between dietary salt intake and circulating aldosterone in causing organ damage has received support in animal experiments, the evidence of this interaction in the clinical setting is much weaker. In this study we have investigated the relevance of dietary salt on aldosterone related cardiac and renal damage in primary hypertension.

Design and method: In 315 untreated, grade1–2, hypertensive patients (age 47 ± 13 yr.; 173 males) we measured anthropometric variables, general biochemistries, plasma active renin and aldosterone levels, glomerular filtration rate, and 24-hour urinary sodium (UNaE) and albumin excretion (UAE), and assessed cardiac

morphology and function by B-mode echocardiography. Secondary forms of hypertension were excluded by exhaustive examination in all patients. For statistical reasons, patients were subdivided into tertiles or quartiles according to their UNaE that was used as a measure of salt intake.

Results: UAE increased progressively across tertiles of UNaE and patients with plasma aldosterone levels above the median of the distribution (125 pg/ml) had significantly higher UAE than patients with lower levels in all tertiles of UNaE. Search for statistical interaction between plasma aldosterone and UNaE in the association with UAE, however, did not reveal interaction. Left ventricular mass index (LVMI) was significantly greater in patients with plasma aldosterone levels above the median than patients with lower levels, but no change of LVMI was observed across quartiles of UNaE. LV geometry and ejection fraction did not differ across quartiles of UNaE and were comparable in patients with high or low plasma aldosterone levels. Both UAE and LVMI were significantly and independently related with age, body mass index, systolic blood pressure, and plasma aldosterone. UNaE was significantly related with UAE, but this relationship was lost after correction for confounders.

Conclusions: In summary, circulating aldosterone contributes to subclinical renal and cardiac damage in primary hypertension, but its contribution is independent of dietary salt intake.

ORAL SESSION

ORAL SESSION 1D
KIDNEY INCLUDING TRANSPLANTATION

1D.01 BLOOD PRESSURE CONTROL AFTER PEDIATRIC KIDNEY TRANSPLANTATION: LONG TERM DATA FROM A SINGLE CENTER

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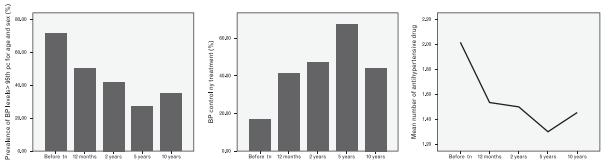
Objective: To assess the prevalence of hypertension and blood pressure (BP) control over years after pediatric kidney transplantation.

Design and method: We reviewed the medical charts of consecutive kidney transplants performed in 71 children and adolescents (age range 2–18 years) between 1990–2012. BP index was used as a measure of the severity of BP elevation. Hypertension was defined as systolic and/or diastolic BP greater than the 95th percentile for age and sex, or as being on antihypertensive medication.

Results: Blood pressure levels as expressed by BP index presented gradual decrease after Tn. BP indexes at 5, and 10 years post Tn were significantly lower than BP indexes before Tn (SBP index = 1.038 before vs. SBP index = 0.881 at 5 years, P = 0.001, and SBP index = 1.038 before vs. SBP index = 0.871 at 10 years, P = 0.001, DBP index = 0.982 before vs. DBP index = 0.895 at 5 years, P < 0.05, and DBP index = 0.982 before vs. DBP index = 0.890 at 10 years, P < 0.05). The number of patients who were receiving antihypertensive treatment increased after Tn (44.7 % before Tn, 69.7% at 12 months, 66% at 5 years and 53.8% at 10 years post Tn). There was an increased likelihood of receiving antihypertensive treatment at 5 and 10 years post Tn, if a patient was under treatment before Tn (5 years OR 3.778, 95% CI 1.308–10.915, P = 0.001, 10 years OR 4.500, 95% CI 1.218–16.622, P < 0.005). The prevalence of hypertension by office BP presented a decreasing trend after Tn (Figure). BP control by antihypertensive treatment was 16.7% before Tn, 41.3% at 12 months, 66.7% at 5 years, and 44.4% at 10 years post Tn and was achieved with a lower number of drugs compared to the number of antihypertensive drugs before Tn (Figure).



Conclusions: Hypertension remains a frequent complication in pediatric kidney recipients even years after kidney Tn, but the severity of BP evaluation may present a significant decrease. BP control seems to peak at 5 years post Tn and can be achieved with fewer drugs with increasing time after Tn.

1D.02 COMPARATIVE EFFECT OF A RENIN INHIBITOR AND A THIAZIDE DIURETIC ON RENAL TISSUE OXYGENATION IN HYPERTENSIVE PATIENTS

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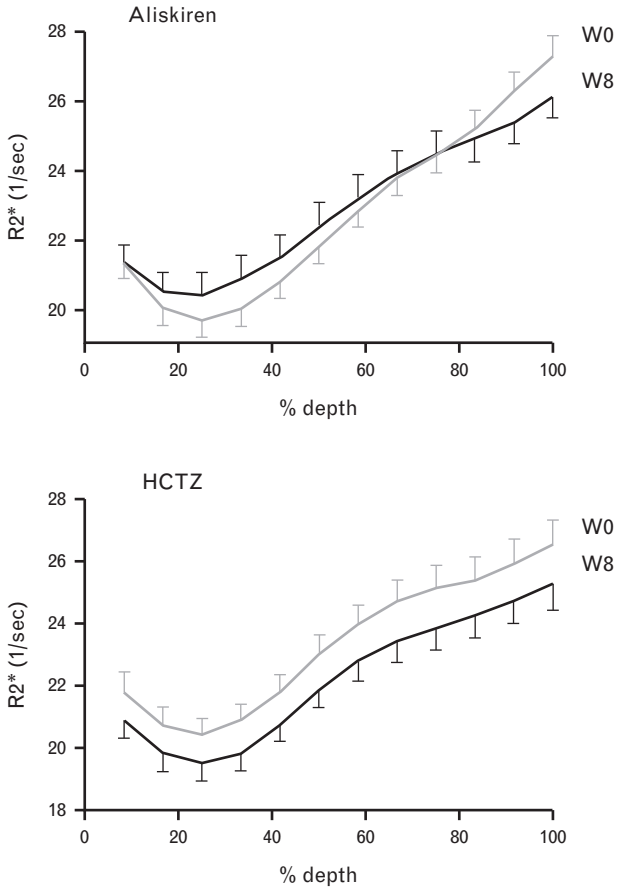
Objective: Renal tissue oxygenation may play an important role in the progression of renal diseases. Today, blockers of the renin-angiotensin system and diuretics are two major drug classes used to treat hypertension in patients with or without chronic kidney diseases. The purpose of the present study was to compare the direct renin inhibitor aliskiren to the diuretic hydrochlorothiazide (HCTZ) in their ability to modulate renal tissue oxygenation in hypertensive patients.



Design and method: Twenty four patients were enrolled in this randomized prospective study and 20 completed the protocol. Patients were randomly assigned to receive either aliskiren 150 titrated to 300 mg/d or HCTZ 12.5 mg titrated to 25 mg/d for 8 weeks. Renal oxygenation was measured by BOLD-MRI at weeks 0 and 8, 30 hours after the last dose. BOLD-MRI data were analyzed using the "onion peel" technique, a newly developed method which measures mean R2* levels in 12 computed layers of equal thickness in the kidney enabling to asses renal oxygenation according to the depth within the kidney, a higher R2* value corresponding to lower oxygenation.

Results: Our results show that aliskiren tended to increase oxygenation in the outer (more cortical) layers and decreased oxygenation in the inner (more medullary) layers whereas HCTZ induced a significant overall decrease in renal tissue oxygenation (Figure 1). This latter finding may be due to the increased sodium reabsorption 30 h after the last dose of HCTZ (FELi: 21.2 ± 9% at W0 and 16.4 ± 6.0% at W8), p = 0.01). Patients responding to treatment by a fall in systolic blood pressure of >10 mmHg also increased renal tissue oxygenation when compared to non-responders.

Conclusions: Taken together these results show that blockade of the renin-angiotensin system with aliskiren has a more favorable impact on renal tissue oxygenation in hypertensive patients than HCTZ. This finding may contribute to explain the renal protective effect of blockers of the renin-angiotensin system.

1D.03 INACTIVE MATRIX GLA PROTEIN IS ASSOCIATED WITH RENAL RESISTIVE INDEX IN A POPULATION-BASED STUDY

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Objective: Renal resistive index (RRI) varies directly with renal vascular stiffness and pulse pressure. RRI correlates positively with arteriolosclerosis in damaged kidneys and predicts progressive renal dysfunction. Matrix Gla-protein (MGP) is a vascular calcification inhibitor that needs vitamin K to be activated. Inactive MGP, known as desphospho-uncarboxylated MGP (dp-ucMGP), can be measured in plasma and has been associated with various cardiovascular (CV) markers, CV outcomes and mortality. In this study we hypothesize that increased RRI is associated with high levels of dp-ucMGP.

Design and method: We recruited participants via a multi-center family-based cross-sectional study in Switzerland exploring the role of genes and kidney hemodynamics in blood pressure regulation. Dp-ucMGP was quantified in plasma samples by sandwich ELISA. Renal doppler sonography was performed using a standardized protocol to measure RRIs on 3 segmental arteries in each kidney. The mean of the 6 measures was reported. Multiple regression analysis was performed to estimate associations between RRI and dp-ucMGP adjusting for sex, age, pulse pressure, mean pressure, renal function and other CV risk factors.

Results: We included 1035 participants in our analyses. Mean values were 0.64 ± 0.06 for RRI and 0.44 ± 0.21 (nmol/L) for dp-ucMGP. RRI was positively associated with dp-ucMGP both before and after adjustment for sex, age, body mass index, pulse pressure, mean pressure, heart rate, renal function, low and high density lipoprotein, smoking status, diabetes, blood pressure and cholesterol lowering drugs, and history of CV disease ($P < 0.001$).

Conclusions: RRI is independently and positively associated with high levels of dp-ucMGP after adjustment for pulse pressure and common CV risk factors. Further studies are needed to determine if vitamin K supplementation can have a positive effect on renal vascular stiffness and kidney function.

1D.04 INVERSE RELATIONSHIP BETWEEN AORTIC ROOT DIAMETER AND RENAL FUNCTION IN HYPERTENSIVE SUBJECTS

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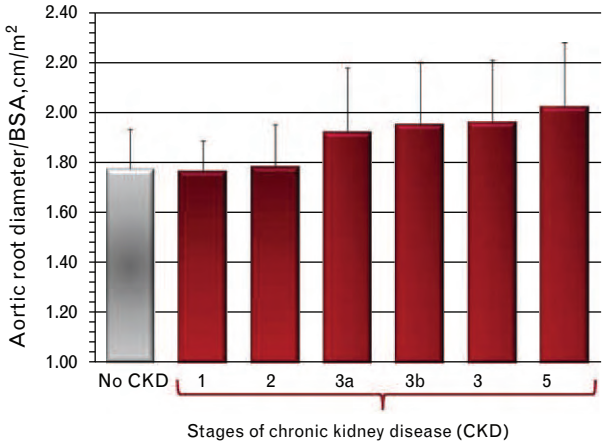
Objective: Recent studies suggest that enlarged aortic root diameter (ARD) may predict cardiovascular events in absence of aneurysmatic alterations. Little is known about the influence of renal function on ARD. Our study was aimed to assess the relationships between glomerular filtration rate (GFR) and ARD in hypertensive subjects.

Design and method: We enrolled 611 hypertensive individuals (mean age: 52 ± 15 years; men 63%) consecutively attending our outpatient unit of Nephrology and Hypertension. Patients on dialysis treatment, with valvulopathy more than mild, bicuspid aortic valve, previous cardiovascular events and genetic aortic diseases were excluded. All the subjects underwent echocardiography. ARD was measured at the level of Valsalva's sinuses by M-mode tracings, under two-dimensional control. In line with the PAMELA study, ARD, ARD indexed to body surface area (ARD/BSA) and to height (ARD/H) were considered increased when they exceeded 3.8 cm, 2.1 cm/m2, 2.3 cm/m in men and 3.4 cm, 2.2 cm/m2, 2.2 cm/m in women, respectively. GFR was estimated by the CKD-EPI equation. The study population was categorized in seven groups: subjects without chronic kidney disease (no CKD) and subjects with increasing severity of CKD (1, 2, 3a, 3b, 4, 5), according to KDIGO classification.

Results: Estimated GFR (eGFR) was lower in subjects with values of ARD, ARD/BSA and ARD/H above the sex-specific cut-offs when compared to those with normal aortic root size (all $p < 0.001$). The analysis of the distribution ARD/BSA in subjects with and in those without CKD, showed a progressive increase of ARD/BSA from the group with normal renal function to the groups with greater severity of CKD (figure).
eGFR correlated significantly with ARD ($r = -0.17$), ARD/BSA ($r = -0.43$) and ARD/H ($r = -0.40$; all $p < 0.001$). The associations of eGFR with ARD/BSA ($\beta = -0.23$) and ARD/H ($\beta = -0.17$; all $p < 0.001$) held in linear multiple regression analyses, after adjustment for various confounding factors.



Conclusions: Our study seems to suggest that a reduced renal function may adversely influence ARD. This may contribute to explain the enhanced cardiovascular risk associated with renal insufficiency.

1D.05 AORTIC-BRACHIAL STIFFNESS MISMATCH IN PRE-DIALYSIS CHRONIC KIDNEY DISEASE

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Objective: The loss of physiological stiffness mismatch between aorta and peripheral arteries was strongly and independently associated with increased mortality in adult dialysis population. The aim of the study was to evaluate if the reversal of arterial stiffness mismatch was present in pre-dialysis patients with chronic kidney disease (CKD).

Design and method: The aortic-brachial arterial stiffness mismatch (pulse wave velocity (PWV ratio) were assessed using carotid-femoral PWV divided by carotid-radial PWV in 112 adult treated hypertensive CKD patients: 54 - with CKD IIIa (age $59,5 \pm 8,4$ years, male 46,3%, brachial blood pressure (BP) $149,6 \pm 10,3/85,8 \pm 9,8$ mmHg), 35 - with CKD IIIb (age $60,2 \pm 7,8$ years, male 45,7%, BP $152,5 \pm 12,5/86,4 \pm 10,2$ mmHg) and 23 with CKD IV (age $57,3 \pm 10,2$, male 43,4%, BP $156,1 \pm 14,3/92,8 \pm 12,4$ mmHg). $P < 0,05$ was considered significant for group comparisons, Spearman correlation test and multivariate regression analysis.

Results: In CKD IIIa aortic PWV was $10,2 \pm 2,0$ m/s, brachial PWV $12,9 \pm 1,6$ m/s, PWV ratio $0,82 \pm 0,25$. In CKD IIIb aortic PWV was $11,3 \pm 2,9$ m/s, brachial PWV $12,2 \pm 1,8$ m/s, PWV ratio $0,90 \pm 0,27$. In CKD IV aortic PWV was $12,7 \pm 3,1$ m/s ($p < 0,05$ vs CKD IIIa), brachial PWV $11,4 \pm 1,6$ m/s ($p < 0,05$ vs CKD IIIa), PWV ratio $1,09 \pm 0,33$ ($p < 0,05$ vs CKD IIIa). Increased aortic stiffness (aortic PWV>10 m/s) was observed in 55,6%, 62,9% and 73,9%, respectively. For the whole study population ($n = 112$) multivariate analysis revealed independent significant correlation between aortic PWV and glomerular filtration rate (GFR) $\beta = -0,36$ ($p < 0,05$), PWV ratio and GFR $\beta = -0,32$ ($p < 0,05$), PWV ratio and age $\beta = 0,44$ ($p < 0,05$).

Conclusions: In the pre-dialysis hypertensive CKD patients worsening of kidney function was associated with discordant changes in aortic and brachial artery stiffness in the reversal of the physiological stiffness mismatch. The loss of this physiological mismatch may promote kidney damage through increased forward pressure wave transmission into the microcirculation. PWV ratio evaluation (in addition to traditional aortic PWV measurement) may be useful for better evaluation of arterial stiffness in pre-dialysis CKD patients.

1D.06 LONGITUDINAL EVALUATION OF CARDIOVASCULAR RISK AFTER PEDIATRIC KIDNEY TRANSPLANTATION

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Objective: Children with chronic kidney disease (CKD) carry an increased cardiovascular risk. Cardiovascular death is the second leading cause of death in children after renal transplantation. The 4C-T (Cardiovascular Comorbidity in Children with CKD and Transplantation) study evaluates cardiovascular target organ damage longitudinally in children prior to and after renal transplantation.

Design and method: The multicenter, prospective, observational 4C study enrolled 736 children aged 6 to 17 years with estimated GFR <40 ml/min/1.73 m2 at 55 Pediatric Nephrology centres from 12 European countries. Of these, 226 have started renal replacement therapy (RRT) and entered the 4C-T sub-study. At annual study visits, the morphology and function of the heart and large arteries were monitored by noninvasive methods.

Results: 176 of the 226 patients on RRT had at least one visit after RRT start and were included in this analysis. 70 patients had started dialysis and 106 received a transplant. 62% of the patients were transplanted pre-emptively. Overall patients carried a higher cardiovascular risk compared to the age-matched general population as documented by elevated age-adjusted aortic pulse wave velocity (PWV) and carotid intima-media thickness (IMT). Factors determining PWV, IMT and left ventricular mass index (LVMI) were analysed using mixed longitudinal modelling (table).

Table. Mixed longitudinal model for PWV, IMT and LVMI

	PWV		IMT		LVMI	
Effect	Estimate	P	Estimate	P	Estimate	P
Dialysis	0.4648	0.0024	0.2793	0.04884	4.1835	0.0068
Tx after Dialysis	0.3980	0.0264	-0.00253	0.9876	3.9145	0.0283
Preemptive tx	Reference		Reference		Reference	
BP	0.04065	<.001	0.01247	0.0212	0.1167	0.0054
PTH	0.009556	<.001	0.003614	0.074	0.07823	0.0003
Male gender	-0.4157	0.0019	-0.3076	0.0135	3,5783	0.0089

Conclusions: Our data is consistent with the hypothesis that transplantation lowers cardiovascular risk. Mixed modeling allowed to decipher the positive effect of transplantation from interfering cardiovascular risk factors such as hypertension, hypercholesterolemia and PTH.

1D.07 LONG-TERM OUTCOME AFTER ANGIOPLASTY IN PATIENTS WITH RENAL ARTERY STENOSIS AND HIGH RESISTIVE INDEX

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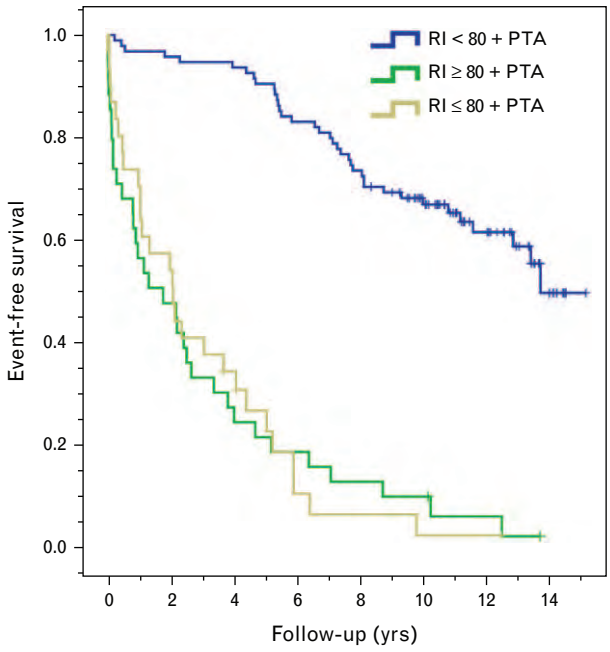
Objective: The benefit of revascularization for renal artery stenosis is currently unclear. A number of prospective, randomised studies showed no advantage of interventional revascularization (PTA) over medical therapy apart from a reduction in the number of antihypertensive drugs. A predictor of a more positive response to interventional treatment is urgently needed. We have shown that patients with a high resistive index (RI, > 80) by Doppler ultrasonography have inferior outcome after interventional revascularization for renal artery stenosis. We here obtained long-term follow up data from the original study collective and compared this to a matched group of recent patients with high resistive index which did not undergo revascularization but had improved medical therapy.

Design and method: We measured the renal RI with Doppler ultrasonography in segmental arteries of both kidneys. 131 patients underwent renal angioplasty, 35 of these had renal RI values > 80. A further group of 31 patients with RI > 80 and renal artery stenosis > 65% did not undergo angioplasty. The combined endpoint was > 50 percent decrease in eGFR, end stage renal failure, or death. Mean (± SD) follow-up was 8.8 ± 4 years.



Results: In patients with high RI (> 80), a decrease in renal function occurred in 74% patients after PTA and 77% without PTA compared to 19% of those with PTA and low RI. 71% and 52% of patients, compared to 17%, required dialysis, and 89% and 48% compared to 31% died (p<0.001 high RI compared to low RI). A total of 94% and 90% with high RI reached the combined endpoint as compared to 39% of those with low RI (multivariate relative risk 16, CI 3.7 to 68; P < 0.001 high RI vs low RI).

Conclusions: Patients with renal artery stenosis and a high renal resistive index do not benefit from angioplasty in long-term follow up for renal and patient survival. Patients with high resistive index continue to suffer a poor prognosis even under improved medical therapy.

1D.08 EFFECT OF PA21, A NEW IRON-BASED PHOSPHATE BINDER ON FIBROBLAST GROWTH FACTOR 23 (FGF23) AND VASCULAR CALCIFICATIONS IN UREMIC RATS

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Objective: Cardiovascular disease is a major cause of mortality in patients with chronic kidney disease (CKD). Elevated serum phosphate and FGF23 are associated with cardiovascular disease in patients with CKD. Current therapy focuses on decreasing serum phosphorus using phosphate binders. PA21 is a new iron-based phosphate binder. Few studies have analysed how to suppress FGF23 up-regulation using phosphate binders.
To evaluate the effects of PA21 compared with other phosphate binders as lanthanum carbonate (La) and sevelamer carbonate (Se) on serum FGF23, phosphorus, calcium, iPTH concentrations and to investigate a potential effect on the development of vascular calcifications in an adenine-induced rat model of CRF.

Design and method: After induction of chronic renal failure through a 4 week adenine-diet, renal function was significantly impaired in all groups. All uremic rats developed severe hyperphosphatemia and serum PTH increased significantly. Phosphate binders were then given for 4 weeks to all uremic rats, except for the uremic control rats. The concentration of each binder (% of binder added to the diet) was chosen to deliver approximately the same amount of active pharmaceutical moiety to each rat: PA21 5% (corresponding to 1% iron), La 2% (1% lanthanum), Se 1.5% (1% sevelamer). A computer-assisted automated quantitative measurement was used to assess the degree of calcification from von Kossa stained vessel sections.

Results: Hyperphosphatemia and increased serum PTH levels were controlled in the phosphate binder treated groups to the same extent. PA21 was the only phosphate binder that was associated with a decrease of FGF23.
In uremic control rats, vascular calcifications were more prominently present in the thoracic aorta compared to the carotids and the abdominal aorta. Vascular

calcifications of thoracic aorta were significantly decreased by the three phosphate binders to a similar extent. PA21 was more efficient than lanthanum carbonate to prevent calcifications in the upper part of the thoracic aorta.

Conclusions: PA21 was as effective in the control of hyperphosphatemia, secondary hyperparathyroidism and vascular calcifications as La and Se. The role of FGF23 as a potential factor of calcification needs to be confirmed.

1D.09 APPLICABILITY OF MEASUREMENT OF RENAL PERFUSION USING 1.5 TESLA MRI ARTERIAL SPIN LABELLING

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Objective: Renal perfusion is a key parameter of kidney function and the decrement of renal perfusion is a marker of target organ damage caused by hypertension. Detecting these changes in renal perfusion could help to manage antihypertensive therapy and evaluate patientsṕrognosis. Measurement of renal perfusion by MRI arterial spin labelling (ASL) is a non-invasive and non-time-consuming method without the need to inject any contrast agent. This study examined reproducibility of renal perfusion measured by 1.5 Tesla MRI.

Design and method: Renal perfusion was measured by ASL technique using an 1.5 Tesla MRI scanner. Subjects were scanned 3 times at two different days in an interval of two weeks to assess the test-retest reproducibility. Renal perfusion was automatically calculated for the cortex and medulla of the kidney by dedicated software.

Results: 14 patients were included with mean age 48.9 ± 12.7 and mean office blood pressure $132 \pm 16/82 \pm 10$mmHg and estimated glomerular filtration rate> 60 ml/min/1.73m^2. The change of the mean total, cortical and medullary renal perfusion from the first examination to the second examination was $0.37 \pm 13/0.62 \pm 18/0.00 \pm 12$ ml/min/100 g kidney weight ($p = 0.915/p = 0.898/p = 0.998$), respectively. There was also no significant difference between the three renal perfusion measurements at one time point. For clinical trials these data indicate that to detect a 5% (10%) difference of cortical renal perfusion due to an intervention (vs placebo) only 38 (14) patients are required in face of the observed standard deviation for the change in renal perfusion.

Conclusions: The inter and intra-session reproducibility of cortical renal perfusion assessed by MRI ASL 1.5 Tesla is excellent and small study cohorts can be used for examination of renal perfusion.

1D.10 PREDICTORS AND OUTCOMES OF CONTRAST-INDUCED ACUTE KIDNEY INJURY IN PATIENTS WITH PRIMARY PERCUTANEOUS INTERVENTION

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Objective: The incidence of contrast-induced acute kidney injury (CI-AKI) is rising due to increased use of coronary angiography and percutaneous coronary intervention (PCI). Patients undergoing primary PCI are at high risk of CI-AKI, a complication that negatively affects outcomes. The aim of the study was to evaluate the incidence, predictors and outcomes of CI-AKI in patients with ST-segment elevation myocardial infarction (STEMI) and primary PCI.

Design and method: 216 patients with STEMI and primary PCI (143 male, 64 ± 13 years ($M \pm SD$), arterial hypertension 90%, previous myocardial infarction 27%, diabetes mellitus 21%, known chronic kidney disease 7%, anemia 14%, heart failure 62%, left ventricular ejection fraction (LV EF) $44 \pm 15\%$) were examined. CI-AKI was defined using 2012 KDIGO Guidelines. Mann-Whitney test was performed. $P < 0.05$ was considered statistically significant.

Results: 20% of patients developed CI-AKI. Stages 1 and 2 of CI-AKI were found in 77 and 33% of cases accordingly. CI-AKI developed in 66% of cases in first 48 hours after PCI. Patients with versus without CI-AKI were older (69 ± 13 vs 63 ± 12 years, $p < 0.05$), had higher baseline serum creatinine (104 ± 31 vs 87 ± 22 μmol/l, $p < 0.001$), lower LV EF (37 ± 10 vs $41 \pm 14\%$, $p < 0.05$), higher rate of CKD (21 vs 3.5%, $p < 0.001$) and higher rate of therapy with nephrotoxic antibiotics (19 vs 3.5%, $p < 0.05$), loop diuretics (72 vs 39%, $p < 0.05$), mineralocorticoid receptor antagonists (56 vs 37%, $p < 0.05$), higher contrast volume (CV) (282 ± 94 vs 236 ± 85 ml, $p < 0.05$), contrast media volume/estimated glomerular filtration rate ratio (CV/eGFR) ($4{,}02 \pm 2{,}15$ vs $2{,}32 \pm 1{,}08$, $p < 0.05$), higher rate of multivessel coronary damage (84 vs 59%, $p < 0.05$). Patients with CI-AKI had higher risk of 30-days mortality (10 vs 3%, $p < 0.05$) and similar rate of 6 months rehospitalizations (66 vs 46%, $p > 0.05$).

Conclusions: CI-AKI in patients with STEMI and primary PCI developed in 20% of cases, predominantly in first 48 hours after PCI. CI-AKI was associated with higher rate of CKD, therapy with nephrotoxic drugs, multivessel coronary damage, higher baseline serum creatinine, CV/eGFR. CI-AKI had negative impact on 30-days mortality.

1D.11 RENAL MICROVASCULATURE AND RENIN SECRETION IN HUMANS WITH MULTIFOCAL RENAL ARTERY FIBROMUSCULAR DYSPLASIA

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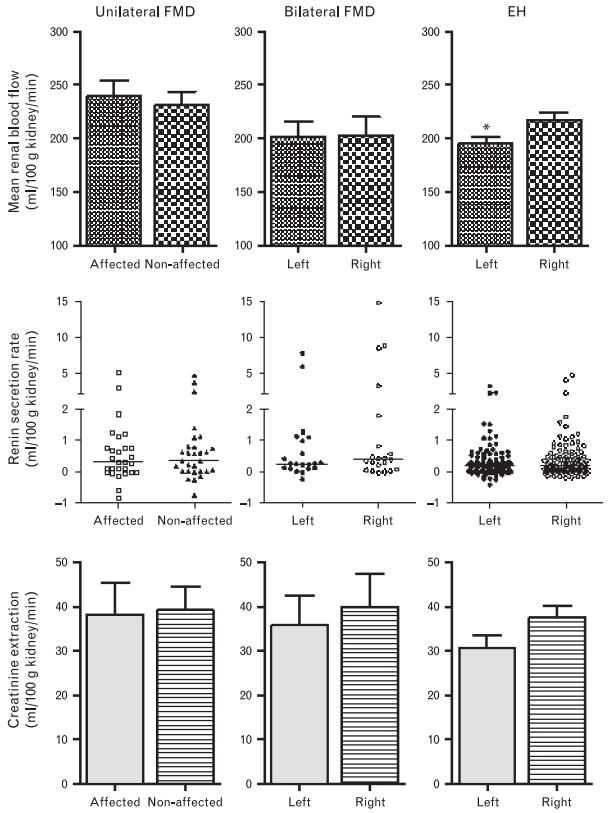
Objective: Although fibromuscular dysplasia (FMD) is the second commonest cause of renovascular hypertension, knowledge on renal microvasculature and renin-angiotensin-system-activity in kidneys with FMD are scarce. Given the fairly good results of revascularization, we hypothesized that renal microvasculature is intact in kidneys with FMD.

Design and method: In 58 patients with multifocal renal artery FMD (off medication) we selectively measured mean renal blood flow (MRBF) in both kidneys using the 133Xenon-washout-method. Blood samples were taken from the aorta and both renal veins to determine renin secretion rate (RSR) and creatinine-extraction (a proxy for glomerular filtration) for each kidney (both calculated as venous-arterial difference*renal plasma flow). Hypertensive patients without renovascular abnormalities (essential hypertension, EH), matched for age, gender, and dietary sodium intake (using 24 h urinary sodium excretion as a proxy) served as controls in a 1:2 ratio.

Results: MRBF was comparable between FMD and EH (Figure). In EH but not in FMD, MRBF was significantly lower in the left kidney as compared to the right (*$p < 0.001$). Although a wide variation was observed, we found that systemic renin levels were somewhat higher in FMD as compared to EH [median 19.6 (interquartile range 12.0–35.2) vs. 12.1 (8.4–19.9); $p < 0.001$)], but without differences in RSR per kidney (Figure). Creatinine-extraction was also comparable between FMD and EH. In unilateral FMD, no differences were found between the affected and non-affected kidney with regard to MRBF, RSR, or creatinine-extraction (left column). MRBF was associated with 24 h urinary sodium excretion in FMD (Beta 0.357;$p = 0.015$), but not in EH.



*$p < 0.001$ vs. right kidney. MRBF and creatinine-extraction expressed as mean and S.E.M. Horizontal line in the middle panel (RSR) indicates median value.

Conclusions: MRBF and creatinine-extraction in kidneys with FMD is comparable to EH and to the unaffected kidney in patients with unilateral FMD, indicating that renal microvascular function is preserved in kidneys with FMD. The association between MRBF and sodium intake supports this hypothesis. Our findings that

MRBF is preserved and RSR is not increased in kidneys with FMD contradict with the commonly held hypothesis on renovascular hypertension that states that hypertension is induced by increased renin secretion in response to decreased blood flow. Therefore, other pathophysiological mechanisms probably (also) play a role.

1D.12 THE CONTRIBUTION OF INFLAMMATION AND ATHEROSCLEROSIS TO HYPERTENSION IN KIDNEY TRANSPLANTS

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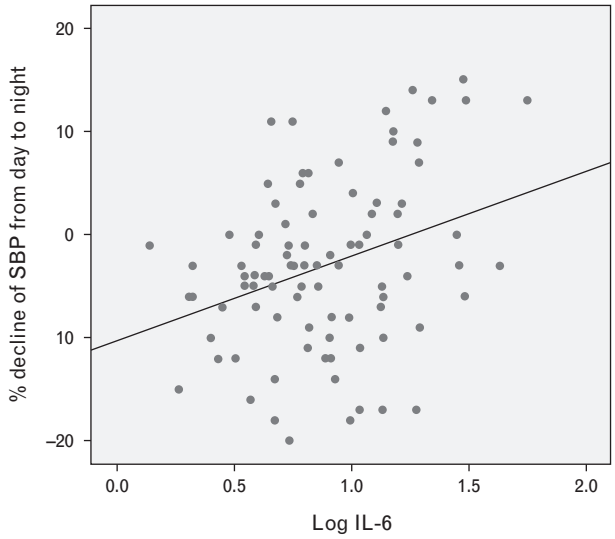
Objective: Hypertension is more severe in kidney transplant patients than in patients with chronic kidney disease (CKD) and similar renal function. The aim is to study the contribution of subclinical atherosclerosis and low grade inflammation to hypertension in kidney transplants.

Design and method: Between June and September 2011, consecutive kidney transplants with an estimated glomerular filtration rate (e-GFR) <60 ml/min/1.73m2, and without previous history of cardiovascular events were included. At entry, 24 h ambulatory blood pressure monitoring (ABPM), pulse wave velocity (PWV) and carotid echography were performed. A serum sample to determinate interleukin 6 (IL-6), soluble tumor necrosis factor receptor 2 (sTNFR2) and intercellular adhesion molecule 1 (ICAM-1) levels was obtained. CKD patients with similar characteristics were recruited at the same time as a control group.

Results: A total of 92 transplants and 30 CKD patients were included. Awake systolic blood pressure (SBP) (135.6 ± 15.3 vs 123.8 ± 15.7 mmHg, p = 0.0001), sleep SBP (131.2 ± 16.2 vs. 113.6 ± 14.3 mmHg, p = 0.0001), Log IL-6 (0.89 ± 0.33 vs 0.71 ± 0.31, p = 0.011) and the total number of carotid plaques (1.17 ± 1.48 vs 0.53 ± 1.07, p = 0.013) were higher and the percentage decline of SBP from day to night was lower in kidney transplants (-3.05 ± 8.19 vs -8.13 ± 7.54, p = 0.003). Independent predictors of awake SBP were urinary protein/creatinine ratio and PWV (R2 = 0.170, p = 0.0001), of sleep SBP were log IL-6 and urinary protein/creatinine (R2 = 0.138, p = 0.001), of percentage decline of SBP from day to night were log IL-6 (figure 1), serum creatinine and total number of carotid plaques (R2 = 0.202, p = 0.0001) and of reverse dipper pattern were log IL6 and total number of carotid plaques.



Conclusions: IL-6 and number of carotid plaques are increased in kidney transplants in comparison with CKD patients and are associated with higher sleep SBP and reverse dipper pattern in transplantation.

ORAL SESSION

ORAL SESSION 2A
COMBINATION TREATMENT

2A.01 BALANCED OPTIMAL MEDICAL THERAPY IS ESSENTIAL IN MANAGEMENT OF PATIENTS WITH CORONARY ARTERY DISEASE: PULSE WAVE VELOCITY LONG-TERM FOLLOW UP STUDY

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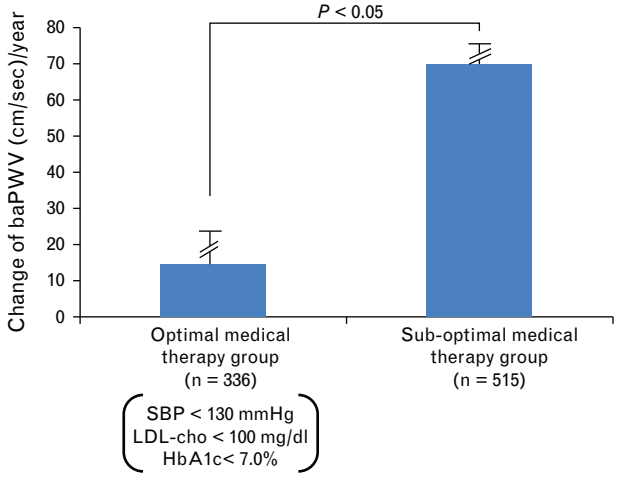
Objective: Global cardiovascular risk stratification is essential in high-risk hypertensive patients. However, it is uncertain how often the strategy is executed in real clinical practice. We sought to evaluate the management of cardiovascular risk in hypertensive patients with coronary artery disease (CAD) using brachial-ankle pulse wave velocity (baPWV).



Design and method: A total of 851 hypertensive patients with CAD (age 65 ± 11) were enrolled and baPWV were measured every year (mean follow up periods 4.5 years). All subjects were devided into two groups: optimal medical therapy group (systolic blood pressure<130mmHg, LDL-cho<100 mg/dl and HbA1c<7.0%) and sub-optimal therapy group.

Results: In optimal medical therapy group, change of baPWV/year were significantly lower than in sub-optimal therapy group ($p < 0.05$) (figure).

Conclusions: These results suggest that combination of optimal medical therapy is essential in management of high-risk hypertensive patients, and it might also reduce cardiovascular risk.

2A.02 REGULATION OF UNCONTROLLED BLOOD PRESSURE WITH THE FIXED-DOSE COMBINED DRUG PERINDOPRIL ARGININ/INDAPAMIDE: RESULTS OF THE PROTECT STUDY

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Objective: The aim of this study was to assess the efficacy of blood pressure (BP) control with fixed-dose combination of perindopril arginine/indapamide (Noliprel) in patients with uncontrolled hypertension.

Design and method: A total of 714 patients with uncontrolled hypertension from the PROTECT (noliPRel – efficacy of blood pressure cOnTrol on nEw diagnosed and unControlled patienTs) database, were included. At the beginning of the study the patients (mean age 64.9 ± 10.5 years; 223 men) were switched from antihypertensive drugs that had proven ineffective in BP control to Noliprel. BP was measured in the third and sixth months of the study. The primary end point was the number of patients reaching target BP levels in the intermediate phases of the study. The SPSS v.17.0 statistical software package was used for data collection and analysis. Results are presented as mean value ± standard deviation. Differences in mean values were analyzed using Student's "paired-simple" test.

Results: Mean systolic BP (SBP)/diastolic BP (DBP) declined significantly from 165.6 ± 14.4/96.8 ± 9.0 mmHg to 132.2 ± 10.7/80.1 ± 6.7 mmHg ($p < 0.0001$) over the course of the study. SBP/DBP reduction at three month was already -18.7 ± 14.2/-10.0 ± 9.6 mm Hg ($p < 0.0001$). Patients with BP values at target (<140/90 mmHg) represented 19.8% at 3 months, and 66.8% at 6 months. At the end of study, Noliprel was prescribed in 19.6% (perindopril arginine/indapamide 2.5 mg/0.625 mg), 61.8% (5 mg/1.25 mg), and 18.6% (10 mg/2.5 mg) of cases, respectively. No adverse effects were observed.

Conclusions: The fixed-dose combination of perindopril arginine/indapamide was effective and safe in patients with uncontrolled hypertension in reducing BP and maintaining it at target levels.

2A.03 DIASTOLIC FUNCTION IN OBESE HYPERTENSIVE PATIENTS USING DIFFERENT FIXED COMBINATION WITH ACE INHIBITOR AND ANTAGONIST CALCIUM

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Objective: Fixed antihypertensive combination with ACE inhibition may be protective in Left Ventricular (LV) Diastolic Function that is additional to its blood pressure–lowering effect.

Aim: To evaluate changes in Left Ventricular (LV) Diastolic Function in obese patients with arterial hypertension treated with fixed combination Lisinopril + Amlodipine (L+A) compared with Perindopril+ Amlodipine (P+A).

Design and method: 72 obese (BMI 33,1 ± 5,3 kg/m2) arterial hypertension (AH) patients (age 50.6 ± 12.6 ys) were randomized to L+A group (n = 38) or P+A (n = 34). All patients underwent clinical, laboratory test and echocardiography in baseline and after 3 months. All patient had normal LV Systolic Function (EF > 55%). LV diastolic function was estimated by Doppler echocardiography and Tissue Doppler imaging.

Results: Before the treatment LV diastolic dysfunction was noted in every obese AH patient. 100% patients had LV DF impairment of the I type. Peak mitral filling velocities during early (E) and late (A) diastole E/A ratio = 0,69 ± 0,08, tissue Doppler E/Em' ratio = 7,9 ± 0,9. Blood pressure goals were achieved in all patients validating further analysis. In 3 months' follow-up LV diastolic function was improved in the both treatment group. Increased in E/A ratio from 0.68 ± 0,08 to 0.72 ± 0,07 in L+A group and from 0.70 ± 0,009 to 0.74 ± 0,087 in P+A group ($p < 0.01$). Decreased in tissue Doppler E/Em ratio from 7.9 ± 0,09 to 6.7 ± 0,69 in L+A group and from 7.8+/- 0,85 to 7.0 +/- 0.67 in P+A group ($p < 0.01$). Significant trends towards E/Em decrease were demonstrated only in L+A-treated patients (delta E/Em 1.2 L+A and 0.8 P+A, $p < 0.05$).

Conclusions: LV diastolic function in obese AH patients demonstrated impairment of the I type. LV diastolic function was improved in response with fixed combination using ACE inhibitor and Antagonist calcium treatment. Both fixed combination L+A and P+A improved in LV diastolic function parameters, whereas only fixed combination with L+A treatment was more significantly associated with trends in E/Em improvement in 3 months' short-term follow-up.

2A.04 WHETHER ACE INHIBITOR/ARB COMBINED WITH CCB IS SUPERIOR TO OTHER COMBINATIONS? A META-ANALYSIS IN 20,669 HYPERTENSIVES

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Center, 1st Department of Propaedeutic Medicine, Laiko Hospital, Medical School, National and Kapodistrian, Athens, GREECE, [5] Diagnosis and Therapeutic Center, Hotel-Dieu Hospital, AP-HP, Paris Descartes University, Paris, FRANCE

Objective: Current clinical evidence and latest guidelines recommended the combination antihypertensive therapy with angiotensin-converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) and calcium channel blocker (CCB) in patients with grade 2 to 3 hypertension. However, data are scarce in the comparison between the ACE inhibitor / ARB + CCB (A+C) therapy and other combinations. We therefore conducted a meta-analysis to see if ACE inhibitor/ARB combined with CCB is superior to other combinations.

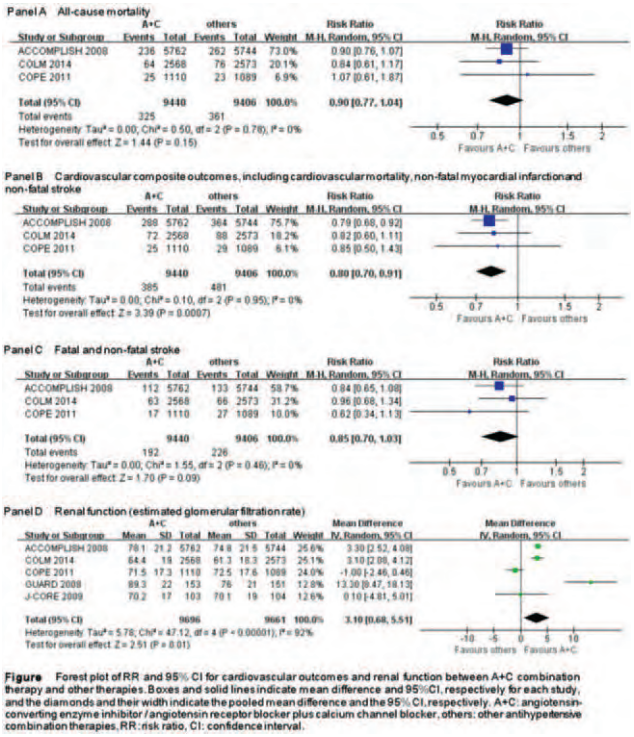

Figure Forest plot of RR and 95% CI for cardiovascular outcomes and renal function between A+C combination therapy and other therapies. Boxes and solid lines indicate mean difference and 95%CI, respectively for each study, and the diamonds and their width indicate the pooled mean difference and the 95% CI, respectively. A+C: angiotensin-converting enzyme inhibitor / angiotensin receptor blocker plus calcium channel blocker, others: other antihypertensive combination therapies, RR: risk ratio, CI: confidence interval.

Design and method: A meta-analysis was conducted in 20,669 hypertensives from 9 randomized controlled trials and we compared the A+C therapy with other combinations, in terms of blood pressure (BP) reduction, clinical outcomes and adverse effects.

Results: BP reduction did not differ significantly between the A+C therapy and other combination therapies, neither in systolic nor in diastolic BP, with P = 0.43 and P = 0.41, respectively. However, A+C strategy, compared with other combination therapies, achieved a significantly lower incidence of cardiovascular composite endpoints, including cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke (Risk ratio [RR] and 95% confidential interval [CI]: 0.80 [0.70, 0.91], P < 0.001, see as Figure), but similar all-cause mortality (0.90 [0.77, 1.04], P = 0.15) and stroke rate (0.90 [0.77, 1.04], P = 0.09). Moreover, A+C combination therapy exhibited a 3.10 ml/min/1.73m2 greater estimated glomerular filtration rate than other combinations (P = 0.01). Lastly, A+C therapy showed a similar incidence of adverse effects as other combinations (P = 0.34), but had a significantly lower incidence of severe adverse effects (0.85 [0.73, 0.98], P = 0.03).

Conclusions: In summary, clinical evidences favor A+C therapy, which is superior to other combinations, in current anti-hypertensive strategy, with greater clinical benefit in cardiovascular outcome and reservation of renal function.

2A.05 EFFICACY OF COMBINATION PERINDOPRIL/AMLODIPINE WITH OR WITHOUT DIURETICS IN EGYPTIAN PATIENTS WITH UNCONTROLLED HYPERTENSION: THE CONTROL STUDY

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Objective: To assess the short-term efficacy and safety of once-daily fixed-dose combination (FDC) perindopril/amlodipine, with or without diuretics, in Egyptian patients with uncontrolled mild-to-severe hypertension.

Design and method: 411 patients with hypertension (systolic blood pressure [BP] >140 and/or diastolic BP >90 mm Hg) uncontrolled by >= 2 previous antihypertensive therapies who were switched to FDC perindopril/amlodipine (5/5, 5/10, 10/5 or 10/10 mg) were enrolled in this 3-month open-label, non-interventional study. Physicians at 35 sites across Egypt collected data on BP, past medical history, lifestyle, risk factors and concomitant treatments at baseline and 1, 2 and 3 months. Diuretic use and adverse events were also recorded. Primary endpoints were mean change in BP and percentage achieving BP control (<140/90 mm Hg or <130/80 mm Hg in diabetics) at 3 months.

Results: After 1 and 3 months' treatment, mean BP fell by 23/12 mm Hg (p < 0.001) and 36/19 mm Hg (p < 0.001), respectively, from 163/98 mm Hg at baseline to 140/86 mm Hg and 127/79 mm Hg. In patients previously on angiotensin-converting enzyme (ACE) inhibitor/calcium channel blocker (CCB), angiotensin receptor blocker (ARB)/CCB, ACE inhibitor/diuretic or ARB/diuretic, mean BP fell by 45/23, 43/20, 33/18, and 35/20 mm Hg, respectively after 3 months. BP control was achieved in 75%, and BP <140/90 mm Hg was achieved in 88%. In patients with grade 1, 2 and 3 hypertension at baseline, BP control was 95%, 89% and 81%, respectively. Diuretic use (mainly indapamide) remained steady at 28%, 29% and 27% at 1, 2 and 3 months, respectively, after rising from 15% at baseline. Most patients (92%, n = 379) completed the study. There were 31 reported adverse events in 22 patients. In 4 patients (1%) who discontinued study treatment prematurely, there were 5 reported adverse events (3 of lower limb oedema and 2 of cough).

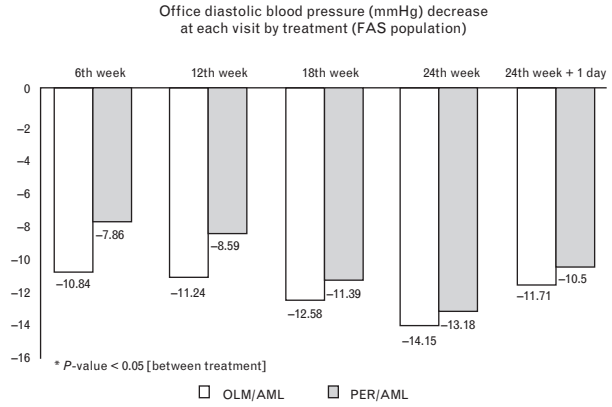
Conclusions: In Egyptian patients with uncontrolled hypertension, FDC perindopril/amlodipine significantly reduced elevated systolic and diastolic BP after 3 months, with BP control achieved in the majority. FDC perindopril/amlodipine was shown to be safe and well tolerated.

2A.06 COMPARATIVE STUDY OF THE EFFICACY OF OLMESARTAN/AMLODIPINE VERSUS PERINDOPRIL/AMLODIPINE IN PERIPHERAL AND CENTRAL BP PARAMETERS AFTER MISSED DOSE IN TYPE 2 DIABETES

J. Redon, Missed Dose Team. *INCLIVA, Hospital Clinico Universitario de Valencia, University of Valencia and CIBERObn, Valencia, SPAIN*

Objective: To determine whether the Olmesartan 20–40 mg + Amlodipine 5–10 mg combination is as effective as the Perindopril 4–8 mg + Amlodipine 5–10 mg combination in reducing ODBP after 24 weeks of treatment, at 48 hours from last administration (missed dose) in diabetes. Assessment of efficacy on OSBP and pulse pressure, on central BP and on the radial artery-derived hemodynamic indices, as well as safety are also evaluated.

Design and method: Non-inferiority trial with randomized, double-blind, double dummy parallel groups. Type II diabetic patients, of both sexes with OSBP 140–179mmHg and DBP 90–109 are recruited. After 2 week running period with Amlodipine 5 mg, patients are randomised to the first 12 weeks of randomised double-blind double dummy treatment; combination of Olmesartan 20 mg + Amlodipine 5 mg (OLM/AML) once a day, or Perindopril 4 mg + Amlodipine 5 mg (PER/AML) once a day, in 1:1 ratio. In patients not normalized by treatment after 12 or 18 weeks, the doses of drug treatment are up-titrated until week 24. At the last visit, patients received placebo treatment in single-blind for 1 day. OBP, aortic BP as large vessels parameters are assessed.



Results: From 335 screened subjects, 260 are randomized (FAS) and 215 evaluated per protocol (OLM/AML 107, PER/AML 108). No differences at baseline are present. Non-inferiority criteria, was reached. OLM/AML reduced hypertension, both ODBP and OSBP, more rapidly than PER/AML in initial treatment phases and OLM/AML effect was constant and longer lasting. After missed dose, decrease of the sitting ODBP value obtained after 24 weeks of treatment was kept after

both treatments. OLM/AML treatment was more effective in maintaining the sitting ODBP values' reduction after missed dose, suggesting a longer lasting effect of OLM/AML. Secondary endpoints evaluated both after 24 weeks of study treatment administration and after missed dose indicated that OLM/AML was more effective than PER/AML and the trend of efficacy was in favour of OLM/AML administration in all performed evaluations.
Conclusions: OLM/AML is safe, well tolerated and as effective as PER/AML in controlling essential hypertension in patients with diabetes mellitus, while the trend of efficacy is in favour of OLM/AML.

2A.07 IMPACT OF STRUCTURED AND INTENSIVE PRIMARY CARE MANAGEMENT AT PROGRESSIVELY HIGHER BLOOD PRESSURE LEVELS IN INDIVIDUALS WITH PERSISTENT HYPERTENSION

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Objective: There is increasing evidence that structured management programs in primary care utilising single-dose, combination anti-hypertensive therapy are effective in lowering the blood pressure (BP) of individuals with seemingly persistent hypertension. However, it is unknown at what point alternative strategies should be applied. We specifically examined the impact of initial BP on the success or failure of this type of program on BP levels at 26 weeks.

Design and method: We analysed outcome data from those individuals with a randomised systolic BP of 140 mmHg or more at the point of randomisation in the multicentre, randomised controlled, Valsartan Intensified Primary carE Reduction of Blood Pressure (VIPER-BP) Study. The impact of the study intervention (a structured and intensified management program facilitated by a computer algorithm for up-titration of combination valsartan-based therapies) over 26 weeks relative to standard care was examined at increasingly higher BP levels.

Results: 1085 participants (63% male, 60 ± 12 years, 71% prior hypertension) were studied. 731 (67%) were randomised (2:1 allocation) to the VIPER-BP intervention. Overall, the higher the initial BP, the greater the fall in BP within 26 weeks. However, BP falls were predominantly higher ($p < 0.05$) in the VIPER-BP intervention group – being $9.2 \pm 13.9/3.5 \pm 8.9$ versus $5.6 \pm 13.1/3.5 \pm 8.9$ mmHg, $15.5 \pm 14.0/8.5 \pm 9.4$ versus $12.2 \pm 13.9/6.2/ \pm 8.8$ mmHg, $25.7 \pm 13.7/12.1 \pm 10.3$versus $19.8 \pm 16.3/10.2 \pm 9.9$ mmHg, $34.6 \pm 13.3/13.2 \pm 9.7$ versus $27.5 \pm 16.9/13.9 \pm 10.5$ mmHg, $33.6 \pm 19.4/16.2 \pm 12.9$ versus $38.5 \pm 16.0/11.2 \pm 10.5$ mmHg for those with an initial systolic BP of 140–149, 150–159, 160–169, 170–179 and > 180mmHg, respectively. Achieving a BP of less than 140/90 mmHg at 26 weeks was not correlated with initial systolic BP. In the intervention group only, independent of baseline profile and BP participants with an initial systolic BP of 170–179 (adjusted OR 3.2, 95% CI 0.89 to 11.2 versus the lowest BP group; $p = 0.073$) and > 180 mmHg (OR 2.7, 95% CI 1.00–7.4; 0.049) were just as likely as those with lower initial BPs to achieve a BP of less than 140/90 mmHg.

Conclusions: Structured and intensive primary care management appears to offer benefits regardless of initial BP in those with persistent hypertension. Indeed, it may benefit those with the highest BPs who don't respond to standard management.

ORAL SESSION

ORAL SESSION 2B
INFLAMMATION AND IMMUNITY

2B.01 IRON OVERLOAD EXERTS SYMPATHOEXCITATORY EFFECTS IN MEN WITH ESSENTIAL HYPERTENSION: MICRONEUROGRAPHIC EVIDENCE

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Objective: A recent hypothesis claims that iron metabolism directly or indirectly, i.e. throughout metabolic (insulin resistance) or inflammatory/autoimmune mechanisms, may be linked to the sympathetic nervous system. In the present study we tested this hypothesis by recording central sympathetic neural outflow in hypertensive patients characterized by normal or elevated circulating plasma levels of ferritin (FE), i.e. a marker of iron load.

Design and method: In 8 untreated male essential hypertensives with elevated plasma FE (HTFE+, age 46.9 ± 2.6 yrs, mean ± SEM), we measured, along with Fe levels and transferrin saturation, body mass index clinic blood pressure (BP), heart rate (HR, EKG), muscle sympathetic nerve traffic (MSNA, microneurography), HOMA index, glucose, tryglicerides and cholesterol levels. Data were compared to those from 7 untreated male essential hypertensive patients with normal FE levels (HTFE-) age matched with HTFE+.

Results: For similar BP, HR and BMI values, HTFE+ displayed FE values significantly greater than those seen in HTFE- (444.3 ± 101 vs 135.4 ± 98 μg/l, $p < 0.05$). This was the case also for transferrin saturation (38.9 ± 24 vs 24.2 ± 9.9 %). IN HTFE+ the increased iron load was accompanied by slightly, although not significantly, greater glucose, cholesterol and triglyceride plasma levels. More importantly, HOMA index values were significantly greater in HTFE+ than HTFE- (2.1 ± 0.4 vs 1.2 ± 0.2 au, $P < 0.05$). This was accompanied by significantly greater values of MSNA, both when expressed as bursts frequency over time (48.5 ± 4.3 vs 39.7 ± 3.5, <0.05) and when corrected for HR (66.4 ± 5.0 vs 50.9 ± 4.4, $P < 0.05$). In the group as a whole there was a significant relationship between MSNA and FE ($r = 0.64, P < 0.01$) whose level of significance was greater than the one related to the relationship MSNA and HOMA index ($r = 0.53, P < 0.05$). HOMA index and FE were also significantly and directly related each other ($r = 0.56$, $P < 0.05$).

Conclusions: These data provide the first evidence that in hypertensive males iron overload exerts marked sympathoexcitatory effects associated with a decrease in insulin sensitivity. It is likely that the iron overload directly or throughout the concomitant hyperinsulinemia may be responsible for this neuroadrenergic response.

2B.02 SERUM URIC ACID LEVEL, BUT NOT RENAL FUNCTION OR ARTERIAL STIFFNESS, IS ASSOCIATED TO WORSE BLOOD PRESSURE CONTROL IN GENERAL PRACTICE: DATA FROM THE BRISIGHELLA HEART STUDY

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Objective: Serum uric acid (SUA) has been associated to incident hypertension and increased risk of cardiovascular diseases. Our aims were to compare the haemodynamic characteristics of normotensives, undiagnosed hypertensives, controlled and uncontrolled hypertensive subjects, and to evaluate if SUA level could also been associated to a different control of blood pressure in pharmacologically treated patients.

Design and method: During the last population survey of the Brisighella Heart Study we identified 146 new cases of arterial hypertension and 394 treated but uncontrolled hypertensive patients. Thus we compared their haemodynamic characteristics with those of age- (58 ± 14 years old) and sex-matched normotensive (N. 324) and controlled hypertensive (N. 470) subjects. Then, by logistic regression analysis, we evaluated which factors were associated to a worse blood pressure control under pharmacological treatment.

Results: Pulse Wave Velocity (PWV) was significantly higher ($p < 0.001$) in undiagnosed hypertensive (9,8 ± 2,4 m/s) and pharmacologically uncontrolled hypertensive (10,3 ± 4,3 m/s) subjects, while controlled hypertensive subjects (8,4 ± 2,1 m/s) had PWV similar to the one of normotensive subjects (8,2 ± 1,9 m/s). A similar result has been observed for augmentation index (AI). SUA level was similar in normotensives and controlled hypertensives (5,1 ± 1,3 mg/dL and 5,1 ± 1,2 mg/dL, respectively), while significantly higher in untreated hypertensive and uncontrolled hypertensive patients (5,4 ± 1,3 mg/dL and 5,4 ± 1,4 mg/dL, respectively). The worse BP control was not associated to age or BMI nor to the estimated glomerular filtration rate, but to SUA (OR 1,377, 95%CI 1,184–1,600), AI (OR 1,066, 95%CI 1,041–1,092) e PWV (OR 1,301, 95%CI 1,189–1,423).

Conclusions: PWV and AI are similarly increased in newly diagnosed hypertensive patients and patients treated but not controlled, whereas PWV is similar in normotensive and well-treated subjects. The main predictors of worse BP control were SUA, AI and PWV.

2B.03 URIC ACID LEVELS RELATED TO OBSTRUCTIVE SLEEP APNEA SYNDROME IN PATIENTS WITH HYPERTENSION FROM XINJIANG OF CHINA

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Objective: Recurrent apnea and hypoxia, which is associated with obstructive sleep apnea syndrome (OSAS), leads to an increase in the degradation of adenosine triphosphatase (ATP) into xanthine, which in turn increases uric acid (UA) concentrations. The study aimed to determine whether an association exists between UA levels and OSAS in patients with hypertension from Xinjiang, China.

Design and method: A total of 1893 hospitalized patients with hypertension who firstly attended Hypertension Center of Xinjiang from 2006 to 2012 were consecutively recruited, all subjects underwent polysomnography recordings for OSAS diagnosis, blood pressure assessment, and biochemical blood analysis.

Results: The mean age of patients with hyperuricemia was younger than that in controls [(45.5 ± 10.2)yr vs.(47.8 ± 10.1)yr, $P < 0.001$ in whole population; (44.9 ± 9.9)yr vs.(46.1 ± 9.7)yr, $P = 0.035$ in males] respectively. Adjusted for age, body mass index, blood pressure, the patients with hyperuricemia presented shorter deep sleep time but greater AHI, mean oxyhemoglobin saturation (SpO2), frequency of SpO2 decreased >=4% and >=5%, and light sleep time. The UA levels significantly increased with the severity of OSAS in whole population and in males, but in females, the lowest level of UA was detected in patients with mild OSAS. Further analysis indicated that waist circumference (WC) displayed lower level in female patients with mild OSAS than those without OSAS. Importantly, AHI and age were significant contributing factors of UA levels in males by stepwise linear regression. While in females, the WC, besides of AHI and age, played as significantly predictor of UA level [β=1.32(0.76–1.88), $P < 0.001$] regardless of OSAS status.

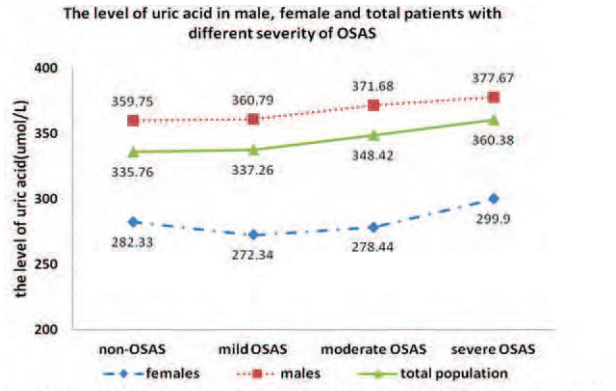

Figure 1 The levels of uric acid in male, female and total patients with different severity of OSAS

Conclusions: A strong association was found between UA levels and OSAS in a large number of hospitalized patients of Xinjiang. Although it does not qualify for a biomarker alone, besides of obesity, UA levels may be involved in OSAS severity and should be considered in sleep apnea management in the future.

2B.04 FACTORS RELATED TO THE LINK BETWEEN URIC ACID AND SYSTOLIC BLOOD PRESSURE IN YOUTHS

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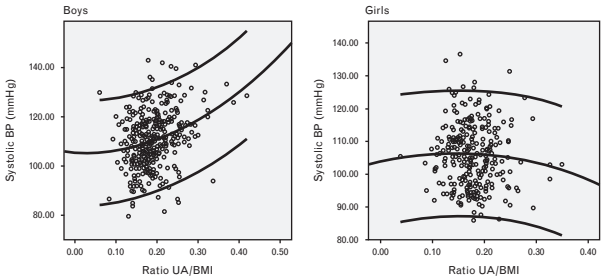
Objective: The present research was undertaken to analyze factors related to the link between uric acid (UA) and office blood pressure (BP) in normotensive, high-normal and untreated essential hypertensive youths.

Design and method: Six hundred and forty three Caucasians of both sexes (321 females), of European origin, predominantly obese, from 6 to 18 years of age (mean age 11.7 2.4) were included. The subjects were divided into 3 groups: normotensives 559 (87%; 92 non-obese), high-normal BP 58 (9%; 19 non-obese) or hypertensives 26 (4%; 5 non-obese) according to the ESH office BP criteria (Lurbe et al, J Hypertens 2009). Fasting blood was obtained and glucose, insulin, lipid profile, and UA were assessed.

Results: In relation to the general characteristics, there were no differences among groups regarding age, BMI, BMI-zscore, HDL and insulin. Uric acid increases across the BP range from normotensive to hypertensive groups. Controlling by age and sex, UA was significantly correlated with BMI (r = 0.180, p = 0.000), BMI Z-score (r = 0.175; p = 0.000), SBP (r = 0.20; p = 0.000), insulin (r = 0.23; p = 0.000), and HDL (r = -0.149; p = 0.000). In a multiple regression analysis office SBP, insulin, and HDL cholesterol were independent determinants of UA when age, sex, and BMI were included (r2 = 0.25). Office systolic BP was the main determinant of UA in a stepwise analysis. Even though UA was corrected by body size, UA/BMI ratio, systolic BP was the main determinant in boys (See figure).



Conclusions: Uric acid is associated with BP, independently of metabolic factors in boys. The clinical implications require further investigation.

2B.05 SUBCLINICAL MYOCARDIAL DYSFUNCTION IN HYPERTENSIVE PATIENTS WITH HYPERURICEMIA

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Objective: Elevated levels of serum uric acid have been associated in population studies with an increased risk of cardiovascular disease. Increasing evidence suggests that serum uric acid may be a useful marker for metabolic, hemodynamic, and functional staging in heart failure (HF) and a valid predictor of survival in HF patients.
The aim of our study was to investigate the association between hyperuricemia and subclinical myocardial dysfunction.

Design and method: The study included 64 hypertensive patients with hyperuricemia (n = 31) or without hyperuricemia, (n = 33) and control group of 33 age and sex matched healthy subjects.
Patients with high variability of the uric acid measurements from the first and second visits were excluded.
Left atrial volume index (LAVI), left ventricular mass index (LVMI), left ventricular dimensions and volume inexes (LVEDV/BSA and LVESV/BSA) and EF were estimated by echocardiography. We measured coresponding velocities from tissue Doppler at the level of the septal mitral annulus (Em, Am, Sm), including isovolumic contraction velocity (IVCv) and E/Em.
Global longitudinal strain (GLS) was derived from two-dimensional speckle-tracking.

Results: Close correlations were found between GLS and E/Em (r = 0.449; p = 0.0004) and IVCv (r = -0.390; p = 0.0008).
Levels of E/Em (7.7 ± 1.5 vs 10.3 ± 1.7 vs 14.6 ± 1.8; p = 0.0007), LVEDV/BSA (91.0 ± 15.3 vs 103.1 ± 23.5 vs 105.8 ± 24.7; p = 0.015), LVESV/BSA (34.5 ± 9.3 vs 42.3 ± 10.2 vs 46.1 ± 15.4; p = 0.001), LVMI (104.2 ± 17.3 vs 112.7 ± 20.5 vs 123.9 ± ± 28.3; p = 0.003) and LAVI (34.9 ± 9.7 vs 40.2 ± 11.8 vs 47.0 ± 12.0; p = 0.0002) progressively increased from the normal group through group of hypertensive patients without hyperuricemia and group with hyperuricemia. Significantly different value of GLS (-22.4 ± 5.0 vs -19.6 ± 4.0 vs -16.6 ± 4.9; p = 0.0002) was obtained between groups too, but with progressively decrease from the normal group through group of hypertensive patients without hyperuricemia and group with hyperuricemia.

Conclusions: According to this observation, uric acid could be considered a new parameter for cardiac remodeling and subclinical myocardial dysfunction in hypertensive patients. This suggests that uric acid may aid in the identification of patients at high risk for development of HF who need preventive treatment. The question of whether uric acid is only a marker rather than a causal factor in the pathogenesis of HF remains.

2B.06 EPIGALLOCATECHIN-3-GALLATE ATTENUATES URIC ACID-INDUCED INFLAMMATORY RESPONSES AND OXIDATIVE STRESS BY MODULATING NOTCH PATHWAY

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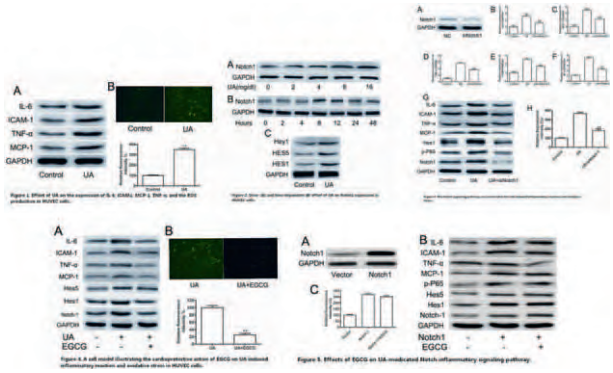
Objective: Hyperuricemia is recently reported to play a role in hypertension, metabolic syndrome and vascular damage. (-)-Epigallocatechin-3-Gallate (EGCG) is a major polyphenol component of green tea with potent antiinflammatory and antioxidant effects. The aim of this study was to further investigate whether EGCG can prevent the UA-induced inflammatory effect of Human Umbilical Vein Endothelial Cells (HUVEC) and the involved mechanisms in vitro.



Design and method: HUVEC were subjected to the action of 8 mg/dl uric acid (UA) with or without 20 μM EGCG treatment. RT-PCR and western blots were performed to determine the level of the inflammation markers. The antioxidant activity was evaluated by measuring scavenged reactive oxygen species (ROS). Functional studies of the role of Notch-1 in HUVEC cell lines were performed using RNA interference analyses. The full cDNA of Notch-1 was cloned in the pcDNA3.1 vector and transfected in HUVEC cells.

Results: UA significantly increased the expression of IL-6, ICAM-1, TNF-α, MCP-1, and the production of ROS in HUVEC cells. Meanwhile, the expression of Notch-1 and its downstream proteins significantly increased. The inhibition of Notch-1 signaling using siRNA considerably impeded the expression of inflammatory cytokines under the treatment by UA. Interestingly, EGCG substantially suppressed the expression of inflammatory cytokines through Notch-1 signal pathways and hindered the generation of ROS.

Conclusions: Taken together, our findings indicated that Notch-1 played an important role in the UA-induced inflammatory response, and the downregulation of Notch-1 by EGCG could be an effective approach to decrease the inflammation and oxidative stress induced by UA.

2B.07 DIASTOLIC BLOOD PRESSURE MODIFIES THE ASSOCIATION OF URIC ACID WITH ALBUMIN/CREATININE RATIO IN PRE-METABOLIC SYNDROME

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Objective: Serum uric acid (UA) has been associated with metabolic syndrome (MetS) and urine albumin/creatinine ratio (ACR). We questioned whether UA and

ACR are associated in pre-metabolic individuals, and whether this association is modified by any component variable of the metabolic syndrome.

Design and method: In a cross-sectional survey of a representative Czech population (n = 3612) aged 25–64 years, urinary albumin and creatinine excretion were determined in an early morning spot urine sample and ACR was calculated. Components of MetS were defined using the joint statement of IDF, NHBLI, AHA, WHF, IAS, and IASO. Individuals presenting with 1 or 2 components were defined as pre-metabolic. Individuals with urinary albumin excretion bellow the detection limit of 1 mg (n = 594), diabetes treated with glucose lowering medication (n = 122), current use of inhibitors of xanthine oxidase (n = 95) and incomplete data (n = 135) were excluded from this analysis. This resulted in 2666 individuals in total.

Results: Six hundred and sixty-five (25%) individuals presented without any component of MetS, and 1248 (46.8%) individuals with 1 or 2 components. In individuals free of any component of MetS, there was no association between UA and ln-ACR. In pre-metabolic individuals, UA significantly correlated with ln-ACR in men (n = 639; standardized beta (SB) 0.091; p = 0.022) and in women (n = 609; SB 0.122; p = 0.003). After multivariate adjustment, UA was independently associated with ln-ACR (SB 0.058; p = 0.004), age (SB -0.247; p < 0.001), gender (SB -0.568; p < 0.001), waist-to-height ratio (SB 0.247; p < 0.001), ln-triglycerides (SB 0.087; p = 0.001), estimated glomerular filtration rate (SB -0.425; p < 0.001), and current use of diuretics (SB 0.054; p = 0.008). An independent interaction of ln-ACR with diastolic blood pressure (DBP), (p = 0.023) in relation to UA was present. In individuals with DBP over the median of 81 mmHg (n = 611), there was independent association between ln-ACR and UA (SB 0.094; p = 0.004), whereas no association between the two variables (SB 0.038; p = 0.176) was present in individuals with DBP bellow or equal to 81 mmHg (n = 637).

Conclusions: Uric acid is independently associated with albumin/creatinine ratio in individuals with pre-metabolic syndrome. This association appears to be largely modified by diastolic blood pressure.

2B.08 SERUM AMYLOID A: INFLAMMATORY EFFECTS ON MACROPHAGES

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Objective: Serum amyloid A (SAA) is an apolipoprotein transported within the high density lipoprotein (HDL) in plasma. The SAA plasma levels increase during inflammatory conditions, e.g., in patients with chronic renal failure (CRF). The SAA-dependent reduction in anti-inflammatory condition of HDL and its pro-inflammatory response in smooth muscle cells was shown previously. The aim of this study was to investigate the signaling pathways of SAA in macrophages and therefore its influence on inflammatory vascular disease.

Design and method: THP-1 (human) monocytes were activated via PMA to macrophages and used for monocyte chemoattractant protein-1 (MCP-1) experiments. Murine RAW264.7 monocytes/macrophages were used for nitrite experiments. MCP-1 production was detected by Luminex™ technology. Nitrite production were measured via Griess Assay. Cell viability was determined via MTS assay.

Results: SAA accumulates in plasma of patients during conditions of CRF. Whereas there is only a slight increase within CRF stage 1 and 2, the plasma level of SAA further increase during CRF stage 3 to 5. Beside the pro-inflammatory potential of SAA to induce MCP-1 in vascular smooth muscle cells, it also induces MCP-1 secretion in human THP-1 macrophages in a dose-dependent manner. In addition, the production of nitrite was dose-dependently increased in murine RAW264.7 cells. Both, MCP-1 and nitrite production induced by SAA were regulated via TLR and SR-BI receptor activation. The TLR2/4 antagonist oxPAPC and the SR-BI antagonist BLT-1 diminished the SAA-induced MCP-1 and nitrite production. The activation of FPR2 seems not to be involved in the signaling pathway in macrophages after SAA stimulation in that experimental condition. Stimulation with receptor agonists confirmed these findings. The concentration used for agonists/antagonists had no significant influence on cell viability of macrophages.

Conclusions: In conclusion, the pro-inflammatory reaction of SAA in macrophages in vitro depends on TLR2/4 and SR-BI activation. The accumulation of SAA plasma levels during CRF may substantially contribute to the increased cardiovascular risk of these patients.

2B.09 ARTERIAL STIFFNESS AND DISEASE-RELATED ORGAN DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective: Increased arterial stiffness has been reported in subjects with systemic lupus erythematosus (SLE) compared with healthy controls, and this association is partially reverted by immunosuppressive treatment. In SLE, indexes of organ damage are related to a poor clinical status and worse prognosis independently from the activity of the disease. Data are controversial about the association between organ damage and arterial stiffness in SLE.

Design and method: 40 subjects with positive history of SLE (mean age 45 ± 12 years, 90% women) and a median disease duration of 12 years (IQR 5–19), underwent assessment of carotid-femoral pulse wave velocity (cf-PWV) by means of applanation tonometry (SphygmoCor). A comprehensive clinical, metabolic and immunological assessment was performed. Irreversible organ damage, not related to active inflammation, was assessed through the Systemic Lupus International Collaborating Clinics (SLICC) damage index. The relationship between cf-PWV and SLICC index was investigated with univariate and multivariate models.

Results: Mean blood pressure was 128/75 ± 16/10 mmHg. 9 subjects (23%) were on anti-hypertensive treatment, 4 (10%) had had previous cardiovascular events, 17 (42%) subjects were treated with steroids, 29 (71%) with hydroxychloroquine and 15 (37%) with other immunosuppressants. Median SLICC index was 2 (IQR 1–3) and average cf-PWV was 7.5 ± 1.9 m/s. cf-PWV significantly increased across SLICC damage index categories (F = 3.141, p < 0.019). The association between cf-PVW and SLICC index persisted after adjustment for age, sex, mean arterial pressure, height, heart rate, disease duration, anti-hypertensive treatment, number of drugs for SLE therapy, C-reactive protein and previous cardiovascular events (p = 0.031).

Conclusions: In a cohort of subjects with SLE under active treatment, SLICC damage index had a significant independent association with cf-PWV. Further studies are needed to explore the role of arterial stiffness as a predictor of disease-related organ damage in SLE.

ORAL SESSION

ORAL SESSION 2C
AGEING

2C.01 FIXED RANKING OF LEUKOCYTE TELOMERE LENGTH IN ELDERLY PEOPLE: RESULTS FROM 8 YEAR FOLLOW-UP OF THE ADELAHYDE COHORT

S. Toupance [1], G. Watfa [2], C. Lakomy [1], A. Kearney-Schwartz [2], C. Labat [1], P. Rossignol [3], P. Lacolley [1], F. Zannad [3], A. Benetos [1,2]. *[1] INSERM UMRS 1116, Nancy, FRANCE, [2] CHU de Nancy, Service de Gériatrie, Nancy, FRANCE, [3] CHU de Nancy, CIC-P Pierre Drouin, Nancy, FRANCE*

Objective: Short leukocyte telomere length (LTL) is associated with atherosclerosis in adults and diminished survival in the elderly. The prevailing view is that LTL is associated with accelerated aging since it serves as a biomarker of the cumulative burden of inflammation and oxidative stress during adult life. However LTL dynamics are mainly defined by LTL at birth, which is highly variable, and its age-dependent attrition thereafter, which is rapid during the first 20 years of life. We examined whether age-dependent LTL attrition during old age can substantially affect individuals' LTL ranking (e.g., longer or shorter LTL) in relation to their peers and which clinical (presence or absence of atheroma) or lifestyle (BMI and smoking) factors can predict it.

Design and method: We measured LTL by Telomeric Restriction Fragment Southern Blot (TRF) in samples donated 8 years apart on average by 76 participants of the ADELAHYDE study. Participants were men and women aged 60 to 85 years with a history of hypertension at the inclusion.

Results: We observed a mean LTL attrition of 27 bp per year which is consistent with previous data on telomere attrition in adults. No clinical or lifestyle risk factors seem to exert significant effect or can predict LTL attrition in elderly people. We observed a close relationship (r = 0.88) between baseline and follow-up LTL values. Ranking individuals by deciles revealed that 87.5% showed no rank change (38.9%) or only one decile change (48.6%) over time. We observed relationships between baseline values of LTL and BMI as well as between LTL and carotid atheroma. No such relationship was observed between LTL and smoking status.

Conclusions: We conclude that in elderly people, LTL ranking changes very little over time. Accordingly, the links of LTL with atherosclerosis and longevity appear to be established early in life. It is therefore unlikely that lifestyle and its modification during old age exert a major impact on telomere length.

2C.02 DO ARTERIAL HEMODYNAMIC PARAMETERS PREDICT COGNITIVE DECLINE OVER A PERIOD OF 2 YEARS IN SUBJECTS OLDER THAN 80 YEARS LIVING IN NURSING HOMES? THE PARTAGE STUDY

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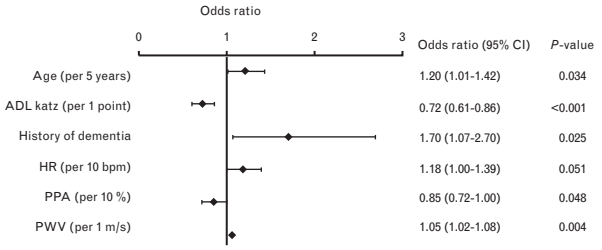
Objective: Several studies have highlighted a link between vascular alterations and cognitive decline. The PARTAGE study showed that arterial stiffness as evaluated by carotid-femoral pulse wave velocity (cfPWV) was associated with a more pronounced cognitive decline over a 1-year period in very old frail institutionalized subjects. The aim of the present analysis was to assess the role of hemodynamic parameters such as blood pressure (BP), heart rate (HR), cfPWV and central/peripheral Pulse Pressure Amplification (PPA) on cognitive decline over a period of 2 years in very old frail subjects.

Design and method: 682 subjects from the PARTAGE study cohort, aged >80 years (mean age at inclusion: 87.5 ± 5 y) and living in French and Italian nursing homes, were analyzed. MMSE score was assessed at baseline (BL) and at the end of the first and second year of follow-up (2y-FU). Subjects with a decrease in MMSE of >=3 points between BL and 2y-FU were considered as "decliners". cfPWV and PPA at baseline were assessed with an arterial tonometer.

Results: After adjustment for baseline MMSE, HR, BMI, age, education level and ADL, cfPWV was higher and PPA lower in "decliners" compared to "non-decliners, while BP did not differ between the 2 groups. Logistic multivariate analysis also revealed that high cfPWV, low PPA, high HR and low ADL were all determinants of MMSE decline.
(Figure: Analysis of baseline factors associated with "decliners" status using multiple logistic regression model).



Conclusions: This 2-year longitudinal study in very old institutionalized individuals shows that arterial stiffness and high heart rate enabled to identify subjects at higher risk of cognitive decline, while blood pressure alone did not appear to have a significant predictive value. These findings highlight the contribution of vascular determinants in cognitive decline even in this very old population.

2C.03 INDEPENDENT PREDICTORS OF NOCTURNAL HYPERTENSION IN ELDERLY SUBJECTS FROM GENERAL POPULATION: THE RISK OF VASCULAR COMPLICATION, IMPACT OF GENETIC IN OLD PEOPLE (ROVIGO) STUDY

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Objective: The role of Nocturnal Hypertension (NH) and its relationship with target organ damage (TOD) and global cardiovascular (CV) risk has been poorly investigated in elderly subjects from general population.

Design and method: In 139 subjects (70 men and 69 women) aged > = 65 years (mean age 72.4 ± 4.6) without anti-hypertensive treatment and taking part of the ROVIGO study, a NH was diagnosed during 24h-ambulatory blood pressure monitoring (ABPM) using a TM- 2430 oscillometric device (NH defined by ABPM values > 120/70 mmHg). Left ventricular hypertrophy (LVH) was diagnosed by 12-leads electrocardiogram (ECG) using the Sokolow-Lion index criterion and renal impairment was defined by an eGFR < 60 ml/min/1.73m2 calculated with the MDRD formula. All subjects collected a 24-h urine sample for the measurement of sodium (urinary 24h_Na +) excretion. Gender specific odds ratio (OR) and 95% confidence intervals (CI 95%) of NH were calculated for independent variables by logistic regression analysis.

Results: NH prevalence was 23.9% and was not different between genders. NH was predicted by LVH (OR 2.05, CI95% 1.06–3.83, p = 0,023) and urinary 24h_Na + (OR 2,71, CI95% 1.20–6.07, p = 0.015) independently of age, clinical BP components, BMI and impaired renal function.

Conclusions: At population level, in untreated elderly patients with NH, LVH and urinary 24hNa+ assessment are mandatory for a better stratification of their global cardiovascular risk.

2C.04 TIMING OF BLOOD PRESSURE AND VASCULAR CHANGES INDUCED BY AGEING IN AORTA AND SMALL MESENTERIC ARTERIES FROM FEMALE SENESCENCE-ACCELERATED MOUSE PRONE (SAMP8)

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Objective: Age is the most important risk factor for cardiovascular diseases. A key requisite to develop new interventions for age-related conditions is the availability of preclinical murine models. We propose prone senescence-accelerated mice (SAMP8) to study vascular ageing in a convenient and standard time course. Our aim was to investigate the effects of ageing on blood pressure and endothelium-dependent relaxation in large and small arterial vessels of female SAMP8 in order to characterize the vascular changes in this experimental model of ageing.

Design and method: Female SAMP8 mice at 3-, 6- and 10-months old (n = 8 in each group) were studied. Thoracic aorta (~1 mm internal diameter) and small mesenteric arteries (SMA ~200 μm internal diameter) were mounted for isometric recording of tension. The endothelium-dependent relaxations to acetylcholine (ACh, 10–9 to 10–5 M) were performed in the absence and in the presence of the NO synthase inhibitor NG-nitro-L-arginine methyl ester (L-NAME, 10–4 M). Blood pressure (n = 6 in each group) was measured using the tail-cuff method. Histological analysis were carried out by hematoxylin-eosin staining.

Results: A decrease in endothelium-dependent relaxation to ACh in SAMP8 aorta was observed at 6-months old (91 ± 3 vs 72 ± 4%, $p < 0.05$) and further decrease was observed at 10-month old (72 ± 4 vs 64 ± 4%, $p < 0.05$). In contrast, in SMA the relaxation decreased at 10-months old (98 ± 4% vs 89 ± 4%, $p < 0.05$). In aorta, the ACh-induced relaxation was completely inhibited by L-NAME, but in SMA were reduced a 38 ± 4% suggesting than other endothelial-derived relaxant factors, distinct from NO, could counterbalance the decreased NO biavailability induced by ageing in small arteries. An increment in blood pressure and hemodynamic parameters are observed at 10-months old.

Conclusions: Ageing induces earlier endothelial dysfunction in aorta than in SMA suggesting that aortic endothelial cells are more sensitive to deleterious effects of ageing. The enhancement of blood pressure match with a decreased endothelium-dependent relaxation in small arteries. Our results support the use of SAMP8 mice to study ageing-associated vascular function in females.

2C.05 CAN WE USE THE CONCEPT OF "ARTERIAL AGING" TO PREDICT BLOOD PRESSURE LEVELS?

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Objective: Arterial aging is one of the fundamental mechanisms underlying blood pressure (BP) increase, and may even precede BP rise. We hypothesized that the extent of arterial aging, quantified as aortic pulse wave velocity (aPWV) graded according to an age-specific reference group with normal BP, would be related to blood pressure classification, based on office and 24 hour ambulatory BP.

Design and method: We measured BP and aPWV twice in the doctors office and performed 24 hour ambulatory BP monitoring with the oscillometric cuff-based mobilograph device (iem, Stolberg, Germany) in untreated and treated patients from a large group practice in internal medicine. APWV was estimated with the recently validated ARCSolver algorithm, based on age, systolic BP and waveform characteristics and was classified as < 50., 51.-95., and > 95 percentile of the age-specific reference group.

Results: We included 839 patients (46.4% females, mean age 58.1 years, range 15–94 years). Mean office BP was 139/90 mm Hg, mean 24 hour BP was 128/80 mm Hg, mean aPWV was 9.6 m/sec. 247 patients were normotensive, 113 had white coat hypertension, 99 masked hypertension, and 380 were sustained hypertensive. 78.4% of the patients had aPWVs above the 95. percentile, 18.8% were between 50. and 95. percentile, and 2.7% were below the 50. percentile. There was a clear increase in the percentage of patients with sustained hypertension across the three categories of arterial aging (4.3%, 16.5%, and 53.6% in patients below the 50. percentile, between 50. and 95., and above the 95. percentile, respectively), and an inverse distribution related to normotension (Table). The differences were statistically highly significant ($p < 0.0001$). The relatively high percentage of patients with masked hypertension in the group < 50. percentile (30.4%) is of concern, but the absolute number is small (n = 7).

Conclusions: Arterial aging, based on age-specific percentiles, may be a useful screening tool for sustained hypertension, based on office and 24 hour ambulatory BP.

	Normotension	White coat hypertension	Masked hypertension	Sustained hypertension
aPWV < 50. percentile	60.9%	4.3%	30.4%	4.3%
aPWV 50.-95. percentile	56.3%	6.3%	20.9%	16.5%
aPWV > 95. percentile	21.9%	15.5%	9.0%	53.6%

2C.06 BLOOD PRESSURE CONTROL IN THE CONTEXT OF SCREENING FOR COGNITIVE AND MOOD IMPAIRMENTS IN THE OCTOGENARIAN AND OLDER HYPERTENSIVE PATIENTS

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Objective: To assess blood pressure control rate and its correlates in a Polish nationwide cohort of the community dwelling persons at or above the age of 80 years.

Design and method: As a part of PolFokus study we did a cross-sectional, nationwide survey of 2500 elderly people treated for hypertension for at least one year. In the current analysis we included data of 384 individuals aged 80+. During the survey visit BP was measured at least twice and the mean value was calculated. Demographic and medical data were collected. Adherence to antihypertensive medications was assessed, and screening tests for cognitive deficits (Abbreviated Mental Test Score, AMTS) and mood disorders (Geriatric Depression Scale, GDS) were performed. Logistic regression models were used to calculate the probability of lack of BP control as a function of cognitive and mood assessment scores. We used both, age-stratified (SBP < 150 mmHg) and unified (SBP/DBP < 140/90 mmHg) definitions of BP control.

Results: Mean (SD) age of 384 (70.1% women) patients was 83.1 (3.1) years. Cognitive impairments were observed in 13.2% and mood disturbances in 45.5%. Mean SBP/DBP were 143.2(16.3)/83.9(9.6) mmHg. According to age-stratified and unified definition of proper BP control, goal BP were achieved in 65.4% and 38.5% of patients, respectively. More than 2/3 of patients were prescribed 3 or more antihypertensive medications. Sixty-nine % of the group adhered to antihypertensive medications, the rest having reported various degree of noncompliance that was associated with geriatric deficits. When unified goal was applied, there was a 17% higher risk of finding lack of BP control per one score lost in AMTS scale ($p = 0.02$). In a corresponding analysis, there was a 7% greater risk of finding lack of BP control per one-score increment in GDS test, however the trend was borderline insignificant ($p = 0.06$). Both trends lost statistical significance when stratified definition of BP goal was used.

Conclusions: The observation, that the subclinical worsening of cognition and mood assessed with the screening tools are related to poorer BP control, lends support to the wide-spread use of the Comprehensive Geriatric Assessment even in apparently self-dependent oldest patients with hypertension.

2C.07 INVOLVEMENT OF THE RENIN-ANGIOTENSIN SYSTEM IN A PREMATURE AGING MOUSE MODEL

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Objective: Changes in the renin-angiotensin system (RAS), known for its critical role in the regulation of blood pressure and sodium homeostasis, may contribute to aging and age-related diseases. Here we characterized the RAS and kidney pathology in mice with genomic instability due to a defective nucleotide excision repair gene (Ercc1d/- mice). These mice display premature features of aging, including vascular dysfunction.

Design and method: Studies were performed in male and female Ercc1d/- mice and their wild type controls (Ercc1+/+) at the age of 12 or 18 weeks before and after treatment with losartan. The renin-activatable near-infrared fluorescent probe ReninSense 680™ was applied in vivo to allow non-invasive imaging of renin activity. Plasma renin concentrations (PRC) were additionally measured ex vivo by

quantifying Ang I generation in the presence of excess angiotensinogen. Kidneys were harvested and examined for markers of aging, and albumin was determined in urine.

Results: Kidneys of 12-week old Ercc1d/- mice showed signs of aging, including tubular anisokaryosis, cell-senescence and increased apoptosis. This was even more pronounced at the age of 18 weeks. Yet, urinary albumin was normal at 12 weeks. The ReninSense 680^{TM} probe showed increased intrarenal renin activity in Ercc1d/- mice versus Ercc1+/+ mice, both at 12 and 18 weeks of age, while PRC in these mice tended to be lower compared to Ercc1+/+ mice. Renin was higher in male than female mice, both in the kidney and in plasma, and losartan increased kidney and plasma renin in both Ercc1d/- and Ercc1+/+ mice.

Conclusions: Rapidly aging Ercc1d/- mice display an activated intrarenal RAS, as evidenced by the increased fluorescence detected with the ReninSense 680^{TM} probe. This increased RAS activity may contribute to the disturbed kidney pathology in these mice. The increased intrarenal activity detected with the ReninSense 680^{TM} probe in male vs. female mice, as well as after losartan treatment, are in full agreement with the literature, and thus not only validate the specificity of the probe, but also support its use for longitudinal imaging of altered RAS signaling in aging.

ORAL SESSION

ORAL SESSION 2D
CORONARY HEART DISEASE

2D.01 EXERCISE SYSTOLIC BLOOD PRESSURE >/=190 MMHG AT MODERATE WORKLOAD PREDICTS CORONARY HEART DISEASE IN HEALTHY, MIDDLE-AGED MEN

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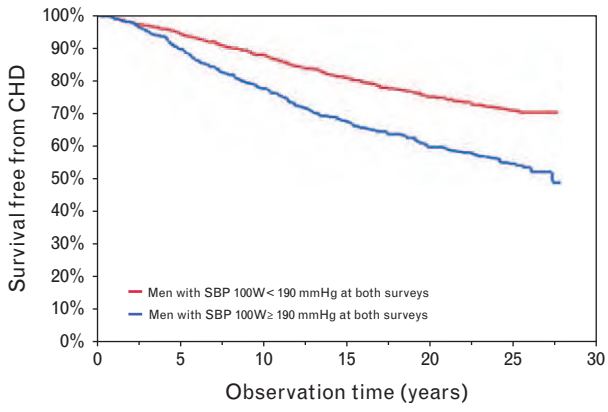
Objective: A hypertensive response to exercise at moderate workload is associated with future risk of coronary heart disease (CHD) and mortality. Yet there is still no consensus regarding the cut-off value for an inappropriate increase in exercise systolic blood pressure. We have previously shown that exercise blood pressure at 100W workload (SBP100W) > 200 mmHg is associated with increased risk of CHD and mortality. We now aimed to investigate the possible association between SBP100W >/= 190mmHg and risk of CHD over up to 28 years follow-up.

Design and method: Of the 1999 apparently healthy, middle-aged men who underwent thorough medical examination and laboratory testing, including a symptom-limited bicycle ergometer test, during 1972–1975, 1392 men were still healthy at survey 2 seven years later and completed a workload of 100 W at both surveys. Systolic blood pressure was measured near completion of the 100W stage (SBP100W). By comparing subjects having SBP100W >/=190 mmHg at baseline, follow-up or both(n=365) with subjects having SBP100W < 190 mmHg at both surveys (n = 1027), we estimated the risk of CHD (angina pectoris, non-fatal myocardial infarction and death from coronary heart disease).

Results: The combined endpoint of CHD occurred in 452 of the 1392 men; 243 events among the 365 men with SBP100W >/= 190 mmHg. When adjusting for survey 1 smoking status, age, systolic blood pressure at rest, total cholesterol and family history of coronary heart disease, there was a 1.38-fold (CI 1.11–1.71, $p < 0.005$) increased risk of CHD. When further adjusting for physical fitness, SBP100W >/=190mmHg was associated with a 1.35-fold (1.08–1.65) increased risk of CHD.

Conclusions: Our findings indicate that a systolic blood pressure of 190 mmHg or more at moderate workload is associated with future risk of CHD among apparently healthy middle-aged men.



2D.02 ACCURACY OF ISOVOLUMETRIC CONTRACTION TIME OBTAINED BY CAROTID ARTERIAL TONOMETRY IN PATIENTS WITH CHRONIC LEFT VENTRICULAR FAILURE

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Objective: The Buckberg index (SEVR: subendocardial viability ratio) is considered a useful parameter for a non-invasive assessment of the relationship between subendocardial oxygen supply and demand. However, his classic calculation does not include the pre-ejection isovolumic contraction time in stroke work evaluation. The aim of our study was to evaluate the accuracy of the isovolumic contraction time obtained through the carotid pulse wave analysis, to be included in SEVR assessment.

Design and method: In 35 patients (mean age ± SD = 66 ± 13 yrs) followed-up for chronic left ventricular systolic failure (EF = 32 ± 8%) with no significant valvular disease, the pressure curve in the common carotid artery by tonometer (PulsePen) and the aortic transvalvular flow by EchocardioDoppler (Philips-EnVisor C-HD) were acquired simultaneously. The synchronization of data acquisition was verified by comparison of the RR intervals in the ECG signals recorded simultaneously to the two methods. The isovolumic contraction time was separately calculated by considering both the delay between the beginning of the aortic flow wave obtained by EchocardioDoppler and the R wave of the corresponding ECG, and the delay between the foot of the pressure wave recorded in the carotid artery by tonometry compared with the R wave of the corresponding ECG. The latter was corrected by considering the delay between ascending aorta and carotid pulses, computed as a function of the carotid-femoral pulse wave speed and of the distance between the point of carotid pulse acquisition and the sternal notch.

Results: The isovolumic contraction time computed by tonometry (68.8 ± 20.2 ms) was closely related to that measured with the EchocardioDoppler approach (68.8 ± 20.5 ms): $y = 0.93x + 4.94$; $r^2 = 0.93$; $p < 0.0001$, with homogeneous distribution in Bland-Altman analysis (mean difference -0.1 ± 7.57 ms). The ratios between isovolumic contraction time and systolic ejection time separately obtained with the two methods (24.8 ± 8.3% and 22.2 ± 8.5%, respectively) were closely related: $y = 0.93x + 1.67$; $r^2 = 0.90$ (mean difference -0.1 ± 2.7%).

Conclusions: Thus, carotid arterial tonometry allows an accurate and simple assessment of the isovolumic contraction time, which can be employed to improve the assessment of SEVR by also considering the isovolumic contraction time in the stroke work evaluation.

2D.03 IMPROVING DIAGNOSTIC STRATEGY IN PATIENTS WITH LONG-STANDING HYPERTENSION, CHEST PAIN AND NORMAL RESTING ECG: VALUE OF THE EXERCISE HIGH-FREQUENCY QRS VERSUS ST-SEGMENT ANALYSIS

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Objective: The novel exercise computer-assisted high-frequency QRS-analysis (ex-HF/QRS) has demonstrated improved sensitivity and specificity over the conventional exercise-ST/ECG-segment-analysis (ex-ST/ECG) in the detection of myocardial ischemia. The aim of the present study was to test the implementation in diagnostic value of the ex-HF/QRS in patient with hypertension and chest pain (CP) versus the conventional ex-ST/ECG anlysis alone.

Design and method: Patients with long-standing hypertension, CP, normal ECG, troponin and echocardiography were enrolled. All patients underwent the ex-ST/ECG and ex-HF/QRS. A decrease >/=50% of the signal of ex-HF/QRS intensity recorded in two contiguous leads, at least, was considered as index of ischaemia, as ST-segment depression >/=2 mm or >/=1 mm and CP on ex-ST/ECG. Exclusion criteria were QRS duration >/=120 msec and inability to exercise. The end-point was the composite of coronary stenosis >50% or acute coronary syndrome, revascularization, cardiovascular death at 3-month follow-up.

Results: Six-hundred thirty-one patients were enrolled (age 61+/-15 y). The percentage of age-adjusted maximal predicted heart rate was 88+/-10 beat-per-minute and the maximal systolic blood pressure was 169+/-22 mmHg. Twenty-seven patients achieved the end-point. On multivariate analysis, both the ex-ST/ECG and ex-HF/QRS were predictors of the end-point. The ex-HF/QRS showed higher sensitivity (88% vs 50%; p = 0.003), lower specificity (77% vs 97%; p = 0.245) and comparable negative predictive value (99% vs 99%; p = NS) when compared to ex-ST/ECG. Receiver operator characteristics (ROC) analysis showed the incremental diagnostic value of the ex-HF/QRS (area: 0.64, 95% Confidence Intervals, CI 0.51–0.77) over conventional ex-ST/ECG (0.60, CI 0.52–0.66) and Chest Pain Score (0.53, CI 0.48–0.59); p = NS on pairwise C-statistic.

Conclusions: In patients with long-standing hypertension and CP submitted to risk stratification with exercise tolerance test, the novel ex-HF/QRS shows a valuable incremental diagnostic value over ex-ST/ECG.

2D.04 YOUNG PATIENTS WITH ACUTE ST-ELEVATED MYOCARDIAL INFARCTION: HOW STIFF ARE THEIR ARTERIES?

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Objective: To evaluate arterial stiffness in young patients from a very high CV risk country presented with a first acute ST-elevated myocardial infarction and to analyse association between increased arterial stiffness and the severity of coronary artery disease.

Design and method: Consecutive patients with age less than 45 years admitted in our department for a first acute STEMI between January 2013 – January 2014 were enrolled in the study after signing a written informed consent. All patients underwent primary PCI at inclusion for evaluation of coronary artery disease (normal, univascular lesions, bivascular lesions, trivascular lesions). Arterial stiffness was assessed by aortic pulse wave velocity, aortic augmentation index, and central aortic systolic blood pressure measurements by an oscillometric device. Association between traditional CV risk factors and the severity of CAD was assessed by bivariate correlation analysis with adjustments for major confounders.

Results: Mean age of the study sample was 40.13 ± 4.36years. Gender distribution showed a male preponderance (86,7%). The majority of the patients (25 cases, 83,33%) had significant atherosclerotic lesions on the MI related artery. More, bivascular and trivascular atherosclerotic lesions were recorded eight cases (13.33%) each, while the majority has univascular lesions (18 cases, 60%).. Mean (range) PWVao values were: PWVao 9.10 ± 1.77m/s (7–14.4m/s), 23.33% of cases having PWVao > 10m/s. Increased PWVao values were correlated with: smoking [rs2 = 0,343; p < 0,0001], increased BMI [rs2 = 0.190; p = 0.001], presence of hypercholesterolemia [rs = rs2 = 0.192; p = 0.001], presence of hypertriglyceridemia rs2 = 0.285; p < 0,0001], hyperglycaemia [rs = rs2 = 0.194; p = 0.001] and the severity of coronary atherosclerotic lesions [rs2 = 0,270; p = 0,003].

Conclusions: Results of our study shows that in young STEMI patients increased arterial stiffness is correlated with both atherosclerotic risk factors (such as smoking, dislipidemic, BMI) and with the severity of coronary artery disease. Although the majority of the patients had significant atherosclerotic lesions, only a minority has PWVao > 10m/s suggesting that the actual cut-off value of this parameter could be lower in this group of patients.

2D.05 RELATIONSHIP OF CORONARY ATHEROSCLEROSIS WITH ARTERIAL STIFFNESS AND CENTRAL SYSTOLIC BLOOD PRESSURE

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Objective: Arterial stiffness, an independent predictor of cardiovascular disease has been associated with the presence and extent of coronary artery calcification (CAC). We sought to assess the relationship between various hemodynamic parameters and presence of coronary atherosclerotic plaques.

Design and method: In a prospective study 213 subjects (76 men and 137 women, mean age 56 ± 9 years) underwent oscillometry (TensioMed Arteriograph, Medexpert Ltd., Budapest, Hungary), CAC scoring and coronary CT angiography (CTA) (256-slice Brilliance iCT, Philips Healthcare, Best, The Netherlands). The association of aortic pulse wave velocity (PWV), brachial and central systolic blood pressure (SBP) with the presence of calcified and non-calcified plaques was analyzed with multivariate logistic regression (SPSS Statistics 17).

Results: Those presenting with CAC were on average 10 years older (n = 47). Subjects with > 0 total CAC score in comparison to subjects with no CAC had a significantly higher brachial (128 ± 16.3 vs. 122 ± 14 mmHg) and central systolic blood pressure (SBP, 129 ± 22 vs. 121 ± 17 mmHg) and aortic pulse wave velocity (10 ± 2 vs. 8 ± 2 m/s), all p < 0.01. Subjects with any calcified or non-calcified plaques on coronary CTA had a higher brachial SBP, aortic PWV (both p < 0.01) and SBP (p < 0.05). Controlling for sex, age and age-squared in a regression, >0 total CACS (B = 0.983, p < 0.01), any atherosclerotic plaque (B = 1.286, p < 0.001) were both significantly associated with higher aortic PWV, but not with brachial or central systolic blood pressure.

Conclusions: Patients with coronary atherosclerosis have a higher arterial stiffness. However, we did not find a association between arterial stiffness and systolic or central blood pressure. Further studies are warranted to evaluate the predictive value of arterial stiffness in coronary atherosclerotic risk assessment.

2D.06 IN HYPERTENSIVE PATIENTS WITH CHEST PAIN AND NORMAL RESTING ECG THE LOW-COST EXERCISE HIGH-FREQUENCY QRS-ANALYSIS IS COMPARABLE TO THE EXERCISE ECHO

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Objective: The novel exercise computer-assisted high-frequency QRS-analysis (ex-HF/QRS) has demonstrated improved sensitivity and specificity over the conventional ST/ECG-segment analysis (ex-ST/ECG) in the detection of myocardial ischemia. The aim of the present study was to compare the diagnostic value of the validated exercise-Echocardiography (ex-Echo), needing skilled cardiologist, with the novel low-cost ex-HF/QRS, including the conventional ST-segment analysis.

Design and method: A prospective cohort study was conducted in the Emergency Department of a tertiary care teaching Hospital, and validated by the Propensity Score Model. Patients with chest pain (CP), normal resting ECGs, troponins, echocardiography and "intermediate-risk" for adverse coronary events underwent the ex-HF/QRS and ex-Echo. An ST-segment depression >/=2 mV or >/=1 mV when associated with CP were considered as index of ischemia, as a decrease >/=50% in HF/QRS intensity or new wall motion abnormalities on ex-Echo. Exclusion criteria were QRS duration >/=120 milliseconds, poor echo-acoustic window and inability to exercise. The endpoint was the composite of coronary stenoses >50% at angiography or acute coronary syndrome, revascularization and cardiovascular death on the six-month follow-up.

Results: In 270 patients enrolled, the ex-HF/QRS and ex-Echo showed comparable predictive values with p = NS for all comparisons as follows: negative predictive value 97% vs 96%, respectively; sensitivity 63% versus 65%, respectively; specificity 64% versus 83%, respectively. The areas on Receiver Operator Characteristics analysis were comparable (ex-HF/QRS: 0.65, 95% CI 0.51–0.77 vs ex-Echo: 0.66, CI 0.56–0.86; C statistic p = NS). On multivariate analysis, both ex-HF/QRS and ex-Echo were predictors of the endpoint.

Conclusions: In "intermediate-risk" CP patients, the novel ex-HF/QRS was a valuable diagnostic tool in the crowed Emergency Departments. The test might be proposed to avoid additional costly imaging also because it did not require specialized personnel. However, additional study are needed before it can be recommended as a replacement for current techniques.

2D.07 NON-INVASIVE CORONARY FLOW RESERVE MEASUREMENTS IN MICE: A STUDY FOR TIME COURSE ASSESSMENT OF ISOFLURANE-INDUCED VASODILATION

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Objective: Coronary flow reserve (CFR) is a predictor of coronary artery disease. Inhalation of high concentration of the anaesthetic isoflurane (ISO) represents a non-invasive method to induce coronary vasodilation in mice avoiding intravenous

adenosine infusion. However, not consistent protocols, especially concerning the time courses of the anesthesia administration, are reported. Aim of this work was to study the correct time course of coronary artery vasodilation.

Design and method: Non-invasive 40 MHz Doppler ultrasound (VEVO2100, VisualSonics) was used to measure left coronary flow velocity at baseline (B, ISO1%) and at hyperemia (H, ISO2.5%). For six adult male mice (strain C57BL6, 6 months), isoflurane concentration was maintained at 1% for a 6-min period and then increased to 2.5% for the further 30 minutes. PW-Doppler images were acquired every two minutes and Velocity Time Integral (VTI) values were calculated for each time point providing VTI-time curves. Two mathematical models (sigmoid and exponential) were used to fit the data and the model providing the best fitting was used to calculate the mean time needed to reach the 90% of the plateau value (TT90). The obtained TT90 value was used to identify the duration of the high-isoflurane inhalation phase and the experiment was then repeated in ten mice (same strain and age) using the new time duration. CFR measurements (calculated as VTI(H)/VTI(B)) obtained in these conditions (CFRnew) were compared with those measured using a hyperemia duration as found in literature (approximately 4 minutes) (CFR4 min).

Results: The fitting with the sigmoid model provided a lower total Absolute-Sum-of-Squares value than the exponential model (211.6 mm^2 vs 405.1 mm^2). The sigmoid model provided a TT90 measurements equal to 17.4 ± 6.9 minutes. Accordingly, the time point for the maximal flow was then fixed to 20.5 minutes (14 minutes of ISO2.5% after 6 minutes of ISO1%). CFR4 min values (2.10 ± 0.57) amounted to the 78.1% of CFRnew (2.8 ± 0.87) and the Bland-Altman analysis provided a significant bias of 0.69.

Conclusions: These data suggest that short hyperemia durations cause a CFR underestimation; moreover, these results might be useful for the optimization of a standardized protocol for the non-invasive CFR evaluation in mice.

2D.08 COMPARISON OF CENTRAL HEMODYNAMIC INDICES FOR PREDICTING THE PRESENCE AND SEVERITY OF CORONARY ARTERY DISEASE USING A BRACHIAL CUFF-BASED OSCILLOMETRIC DEVICE

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Objective: Various indices of central hemodynamics, such as aortic pulsatility, pulse pressure amplification (PPA) and augmentation index, have been proposed as novel predictors for coronary artery disease (CAD). However, it remains unknown which parameter is most appropriate for risk estimation. The aim of this study was to compare the predictive value of these indices using an easy-to-use, brachial cuff-based oscillometric device.

Design and method: Consecutive 139 patients undergoing elective coronary angiography were enrolled in this study. Augmentation index adjusted to 75 beats/min (Aix@75), brachial and aortic BP indices were measured with Mobil-O-Graph®. We defined fractional pulse pressure (FPP) as pulse pressure (PP) per mean BP and PPA as brachial PP minus aortic PP. Significant CAD was defined as having more than 50% stenosis in major coronary arteries, and the severity was evaluated with Gensini score.

Results: Compared with no CAD patients, CAD patients showed significantly higher PPs and FPPs (brachial PP 48.4 ± 15.5 vs 55.0 ± 16.2mmHg, aortic PP 51.7 ± 19.4 vs 62.2 ± 19.9mmHg, brachial FPP 0.42 ± 0.09 vs 0.49 ± 0.11, aortic FPP 0.46 ± 0.13 vs 0.57 ± 0.14; all $p < 0.05$) and lower PPA (-3.3 ± 8.7 vs -7.2 ± 7.8; $p < 0.05$). Other indices including Aix@75 did not differ significantly. Logistic regression analysis revealed aortic PP, brachial FPP, aortic FPP and PPA each correlated with the presence of CAD after adjustment for potential confounders (odds ratio (OR) [95% confidence interval]: aortic PP per 10 mmHg OR = 1.50 [1.08–2.08], brachial FPP per 0.1 OR = 2.26 [1.30–3.94], aortic FPP per 0.1 OR = 2.15 [1.35–3.42], PPA per 1 mmHg OR = 0.93 [0.87–0.99], respectively). However, when aortic FPP plus either aortic PP, brachial FPP, or PPA were included in the model, only aortic FPP remained significant. These indices were all associated with the severity of CAD expressed as Gensini score (correlation coefficient: aortic PP 0.28, brachial FPP 0.37, aortic FPP 0.42, PPA -0.24; all $p < 0.05$). When compared with PPA using z statistics, the strength of correlation was significantly higher only for aortic FPP (p value: aortic PP 0.72, brachial FPP 0.29, aortic FPP 0.03).

Conclusions: Aortic FPP is most strongly associated with the presence and severity of CAD among hemodynamic indices derived from a brachial cuff-based oscillometric device.

2D.09 THE EFFECT OF IVABRADINE ON SILENT AMBULATORY MYOCARDIAL ISCHEMIA

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Objective: Heart rate (HR) reduction is a powerful method used to reduce myocardial oxygen demand thus reducing the frequency and duration of angina in chronic ischemic heart disease (CIHD). Ivabradine selectively inhibits the Na+/K+ current (If current) in pacemaker cells of the sinoatrial node thus reduces the slope of diastolic depolarization resulting in slower HR without causing other side effect on myocardial contractility or AV conduction. Treating silent myocardial ischemia has a prognostic effect and may improve long term mortality of (CIHD). The effect of Ivabradine on angina frequency was already studied but its effect on silent ambulatory myocardial ischemia (SAMI) has not been reported yet. In this study we report the effect of ivabradine on (SAMI).

Design and method: We enrolled 50 patients with proven stable coronary artery disease (CAD) and at least one episode of ST-segment depression on ambulatory ECG monitoring. All of them were receiving optimal therapy for CIHD. 25 patients were randomized to receive Ivabradine 5–7.5 mg bid. And the other 25 patients received placebo. Ambulatory monitoring was repeated after 4 to 6 months of therapy. The two groups were comparable with respect to baseline characteristics, number of episodes of ST-segment depression, and baseline serum cholesterol levels. Holters were read by a blinded cardiologist.

Results: The Ivabradine group had lower mean HR at study end and experienced a significant reduction in the number of episodes of ST-segment depression compared with the placebo group. ST-segment depression was completely resolved in 9 of 25 patients (36%) in the Ivabradine group versus 3 of 25 (12%) in the placebo group. The Ivabradine group exhibited a highly significant reduction (SAMI) ($P < .001$). By logistic regression, treatment with Ivabradine was an independent predictor of (SAMI) resolution.

Conclusions: Conclusions: Further lowering of HR with Ivabradine can result in reduction or resolution of (SAMI) recorded as episodes of ST-segment depression in ambulatory monitoring of the ECG. A larger study is required to confirm this theory and to see the effect of SAMI reduction on long term mortality of CIHD.

ORAL SESSION

ORAL SESSION 3A

EPIDEMIOLOGY OF HYPERTENSION AND BLOOD PRESSURE CONTROL

3A.01 EFFECTS OF ACUTE EXPOSURE TO HYPOBARIC HYPOXIA AT INTERMEDIATE ALTITUDE ON CONVENTIONAL AND AMBULATORY BLOOD PRESSURE VALUES. DATA FROM THE HIGHCARE-SESTRIERE STUDY

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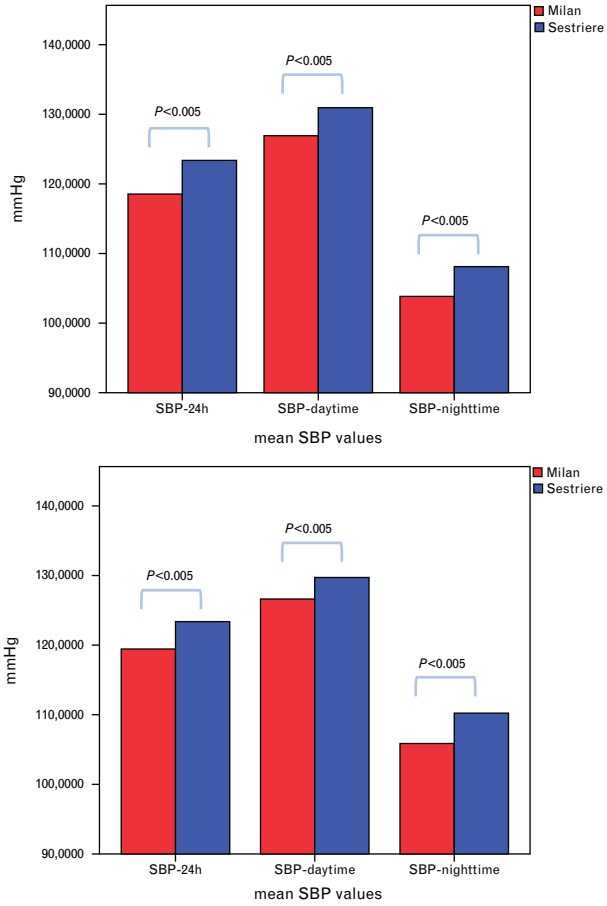
Objective: A blood pressure (BP) rise and sleep disturbances are known effects of high altitude exposure. Most available data have been collected at altitudes >3300m, while the possible effects of moderate altitude (MA) exposure (around 2000 m) are still poorly understood in spite of the fact that such altitude is easily reachable even by subjects suffering from cardiovascular diseases. Aim of HIGHCARE (HIGH altitude CArdiovascular REsearch)-Sestriere study was thus to evaluate the effect of exposure to an altitude of 2035m (Sestriere, Italy) on BP and sleep disturbances.



Design and method: 58 healthy lowlanders were evaluated both at sea level (SL,Milan, Italy) and during acute exposure to MA (2035m, barometric pressure 80% of that at SL). 46 individuals (18 male, 28 females, age 41.52 ± 12.65y) completed the study, having conventional BP measures and 24 h ambulatory BP monitoring (ABPM, validated oscillometric TM-2430 A&D device; measurements every 15 minutes during daytime and 20 minutes during nighttime) performed both at SL and at MA. During both study conditions subjects' daily life behaviour was carefully standardized, only light physical exercise being allowed.

Results: During MA exposure mean 24 h systolic (S) and diastolic (D) BP significantly increased compared to SL ($p < 0.005$), with no difference between day and night (Figure1). This was the case also for mean daytime and nighttime SBP and DBP (respectively, $p < 0.05$) and for heart rate ($p < 0.005$) (Figure1). No statistically significant between-condition differences were found for conventional BP nor for nocturnal BP dipping, and there were no effects of age, gender or BMI. Low sleep quality was reported by 22% of individuals (sleep quality questionnaire), with no correlation between reported sleep quality and BP nocturnal dipping.

Conclusions: Our data offer the first demonstration, in healthy subjects, that exposure to an easy-to-reach MA is associated with an increase in 24 h ambulatory BP. No changes were observed in conventional BP, further emphasizing the superior sensitivity of ABPM in assessing BP response to environmental challenges. Our results may have clinical implications for the protection of cardiovascular patients travelling to such altitude for either leisure or work.

3A.02 PREVALENCE OF HYPERTENSION AND ASSOCIATED FACTORS AMONG RESIDENTS OF IBADAN-NORTH LOCAL GOVERNMENT AREA OF OYO STATE, NIGERIA

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Objective: This study aimed to investigate the prevalence of hypertension and associated factors among the residents of Yemetu community; an urban-slum in Ibadan-North Local Government Area of Oyo State, Nigeria.

Design and method: A descriptive cross-sectional design was used. The study involved 806 respondents aged from 18–90 years from 171 households. They were selected by cluster sampling technique. It was a house-to-house survey. Behavioural risk factors were measured using World Health Organisation (WHO) STEPwise approach to chronic disease risk factor surveillance (STEPS 1 & 2), while physical activities were measured using International Physical Activity Questionnaire (IPAQ). Hypertension was defined according to WHO/International Society for Hypertension citeria (ISH). Data were analysed using descriptive statistics, Chi-square and binary logistic regression tests at $p < 0.05$.

Results: The overall prevalence of hypertension was 33.1% (male 36.8% and female 31.1%). The proportion of self reported hypertension was 11.1%, while 5.1% were currently on anti-hypertensive medication. Prior to the survey, 52.0% had checked their blood pressure within the past 12 months, 29.4% had checked more than a year ago, while 18.6% had never checked. The mean age of the respondents was 38.8 ± 15.6 years. The body mass index of the respondents was 5.2%, 52.0%, 29.5% and 13.3% for underweight, normal, overweight and obese, respectively. Alcohol and tobacco use were found in 11.5% and 3.2%, respectively. The result of binary logistic regression analysis revealed that hypertension was significantly associated with being in age groups 30–49 years (OR 2.258, 95% CI: 1.311 - 3.884), 50 years or more (OR 7.145, 95% CI: 3.644 - 14.011), and being overweight or obese (OR 2.281, 95% CI: 1.022 – 5.088). However, hypertension was inversely associated with being underweight (OR 0.537, 95% CI: 0.395 – 0.832).

Conclusions: This study revealed a high prevalence of hypertension among the inhabitants of Yemetu community, which puts them at risk for cardiovascular disease. These data underscores the need for urgent steps to create awareness and implement interventions for prevention and early detection of hypertension especially among those aged 30 years or more and the overweight/obese.

3A.03 HYPERTENSION IN PATIENTS AFTER LIVER TRANSPLANTATION

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Objective: A cardiovascular diseases are a frequent cause of death of patients after liver transplantation. The aim of the study is to estimate the prevalence of arterial hypertension among patients who underwent liver transplantation and the role of immunosuppressive drugs in the pathogenesis of hypertension in these patients.

Design and method: 91 patients (age 47 ± 12; 33 women, 58 men) after liver transplantation who survived 12 months were analyzed retrospectively. 84 of them completed 24 months follow-up. The statistical analysis was performed using the following tests: χ^2, Spearman's correlation, Mann-Whitney U and multiple regression analysis. The results are presented as means with standard deviation.

Results: One, 12 and 24 months after liver transplantation the prevalence of hypertension were 46%, 56% and 63%, respectively (the difference between 1 and 24 months: p = 0.02). Systolic blood pressure (SBP) and eGFR in above mentioned months were 126 ± 18; 134 ± 20; 136 ± 18 and were 78 ± 34; 75 ± 31; 76 ± 29 respectively. 24 months after transplantation 60 (78%) patients were treated with tacrolimus, 10 (13%) cyclosporine A, 10 (13%) everolimus and 70 (91%) prednisone. Hypertension was found significantly more frequently in patients treated with cyclosporine A than with tacrolimus (p = 0.008) and everolimus (p = 0.02) (100% vs 56% vs 60%, respectively). There were significant correlations between tacrolimus blood concentration and SBP after 24 months (R = 0.29; p = 0.04). Multiple regression analysis performed in the group of patients treated with tacrolimus, with SBP as the dependent variable and eGFR, tacrolimus blood concentration as independent 24 months after liver transplantation showed that SBP significantly depends both on eGFR (p = 0.02) and tacrolimus blood concentration (p = 0.01).

Conclusions: 1. Arterial hypertension occurs in more than 50% of patients after liver transplantation. 2. Calcineurin inhibitors may participate in the high incidence of arterial hypertension in these patients 3. Clinical importance of these findings and the influence on cardiovascular outcome of the liver transplant patients need to be elucidated.

3A.04 OBJECTIVE FOR 2015: 70% OF TREATED AND CONTROLLED HYPERTENSIVE PATIENTS. HOW FAR FROM THIS GOAL WAS FRANCE IN 2014?

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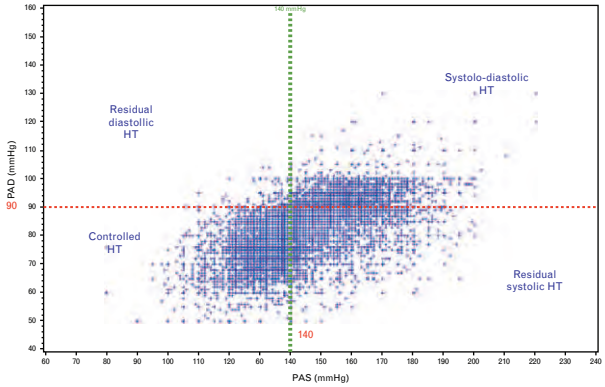
Objective: One of the main objectives of the French plan against stroke is to achieve a goal of 70% of treated and controlled hypertensive patients in 2015. Since 2000, very few registries evaluated the rate of BP controlled patients in general practice. The aim of the PASSAGE registry was to evaluate the rate of BP control in outpatient hypertensive patients attending general practitioners offices.

Design and method: A representative sample of 1000 French practitioners was requested to include the first consecutive 20 hypertensive patients. Controlled hypertension was defined as SBP <140 mm Hg and DBP <90 mm Hg in patients <80 yo and SBP<150 mmHg in patients >80 yo. The recruitment period held from november 2013 to february 2014.

Results: 21278 patients (mean age 66 ± 12 y; 50.7% of males) were included. 14.2% were >80 yo. 47% had treated dylipidemia and 11.6% were active smokers. Monotherapy, dual therapy were used in 48.7% and 31.8% respectively, whereas 3 treatments and more were prescribed in 16.4% of patients. Mean BP was 140 ± 16 / 80 ± 10 mmHg. Although GP's declared that BP goal was achieved 69.6% of patients, only 54.4% of patients strictly fit BP control definition. 73% of patients >80 yo were at goal. The figure demonstrates that the majority of uncontrolled hypertension was due to SBP not at goal.



Conclusions: The PASSAGE registry provides updated data on blood pressure control in general practice in France. The percentage of controlled patients seems stable compared to the most recent surveys in the general population. In addition, the application of a specific threshold for octogenarians explains the satisfactory control rate in this subgroup. The percentage of controlled subjects contrasts with the evaluation of practitioners, which can be explained by optimal ambulatory BP measurements, or more probably by an important therapeutic inertia as suggested by the high percentage of patients on monotherapy. The implementation of updated national recommendations as well as the setup of large-scale assessment tools must continue to evaluate the quality of blood pressure control and to identify barriers to the achievement of national goals.

3A.05 HYPERTENSION AND RISK OF EVENTS ASSOCIATED TO REDUCED EGFR. THE ESCARVAL-RISK STUDY

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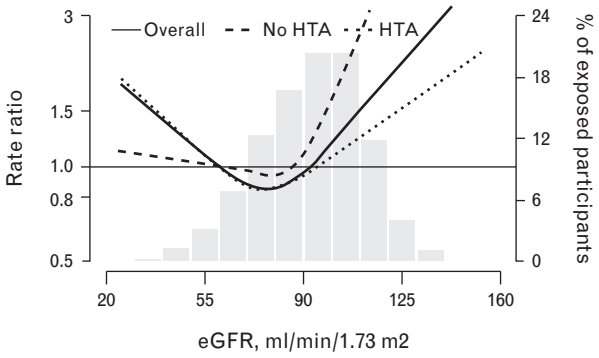
Objective: The objective of the present study was to evaluate the potential impact of hypertension in the increased CVD risk associated with CKD in a population with at least one main CV risk factor (CVRF), hypertension, dyslipidemia or diabetes.



Design and method: 54,620 men and women aged 30 years or older with at least one of main CVRF (hypertension, diabetes mellitus and/or dyslipidemia), who attended for routine health maintenance have been selected. Patients with a history of a previous CVD event were excluded. At the time of inclusion information about CVRF

and their active treatments as well as smoking habit and biochemistry lab values were collected from the EHR. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI. Participants were followed-up for the first episode of hospitalization for myocardial infarction or stroke and all cause of death were collected. Interaction terms for dichotomous eGFR (>=60, <60 ml/min/1.73 m2) with the corresponding indicator variables for subgroups defined by sex, hypertension, diabetes, dyslipidemia, and obesity in separate models were calculated using the Wald test.

Results: 54,620 patients were included. Hypertension was present in 76%, dislipidemia 86%, diabetes in 35.5% and obesity in 41,8%. A total of 7884 (14.4%) patients had eGFR below 60 ml/min/1.73 m2 and among them 1807 (3.3%) 45 ml/min/1.73 m2 or lower. During a time follow-up of 3.2 years, patients years exposure, 960 death were recorded. A significant increment in the risk for total mortality was observed in subjects with eGFR 45 ml/min/1.73 m2 or below adjusted for multiple potential confounders (HR 1.83, 1.28–2.62; CI 95th). In normotensive subjects the risk did not increase below 60 ml/min/1.73 m2 in contrast with the increment in hypertensives. (Figure 1 on the previous page).

Conclusions: eGFR is a prevalent condition in patients with the main CV risk factors. eGFR below <45 ml/min/1.73 m2 increases mortality risk. Hypertension by itself had an important role in the risk of mortality in patients with low eGFR on top of other CV risk factors.

3A.06 LESS THAN HALF OF CITIZENS, AGED 55–64 YEARS, HAD A NORMAL BLOOD PRESSURE IN A DANISH POPULATION. PREVALENCE OF HYPERTENSION USING TELEMEDICALLY TRANSMITTED HOME BLOOD PRESSURE

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Objective: Hypertension is the most important modifiable risk factor for cardiovascular disease. It is debated which method is optimal for diagnosing and treatment monitoring. Home blood pressure (HBP) is prognostically superior to office blood pressure (OBP) and similar to ambulatory BP. We wanted to determine the prevalence of hypertension, well treated, untreated and insufficiently treated, white coat and masked hypertension using HBP with telemedical data transmission in the municipality of Holstebro, Denmark (57.000 citizens).

Design and method: Using the Civil Registration System, we invited all citizens aged 55–64 years to have there OBP and HBP measured using telemedical data transmission for the latter. OBP was the mean of three measurements and an elevated OBP was defined as 140/90 mmHg or more. HBP was measured three times daily on three consecutive days with three measurements on each occasion. HBP was the mean of all measurements on day to and three, and hypertension was defines as 135/85 mmHg or more. Awareness of hypertension was registered using a questionnaire.

Results: We invited 6405 citizens and 3102 were included with twelve or more home BP measurements during day two and three. Group 1: (n = 1464, 47%) had both normal OBP and HBP. Group 2: (n = 838, 27%) had both elevated OBP and HBP indicating lack of treatment. Group 3: (n = 560, 18%) had elevated OBP and normal HBP indicating white coat hypertension. Group 4: (n = 240, 8%) had normal OBP and elevated HBP indicating masked hypertension. Thus, 1078, (35%, groups 2 and 4) were untreated or insufficiently treated and 800 (26%, groups 3 and 4) had wrong diagnosis. Awareness of hypertension were registered in 950 patients (31%) and of those only 467 (49%) had a normal HBP.

Conclusions: One third of the age group 55–64 years had an abnormally high HBP, and one fourth had a wrong diagnosis, either white coat or masked hypertension. Improvements in diagnosing and treating hypertension seem necessary, and telemedically transmitted home blood pressure measurements might by an effective procedure to reach the goal.

3A.07 NIGHT-TIME HEART RATE IS A LONG-TERM PREDICTOR OF MICROALBUMINURIA IN SUBJECTS SCREENED FOR STAGE 1 HYPERTENSION

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Objective: Heart rate (HR) has been found to be associated with target organ damage in hypertension but the predictive capacity of resting HR vs ambulatory HR in longitudinal studies is not well known. We did a prospective study to investigate whether clinic HR and ambulatory HR assessed at baseline were independent predictors of albumin excretion rate (AER) and microalbuminuria (MA) in the early stage of hypertension.

Design and method: The study was conducted in a cohort of 621 white stage 1 hypertensive subjects from the HARVEST never treated for hypertension (mean age 33.8 ± 8.4 years, 449 men). Clinic HR was the average of 6 readings. Clinic HR, daytime HR and night-time HR were included separately in linear (for AER) and logistic (for MA) regressions and were adjusted for baseline logAER, age, gender, body mass index, blood pressure, physical activity, smoking, alcohol consumption, and follow-up time.

Results: During a median follow-up of 8.5 years AER increased from a median value of 5.7 mg/24 h to 7.2 mg/24 h ($p < 0.001$ for log-transformed data), and 42 subjects developed MA (AER > = 30 mg/24 h). In both linear and logistic regressions average night-time HR was an independent predictor of final AER ($p = 0.014$) and MA ($p = 0.007$), whereas clinic HR and daytime HR were not associated with these outcomes (p = NS for both). Night-time HR was 62.6 ± 8.3 bpm in the 579 subjects who did not develop MA and was 66.6 ± 7.7 bpm in the 42 subjects who developed MA ($p = 0.002$). Baseline BMI was another independent predictor of final AER ($p = 0.007$) and final MA ($p = 0.001$) and its inclusion into the models slightly attenuated the association of night-time HR with AER ($p = 0.029$) and MA ($p = 0.016$).

Conclusions: HR is an independent predictor of microalbuminuria in young persons screened for stage 1 hypertension suggesting that the chronic hemodynamic stress related to tachycardia may play a role in the development of renal damage in hypertension. In agreement with previous results, HR measured during sleep seems to be more representative of the overall hemodynamic load on the arteries than HR measured during waking hours or in the doctor's office.

ORAL SESSION

ORAL SESSION 3B
CHILDREN AND ADOLESCENTS

3B.01 PERFORMANCE OF TARGETED SCREENING FOR THE IDENTIFICATION OF HYPERTENSION IN CHILDREN

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Objective: As universal screening of hypertension performs poorly in childhood, targeted screening to children at higher risk of hypertension has been proposed. Our goal was to assess the performance of combined parental history of hypertension and overweight/obesity to identify children with hypertension. We estimated the sensitivity, specificity, negative and positive predictive values of overweight/obesity and parental history of hypertension for the identification of hypertension in children.

Design and method: We analyzed data from a school-based cross-sectional study including 5207 children aged 10 to 14 years from all public 6th grade classes in the canton of Vaud, Switzerland. Blood pressure was measured with a clinically validated oscillometric automated device over up to three visits separated by one week. Children had hypertension if they had sustained elevated blood pressure over the three visits. Parents were interviewed about their history of hypertension.

Results: The prevalence of hypertension was 2.2%. 14% of children were overweight or obese and 20% had a positive history of hypertension in either or both parents. 30% of children had either or both conditions. After accounting for several potential confounding factors, parental history of hypertension (odds ratio (OR): 2.6; 95% confidence interval (CI): 1.8–4.0), overweight excluding obesity (OR: 2.5; 95% CI: 1.5–4.2) and obesity (OR: 10.1; 95% CI: 6.0–17.0) were associated with hypertension in children. Considered in isolation, the sensitivity and positive predictive values of parental history of hypertension (respectively 41% and 5%) or overweight/obesity (respectively 43% and 7%) were relatively low. Nevertheless, considered together, the sensitivity of targeted screening in children with either overweight/obesity or paternal history of hypertension was higher (65%) but the positive predictive value remained low (5%). The negative predictive value was systematically high.

Conclusions: Restricting screening of hypertension to children with either overweight/obesity or with hypertensive parents would substantially limit the proportion of children to screen (30%) and allow the identification of a relatively large proportion (65%) of hypertensive cases. That could be a valuable alternative to universal screening.

3B.02 24-HOUR AMBULATORY CENTRAL BLOOD PRESSURE VARIABILITY AND TARGET-ORGAN DAMAGE IN ADOLESCENTS AND YOUNG ADULTS

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Objective: Some studies suggested that ambulatory blood pressure (ABP) variability may provide useful information beyond that of average ABP levels. This study investigated the relationship between central ABP variability and target-organ damage in young individuals in whom the central-peripheral blood pressure discrepancy might be considerable.

Design and method: Apparently healthy adolescents and young adults referred for elevated blood pressure and healthy volunteers (age 12–26 years) were subjected to: (i) 24-hour monitoring of central ABP using a noninvasive brachial cuff-based oscillometric device (Mobil-O-Graph 24 h PWA); (ii) 24-hour pulse wave velocity (PWV) monitoring (Mobil-O-Graph 24 h PWA); (iii) echocardiographic determination of left ventricular mass index (LVMI); (iv) measurement (ultrasonography) of the common carotid intima-media thickness (IMT). The standard deviation (SD) of ABP (24-hour weighted/awake/asleep), as well as the respective coefficients of variation (CV) were used for assessing variability.

Results: The study included 68 individuals (mean age 18.7 ± 4.7 years, 52 males, body mass index [BMI] 24.5 ± 4.7 kg/m^2, 24 volunteers, 15 with hypertension [24-hour peripheral ABP >=95th percentile for adolescents or >=130/80 mmHg for adults]). LVMI was correlated with 24-hour/awake/asleep central systolic ABP (r=0.50/0.49/0.40, all $p < 0.01$), as well as with 24-hour weighted/awake/asleep SD of central systolic ABP (r = 0.40/0.37/0.30, all $p < 0.05$), whereas no association was observed for the respective CV. IMT was correlated with 24-hour/awake/asleep central pulse pressure (PP) (r = 0.37/0.33/0.27, all $p < 0.05$), 24-hour weighted/awake/asleep SD of central PP (r = 0.43/0.40/0.36, all $p < 0.01$) and the respective CV (r = 0.28/0.26/0.25, all $p < 0.05$). Regarding 24-hour PWV, there was a significant association with 24-hour/awake/asleep central systolic ABP (r = 0.94/0.88/0.84, all $p < 0.001$) and 24-hour weighted/awake/asleep SD of central PP (r = 0.48/0.51/0.25, all $p < 0.05$), but not with the respective CV. In multivariate regression analyses (independent variables: age, gender, BMI, central ABP and SD/CV of ABP values), LVMI and 24-hour PWV were determined by BMI, age, and 24-hour central systolic ABP, and IMT by male gender and 24-hour weighted SD of central PP.

Conclusions: In young individuals, 24-hour central ABP variability appears to be associated only with early carotid damage when accounting for ABP levels, whereas LVMI and PWV are mainly determined by average ABP levels.

3B.03 BLOOD PRESSURE SPECIFITIES IN PREADOLESCENT YOUNG ELITE FOOTBALLERS

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Objective: Exaggerated blood pressure (BP) response during exercise is associated with increased risk of worsening hypertension in normotensives, as well as in athletes with high normal blood pressure. To date, conflicting data have been reported concerning the nature (physiologic versus pathologic) remodeling in athletes. Data regarding preadolescents are limited.. Objective: The aim of the study was to evaluate the influence of the rest and maximal exercise BP values to the cardiac dimensions in professional elite young preadolescent footballers.

Design and method: Ninety-four highly trained male footballers (mean aged 12.85 ± 0.84) competing in our Football League (at least 7 training hours/week) and 47 age-matched healthy male controls were enrolled in the study. They were screened by ECG and echocardiography at a tertiary referral cardio centre. The control group had sedentary life style (less than 2 training hours/week). Echocardiographic parameters were obtained by standard measurements.

Results: All participants had normal blood pressure (BP). Mean BP in footballers was 109.95+/-65.75 and mean BP in controls was 108.19+/-60.75. There was no difference in SDP between these two groups ($p > 0.05$), but footballers had significantly higher values of the DBP ($p < 0.01$).
The data indicate significant increases in absolute values of LV dimensions, but especially in the dimensions of the aortic root size ($p < 0.001$) in preadolescent professional footballers compared with the values expected for age-matched controls, whereas there are no differences in absolute values of ventricular septal and posterior wall thickness, LV wall thickness and LVM ($p > 0.05$). However, regarding aortic root dimensions there is a significant difference even in absolute values. ($p < 0.001$).
No significant correlations between LVMI and rest values of BP were detected. Dimensions of the left atrium and aortic root however significantly correlated with

SBP and DBP ($p < 0.01$). However, significant correlations were described between LVMI and maximal systolic BP ($p < 0.01$) as well as diastolic BP ($p = 0.047$).

Conclusions: Elite preadolescent footballers had significantly higher DBP compared to sedentary controls. Left atrial and aortic root dimensions correlate with resting SBP as well as DBP, while LWMI correlates with maximal SDP and maximal DBP.

3B.04 IMPAIRED ENDOTHELIAL VASODILATOR FUNCTION IN NORMOTENSIVE ADOLESCENTS WITH EXAGGERATED EXERCISE BLOOD PRESSURE RESPONSE

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Objective: To evaluate endothelial function in normotensive adolescents with exaggerated blood pressure response during exercise.

Design and method: This was a cross-sectional study conducted with 157 high school students (80 boys and 77 girls), aged between 13 to 18 years old (15.0 ± 1.6), normotensive, without smoking habits, non-obese, normolipidemic and normal glucose. An exaggerated blood pressure response was defined as a systolic pressure rise of more than 70 mm Hg, during the treadmill test with Bruce protocol. The endothelial function was assessed through endothelium-dependent vasodilation with reactive hyperemia test by high-resolution vascular ultrasound. The cohort was split into quartiles, according to flow-mediated dilation (FMD). The study comparison was made between the lowest quartile versus the rest of them.

Results: An exaggerated blood pressure response was observed in 13 adolescents (8.3%), 10 (13.0%) females and 3 (3.8%) males ($P = 0.036$). For adolescents in the lowest FMD quartile, a higher prevalence of exaggerated blood pressure response was observed, in comparison with the others quartiles (17.5 vs 5.1%, respectively; $P = 0.014$). Even after adjustment for factors known to affect endothelial function, the logistic regression analysis revealed that an exercise-induced hypertension was a predictor of impaired FMD (OR = 3.924; I.C. 95%: 1.233–12.488).

Conclusions: Normotensive adolescents with exercise-induced hypertension have impaired endothelium-dependent vasodilation. Exercise blood pressure may thus be a useful marker of nitric oxide bioactivity, and hence an important cardiac prognostic factor.

3B.05 COMPARISON OF INCIDENT HYPERTENSION, OVERWEIGHT AND OBESITY IN A REPRESENTATIVE POLISH JUNIOR HIGH-SCHOOL POPULATION IN 2005 VS. 2014

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Objective: Body fat excess and incident hypertension are well recognized risk factors for cardiovascular morbidity and mortality in adults. At the same time, there is growing recognition of the increasing prevalence of these risk factors in younger populations regardless the implementation of several nation-wide preventive measures. The aim of our study was to compare incident hypertension and body mass status in a representative Polish junior high school population in the year of 2005 and 2014.

Design and method: We recruited consecutive junior high-school students aged between 14 and 16 years old in urban-rural Gniewkowo County in central part of Poland. In the year of 2005 a total of 655 students and 438 students in 2014 would meet age-based inclusion criterion. Measurements included anthropometric assessment eg. height, weight, and body mass index (BMI) and office blood pressure measurements (three measurements, which allowed for averaging of the second and the third). Both hypertension and obesity was diagnosed if the result was equal or greater to 95 percentile. Analogically, the prehypertension state and overweight were determined with 85 percentile. The percentiles distribution in Polish adolescent population was adopted from OLAF study (www.olaf.czd.pl).

Results: In 2005 a total of 631 students and corresponding 418 students in 2014 completed the study which accounted for 93% and 95% response-rates, respectively. There was a comparable occurrence of hypertension in two time-points of the study (17.6% vs.17.5% in 2005 and 2014, respectively), however, a significant increase in prehypertension state was noted in 2014 (14.1%) vs. 2005 (8.6%); $P<0.01$. Accordingly, the percentage of junior high-school population with abnormal BMI (>25 kg/m2) was significantly higher in 2014 (11% vs. 22% in 2005 and 2014, respectively; $P<0.01$).

Conclusions: There is an alarming trend in the incidence of prehypertension state and an increased body weight in junior high-school population in the last decade in Poland.

3B.06 CARDIOVASCULAR RISK IN PEDIATRIC RECIPIENTS OF STEM CELL TRANSPLANTATION

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Objective: Different from recipients of a solid organ transplant, stem cell transplantation (SCT) recipients do not receive long term immunosuppressive treatment that may cause renal and cardiovascular damage. Despite this fact, adult SCT recipients have been shown to be at increased cardiovascular risk supposedly due to cardiotoxic conditioning treatment. We analyzed blood pressure (BP) and markers of cardiovascular risk in pediatric SCT recipients.

Design and method: We have currently investigated 41 pediatric recipients of allogeneic SCT. Patients were 6–25 years old and had been transplanted between 3 months to 10 years ago. We assessed casual BP, aortal pulse wave velocity (PWV) and carotid intima-media thickness (IMT). In 32 patients, we also performed ambulatory BP measurements (ABPM). All values were normalized for age and expressed as SDS values.

Results: None of the patients was hypertensive (> 95. percentile for gender, age, height) based on casual BP measurements at time of the investigation; with two patients receiving antihypertensive therapy. However, hypertension was discovered in 6 patients by ABPM. Mean PWV was 0.2 ± 1.09 SDS adjusted for age; 1 patient showed PWV values elevated > 95. percentile. Mean IMT was 1.64 ± 1.00 SDS adjusted for age; 8 patients (47%) showed IMT values > 95. percentile.

Conclusions: Pediatric SCT recipients showed a high incidence of masked hypertension, i.e. hypertension detected only by ABPM in presence of normal casual BP values. The cardiovascular risk induced by masked hypertension is similar to the risk seen with true hypertension (detected also by casual BP). Accordingly, IMT reflecting atherosclerotic changes was prominent in these patients. In conclusion, ABPM should be performed routinely in SCT recipients to detect masked hypertension.

3B.07 MID-REGIONAL PRO-ATRIAL NATRIURETIC PEPTIDE AND BLOOD PRESSURE IN ADOLESCENTS: EFFECT OF GENDER AND PUBERTAL STAGE

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Objective: To study the relationship between blood pressure, circulating natriuretic peptide concentrations, gender, and pubertal stage in generally healthy adolescents.

Design and method: Cross-sectional study of 15-year-old females and males ($n = 335$) from the Danish site of the European Youth Heart Study. Blood pressure was measured using a standardised protocol, sexual maturity was assessed according to Tanner's stages, and as a surrogate for atrial natriuretic peptide, we measured mid-regional pro-atrial natriuretic peptide in plasma.

Results: Compared with boys, girls had lower systolic blood pressure (mean ± standard deviation: 109.6 ± 9.9 mm Hg vs. 116.9 ± 11.4 mm Hg, $P < 0.0001$) and higher plasma mid-regional pro-atrial natriuretic peptide concentrations (median (interquartile range): 42.1 pmol/L (31.9–50.2) vs. 36.6 pmol/L (30.6–44.9), $P = 0.0046$). When female adolescents were further subdivided according to Tanner's stages, there were no differences in blood pressure and plasma mid-regional pro-atrial natriuretic peptide concentrations between post-pubertal and pubertal girls ($P > 0.17$). In contrast after similar subdivision, post-pubertal boys had higher systolic blood pressure (mean ± standard deviation: 117.7 ± 11.7 mm Hg vs. 111.4 ± 7.9 mm Hg, $P = 0.029$) and lower plasma mid-regional pro-atrial natriuretic peptide concentrations (median (interquartile range): 36.2 pmol/L (30.6–43.1) vs. 46.4 pmol/L (30.3–51.1), $P = 0.043$) compared with pubertal boys.

Conclusions: Given their higher systolic blood pressure, boys had lower than expected plasma concentrations of mid-regional pro-atrial natriuretic peptide com-

pared with girls, and given their higher systolic blood pressure, post-pubertal boys had lower than expected plasma concentrations of mid-regional pro-atrial natriuretic peptide compared with pubertal boys. Therefore, our study adds to the growing body of evidence to suggest that in healthy individuals a lower circulating amount of atrial natriuretic peptide, resulting in diminished vasodilation and natriuresis, leads to higher blood pressure. Furthermore, our study provides further evidence to suggest that testosterone lowers circulating atrial natriuretic peptide concentrations, and thereby our study offers one possible explanation of why boys and younger men have higher blood pressure and higher risk of hypertension compared with girls and younger women.

ORAL SESSION

ORAL SESSION 3C
BLOOD PRESSURE MEASUREMENT

3C.01 ADVERSE PROGNOSTIC VALUE OF PERSISTENT OFFICE BLOOD PRESSURE ELEVATION IN WHITE COAT HYPERTENSION

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Objective: Stratification of cardiovascular (CV) risk is of fundamental importance in white coat hypertension (WCH) to identify individuals in need of closer follow up and perhaps antihypertensive drug treatment.

Design and method: In subjects representative of the general population of Monza (Italy), the risk of CV and all-cause mortality was assessed over 16 years in stable and unstable WCH individuals, i.e, those in whom ambulatory BP normality was associated with a persistent or non persistent office BP elevation at two consecutive visits, respectively. Data were compared with those from an entire normotensive group, i.e ambulatory and persistent office BP normality.

Results: Compared to the normotensive group, the risk of CV and all cause death was not significantly different in unstable WCH, whereas in stable WCH the risk was increased also when data were adjusted for baseline confounders, including ambulatory BP(hazard ratio 12.39 p=0.0021 for CV, and 1.91 p=0.0178 for all cause death).At a multivariable analysis, office BP was among the factors indipendently predicting death, and results were superimposable with use of Monza population- and guidelines-derived cutoff values for ambulatory BP normality (125/79 and 130/80 mmHg, respectively).

Conclusions: Thus, only when office BP is persistently elevated does WCH reflect the existence of an abnormal long term mortality risk. This means that in WCH office BP is prognostically relevant and that repeated collection of office BP values should be regarded as necessary.

3C.02 IN WHITE COAT HYPERTENSIVES CENTRAL PRESSURE AND HEMODYNAMIC VALUES ARE MORE CLOSE TO NORMOTENSIVES THAN TO TREATED HYPERTENSIVES FOR SIMILAR AGE, 24-H AND NIGHTTIME PRESSURES

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Objective: It is controversial whether subjects with white coat hypertension (WCHT) have hemodynamic and structural abnormalities versus normotensives (NT) and hypertensives (HT). Patterns of nighttime BP as non-dippering = ND and data from central hemodynamics/central pressures (pulse wave velocity, PWV and augmentation index (AIx) estimating aortic wave reflection reflects cardiovascular prognosis.

Design and method: We compared PWV, AIx, augmentation pressure (AugP) and pulse pressure amplification (PPA) from aortic wave, between NT (n = 175), WCHT (n = 315) and treated HT (n = 691) all with 24 h BP < 130/80 and nighttime BP < 120/70 mm Hg i.e normal nighttime BP values. Groups were compared separately for 24 h Systolic BP < 120 mm Hg and between 120–129 mm Hg, after adjustment (ANCOVA) for age, gender, BMI and diabetes.

Results: The percentage of ND was 40.8% in NT, 31.5% in WCHT and 38.3 in HT (χ^2p = 0.048). For 24 h SBP < 120 mmHg aortic stiffness was higher in HT (n = 306, PWV = 10.8 + 2.5 m/s and AASI 0.32 + 0.17, p < 0.045) than in WCHT (n = 75, PWV = 10.0 + 2.8 m/s and AASI 0.27 + 0.13) and NT (n = 109, PWV = 9.7 + 2.2 m/s and AASI 0.26 + 0.16); AugP and AIx were higher (p < 0.01) in HT (12.5 + 8.1 mmHg and 29.7 + 14.1) than in WCHT (10.9 + 7.5 mmHg and 22.9 + 15.7) and NT (10.7 + 6.2 mmHg and 24.3 + 12.3). For 24 h SBP 120–129 mm Hg aortic stiffness was higher in HT (n = 494, PWV = 10.9 + 2.7 m/s and AASI 0.36 + 0.15, p < 0.01) than in WCHT (n = 241, PWV = 9.7 + 2.4 m/s and AASI 0.29 + 0.17) and NT (n = 66, PWV = 9.3 + 2.0 m/s and AASI 0.28 + 0.16); AugP and AIx were higher (p < 0.01) in HT (14.9 + 8.5 mmHg and 29.5 + 11.7) than in WCHT (12.1 + 8.2 mmHg and 26.0 + 14.9) and NT (12.3 + 6.9 mmHg and 27.0 + 12.8).

Conclusions: For similar age, gender distribution, and 24 h and nighttime BP the values of aortic stiffness, central aortic pressures and wave reflection of subjects with WCHT are more close to those of normotensives than to those of treated HT reinforcing the concept that WCHT may be a much more benign condition than treated true hypertensive patients for similar 24 h and nighttime BP levels.

3C.03 OPTIMAL DURATION OF HOME BLOOD PRESSURE MEASUREMENTS FOR THE DIAGNOSIS OF ARTERIAL HYPERTENSION: A PROSPECTIVE MULTICENTER STUDY

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Objective: The optimal measurements duration and cut off values for home blood pressure monitoring (HBPM) are not well defined for the first diagnosis of hypertension. In this study, we compare three measurement duration protocols (3 day, 5 day and 7day) of HBPM considering 24 h ambulatory blood pressure monitoring (ABPM) as a reference standard for the diagnosis of hypertension.

Design and method: Two hundred and sixty six subjects who are suspected to have hypertension in office BP were completed to 24 h ABPM and to 7 days HBPM protocol from 4 university hospitals. HBPM protocol consists of three measurements taken 2 h in waking up (between 7:00 and 9:00 a.m.) and three measurements taken before sleep (between 9:00 and 11:00 p.m.) for 7 days. Hypertension was defined as BP more than 130/80 mmHg for ABPM.

Results: The area under the ROC curve (95% confidence interval) was 0.801 (0.735–0.867) for the 3-day measurements, 0.787 (0.719–0.856) for the 5-day measurements, and 0.789 (0.720–0.859) for the 7-day measurements for the diagnosis of hypertension. There were no significant difference of intraclass correlation coefficients of systolic and diastolic blood pressure between measurement duration protocols and ABPM. Bland–Altman plots showed smaller and random dispersion for the 3-day HBPM measurements. Optimal cut off values of 3 day HBPM measurements by Youden index were 132.1 mmHg in systolic BP (sensitivity: 70% and specificity: 72%) and 81.8 mmHg in diastolic BP (sensitivity: 88% and specificity: 59%).

Conclusions: A 3-day protocol of HBPM has not inferior accuracy than a 5-day and 7-day measurement of HBMP for the diagnosis of hypertension considering ABPM as a reference. Optimal BP threshold values of the 3 day HBPM protocol are lower than HBPM values of current guideline (135/85mmHg).

3C.04 THE EFFECT OF HEART RATE ON AMBULATORY PULSE PRESSURE IS SENSITIVE TO THE VARIATION OF ARTERIAL STIFFNESS WITH PRESSURE

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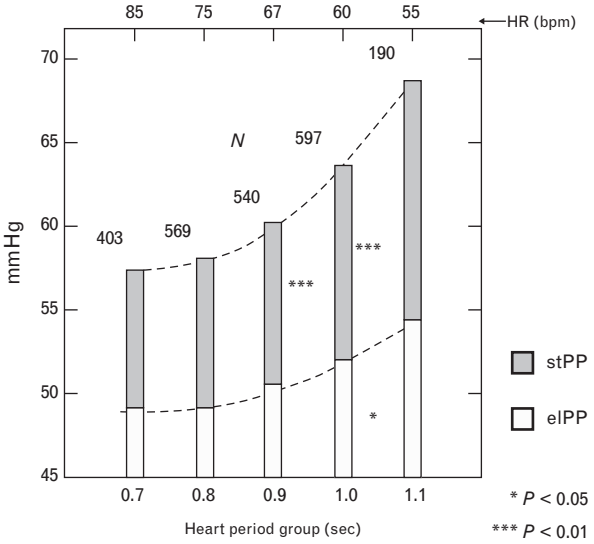
Objective: We have previously shown that given repeated blood pressure (BP) measurements the mean pulse pressure (PP) can be expressed as a sum of two components: one corresponds to purely elastic artery with constant stiffness (elPP) and the other, to the tendency of arteries to stiffen at elevated pressures (stPP). Prognostic significance was demonstrated only for stPP in hypertensive patients with lower-than-median heart rate (HR). In the present work we investigated the HR dependence of these PP components.



Design and method: Given 24-hour ambulatory BP measurements (ABPM) elPP and stPP were determined from the ratio between the variability of systolic BP (SBP) and diastolic BP (DBP) following previously described procedure. The effect of HR on PP, elPP and stPP was investigated by ANOVA taking for convenience, as the factor, grouped values of heart period (HP, equals 60/HR) with covariates adjustment for age, gender, body mass index, treated hypertension and diabetes, and SBP and HR dipping, and applying post-hoc comparisons.

Results: ABPM records of 1,999 hypertensive patients were analyzed [age 56 ± 16 years, 55% women, 60% on medication and 9% diabetes, average BP 139/79 mmHg and HR 71 beats per minute (bpm)]. HP grouped values 0.7;0.8;..,1.0;1.1 sec corresponded to HP <0.75;0.75–0.85;. . .,0.95–1.05; > 1.05 sec, respectively. Mean ± SD of PP, elPP and stPP were 60 ± 14, 50 ± 10 and 10 ± 8 mmHg. Both PP components increased for greater HP, i.e. lower HR (see figure). The absolute differences in PP, elPP and stPP between the first-to-last HP-groups were 11.3, 5.2 and 6.1 mmHg (P<0.00001 for all) and % difference/mean were 19%, 10% and 61%, respectively. The most significant changes in PP components occurred in the slow HR range (see figure). A similar analysis by ANOVA showed gradual DBP decrease by 11 mmHg (14%, P < 0.00001) and a SBP reduction by 4 mmHg (3%, P = 0.05).

Conclusions: Slower heart rate in hypertensive patients is accompanied by greater ambulatory pulse pressure, largely contributed by the tendency of arteries to stiffen at elevated pressures, and lower diastolic pressure, probably caused by the prolonged pressure decay during the longer diastole accompanied by greater stroke volume.

3C.05 DIAGNOSTIC AGREEMENT OF THE EUROPEAN SOCIETY OF HYPERTENSION HOME BLOOD MONITORING SCHEDULE WITH AMBULATORY BLOOD PRESSURE MONITORING IN UNTREATED AND TREATED SUBJECTS

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Objective: To assess the diagnostic performance of the European Society of Hypertension (ESH) minimum (3-day) and full (7-day) home blood pressure monitoring (HBPM) schedule compared to ambulatory blood pressure monitoring (ABPM) in detecting hypertension phenotypes in untreated and treated subjects.

Design and method: 638 adults attending a hypertension clinic (mean age 53.7 ± 10.9 years, men 56.4%, untreated 66%) had measurements of clinic blood pressure (CBP) (3 visits, triplicate measurements), HBPM (7 days, duplicate morning and evening measurements) and 24-hour ABPM within 6 weeks. The diagnostic accuracy of 3-day and 7-day HBPM schedules was assessed by taking ABPM as reference.

Results: Using the day 2–7 HBPM schedule and taking awake ABPM as reference, sustained hypertension, masked hypertension phenomenon and white coat phenomenon were diagnosed in 49.2/8.3/8.3% of the participants respectively. The sensitivity, specificity, positive and negative predictive value of HBPM in detecting sustained hypertension were 91/77/90/78% respectively (agreement 87%, kappa 0.68) in untreated and 87/93/83/95% (agreement 92%, kappa 0.79) in treated subjects; masked hypertension phenomenon 66/98/78/96% (agreement 94%, kappa 0.68) in untreated and 56/86/57/88% (agreement 80%, kappa 0.41) in treated subjects; white coat phenomenon 41/93/43/92% (agreement 87%, kappa 0.35) in untreated and 68/96/74/94% (agreement 92%, kappa 0.66) in treated subjects. In untreated subjects a 3-day schedule provided similar agreement with ABPM as the 7-day schedule for diagnosing hypertension phenotypes, whereas in treated the diagnostic agreement was improved when including measurements beyond the third day. In untreated subjects discarding the first HBPM day had no impact on the diagnostic agreement with ABPM, whereas in treated there was a small improvement in the agreement. Using 24-hour instead of awake ABPM gave marginally superior agreement with HBPM.

Conclusions: In both untreated and treated subjects the minimum HBPM schedule (3-day) recommended by the ESH appears to have comparable diagnostic agreement with ABPM as the full 7-day schedule. Discarding the first day seems to have no impact in untreated subjects, whereas in treated it slightly improves the diagnostic performance.

3C.06 EMOTIONAL INTELLIGENCE AND PSYCHOLOGICAL STATUS WERE RELATED WITH WHITE COAT EFFECT AND MEAN AMBULATORY BLOOD PRESSURE LEVELS IN PATIENTS WITH ARTERIAL HYPERTENSION

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Objective: The aim of our study was to determine relationship between emotional intelligence (EI), psychological status (PS) and mean ambulatory blood pressure monitoring (ABPM) level, white coat effect (WCE) in untreated patients with arterial hypertension (AH).

Design and method: We analyzed 150 ambulatory blood pressure monitoring (ABPM) data of AH patients without serious concomitant diseases. ABPM monitor (Spacelabs 90207) was applied after the washout period. We defined daytime period as 8.00–22.00 (BPd), nighttime – 0.00–6.00 (BPn). After ABPM session patients completed the PS and EI questionnaire: "Minnesota Multiphase Personality Inventory"(MMPI) and "EmIn Questionnaire (by Lyusin D.). We assessed following EmIn scale scores: I - emotion self-awareness; II- management of one's own emotions; III - control of emotional expression; IV - understanding others' emotions; V - management of others' emotions. We used Spearman Partial Coefficient for correlation (r) analysis adjusted for age, sex and duration of AH.

Results: The mean daytime systolic BP (SBP) was 139.1 ± 12.7, diastolic (DBP) - 83.1 ± 9.9 mm Hg (M ± SD). We found the following correlations (p > 0.05): 1) 9 MMPI scale scores (energy, optimism, good mood) with WCE for SBP (r = -0.28) and mean clinical SBP (r = -0.25); 2) III scale scores (control of emotional expression) with WCE for DBP (r = -0.24); 3) I scale scores (emotion self-awareness) with mean clinical SBP (r = 0.27); 4) IV scale scores (understanding others' emotions) with mean clinical DBP and SBP (r = 0.34, r = 0.31) and with mean ambulatory DBP and SBP. For mean 24 hours SBP, SBPd r = 0.25 and r = 0.25, for 24 hours DBP, DBPd, DBPn r = 0.30, r = 0.29, r = 0.24 respectively.
Energy, optimism, good mood (9 MMPI scale scores) and good emotion self-control levels (I scale scores) had a negative correlation with WCE levels and mean clinical SBP. Perception of own or other people's emotions (II and IV scale scores) positively correlated with levels of clinical and ambulatory BP.

Conclusions: Energy, optimism, good mood and good emotion self-control in AH patients at the clinic may reduce WCE and mean clinical SBP levels. Excessive perception of their own or other people's emotions (II and IV scale scores) can lead to increased clinical and ambulatory BP levels.

3C.07 ARE THE PHYSICIANS RELUCTANT TO PRACTICE TELEMEDICINE IN HYPERTENSION?

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Objective: The high number of patients with uncontrolled hypertension is still a public health pattern. The e-health contains all electronic health services used in order to improve communication between all the different actors. In arterial hypertension, few data exists on the possibilities: 1/ for patients to easily e-transfer their results of home blood pressure measurement (HBPM); 2/ for practitioners to receive and assess these HBPM results. Furthermore, physician's reluctance is often reported as a constraint for telemedicine development. Thus, we aimed to collect data on technical equipment of physicians, and on their expectations about this new way of relationship.

Design and method: 57 physicians, hypertension specialists (36 ± 8 years old, 56% men, mostly (88%) hospital practitioners) completed a self-administered questionnaire.

Results: The prevalence of technical equipment is summarized in Table 1. 77.1% of physicians thought that telemedicine could improve the control of hypertension, 29.8% thought they could provide less frequent consultations to their patients and

24.5 % that HBPM information would contribute to the fight against inertia. 83.2% of physicians would agree that HBPM data be transferred to a non- medical staff, a nurse in most cases (59.5%). Finally, while 89.5% of physicians declared they support the development of telemedicine in their daily practice, 100% of them found 3 kinds of "limits" to this exchange method. The main obstacles were: budget (49%), lack of legal frame (43%), medical reluctance (42%), difficulties in accessing or in mastering informatics tool (38.5%), confidentiality (28%), absence of direct benefit (21%), patient reluctance (21%).

Table 1

	Physicians (n=57)
Mobile phone	53 (93%)
Smartphone	53 (93%)
- With Bluetooth	44 (77%)
- With Internet Access	53 (93%)
- With medical applications	37 (65%)
Digital tablet	28 (49%)
Laptop	55 (96%)
Desktop	42 (81%)
Internet at home	56 (98%)
Box with Wi-Fi at home	56 (98%)
Acceptance of transferring medical data via Internet from mobile devices	49 (86%)

Conclusions: The equipment of physicians in home or mobile devices appears no longer an obstacle for the development of a program dedicated to telemedicine. The majority of medical practitioners working in specialized hypertension department agreed with Internet e-transfer of HBPM data, including paramedics. However, all physicians highlighted various obstacles to its expansion: technical support, lack of legal frame, and financial limits.

3C.08 24H CENTRAL BLOOD PRESSURE AND PULSE WAVE VELOCITY MONITORING IN NORMOTENSIVE, HYPERTENSIVE, WHITE COAT HYPERTENSION AND MASKED HYPERTENSION YOUNG ADULTS

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Objective: To investigate CBP and PWV in 24 hours, awake and sleep periods in individuals 18 to 50 years old classified according to the behavior of office BP and 24 h monitoring brachial BP.

Design and method: A total of 104 subjects (60 females (57.7%) and 44 males (42.3%)), 48 (46.2%) individuals 18–35 yo and 56 (53.8%) individuals 36–50 yo. Exclusion criteria were: use of antihypertensive drugs, body mass index > =35 kg/m2, eGFR < 60 ml/min, diabetes, and smoking. All were submitted to clinical and laboratory evaluation, measurement of office BP with oscillometric sphygmomanometer OMRON, model HEM-705CP, and 24 h brachial BP, CBP, Augmentation Index (AIx) and PWV monitoring with Mobil-O-Graph equipment (DINA MAP cardios - ESI GmbH, Stolberg, Germany). They were classified in normotensives (N), hypertensives (H), WCH and MH, according to the presence or not of abnormal BP in office BP and/or awake brachial BP.

Results: Study population was 36.99 ± 8.53 yo, and BMI mean was 25.80 ± 3.82 kg/m2. There were 56.7% true normotensives (N), 13.5% true hypertensives (H), 19.2% WCH, and 10.6% MH. Systolic CBP means (24 h, awake and sleep periods) were different among the groups. For 24 h and awake periods, group H showed higher means than N and WCH, but MH did not differ from H ($p < 0.001$). For sleep period, H presented higher means than N. WCH and MH were not different from H ($p = 0.001$). 24 h and sleep diastolic CBP presented higher means in group H than in group N ($p = 0.001$), although WCH and MH groups did not differ from H. For awake diastolic CBP, higher means were observed in group H than N, WCH and MH ($p < 0.001$). Group H showed higher PWV means in 24 h ($p = 0.003$) and awake ($p = 0.002$) periods than group N; WCH and MH were not different from H. MH showed higher sleep PWV mean than N ($p < 0.007$).

Conclusions: MH and WCH showed intermediate 24 h, awake and sleep CBP and PWV means, between normotension and hypertension, and most comparisons did not show differences to true hypertension. These results suggest that central BP and PWV could contribute to risk stratification in WCH and MH young adults.

3C.09 STRATEGIES FOR CLASSIFYING PATIENTS BASED ON OFFICE, HOME AND AMBULATORY BLOOD PRESSURE MEASUREMENT

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Objective: Hypertension guidelines propose home (HBP) or ambulatory (ABP) blood pressure monitoring as indispensable after office measurement (OBP). However, whether preference should be given to HBP or ABP remains undetermined.

Design and method: We recruited 831 consecutive patients (mean age, 50.6 years; 49.8% women) referred for ABP monitoring to our clinic, if they had never taken (~90%) or had discontinued antihypertensive medication for at least 2 weeks (~10%). SpaceLabs 90217 monitors were programed to obtain 24-h ABP recordings. OBP was measured at three visits at 1 week intervals using the Omron HEM-7051 device. Patients were requested to measure their HBP three times in the morning and three times in the evening at 1 minute intervals during 7 consecutive days. We applied hypertension guidelines for cross-classification of patients based on OBP, HBP and ABP into normotension (NT) or white-coat (WCH), masked (MH) or sustained (SH) hypertension. Aortic pulse wave velocity was measured by the SphygmoCor system and a first-morning urine sample was collected for the measurement of urinary albumin-to-creatinine ratio.

Results: Based on OBP and HBP, the prevalence of NT, WCH, MH and SH was 442 (53.2%), 61 (10.3%), 166 (20.0%) and 162 (19.5%), respectively. Using daytime ABP (30 readings from 8 AM to 6 PM) instead of HBP, confirmed the cross-classification based on OBP and HBP in 575 patients (69.2%), downgraded risk from MH to NT (n = 24) or from SH to WCH (n = 9) in 33 (4.0%), but upgraded risk from NT to MH (n = 179) or from WCH to SH (n = 44) in 223 (26.8%). Analyses based on 24 h ABP were confirmatory. In adjusted analyses, both the urinary albumin-to-creatinine ratio (+20.6%; CI, 4.4–39.3) and aortic pulse wave velocity (+0.30 m/s; CI, 0.09–0.51) were higher in patients who moved up to a higher risk category. Both indexes of target organ damage were positively associated ($P < 0.008$) with the odds of being reclassified.

Conclusions: For reliably diagnosing HT and starting treatment, OBP should be followed by ABP monitoring. Using HBP instead of ABP misses the high-risk diagnoses of MH or SH in over 25% of patients.

ORAL SESSION

ORAL SESSION 3D
BLOOD PRESSURE VARIABILITY

3D.01 VISIT-TO-VISIT BLOOD PRESSURE VARIABILITY INCREASES RISK OF STROKE OR CARDIAC EVENTS IN PATIENTS GIVEN VALSARTAN OR AMLODIPINE IN THE VALUE TRIAL

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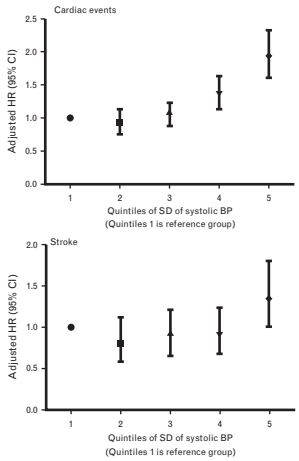
Objective: High blood pressure variability has been associated with an increased risk of cardiovascular events. We aimed to assess if increased visit-to-visit variability in systolic blood pressure increases the risk of stroke or cardiac events (fatal/non-fatal coronary or heart failure events) in the VALUE population.

Design and method: The VALUE trial was a randomised-controlled, double-masked investigation of valsartan versus amlodipine in patients 50 years or older with hypertension and high risk of cardiovascular events. Mean follow-up time was 4.2 years. We calculated the standard deviation (SD) of mean systolic blood pressure from visits from 6 months onward, excluding patients with less than 2 visits, or stroke or cardiac events during the first 6 months. In the pooled treatment arms, we grouped SD in quintiles and compared the risk of stroke or cardiac events in the highest and the lowest quintile, using a Cox regression model, adjusting for a number of prognostic variables, including randomised treatment and mean BP from 6 months onwards.



Results: Of 14.146 patients included, 1278 (9.0%) experienced a cardiac event and 473 (3.3%) experienced a stroke. Compared to patients with the lowest variability, those in the highest quintile had an increased risk of stroke or cardiac events (HR 1.4, 95% CI 1.0–1.8, $p = 0.045$ and HR 1.9, 95% CI 1.6–2.3, $p < 0.0001$, respectively, Figure).

Conclusions: Visit-to-visit systolic BP variability predicts stroke and cardiac events in high risk hypertensive patients receiving valsartan or amlodipine, and independent of mean BP. Systolic blood pressure variability was a stronger predictor of cardiac events than of stroke.

3D.02 BLOOD PRESSURE VARIABILITY INCREASES WITH ADVANCING CHRONIC KIDNEY DISEASE STAGE. A CROSS-SECTIONAL ANALYSIS OF 14,382 HYPERTENSIVE PATIENTS FROM SPAIN

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Objective: Increased blood pressure (BP) variability has been related to cardiovascular morbidity and mortality in hypertensive patients. We aimed to assess short-term BP variability by means of ambulatory BP monitoring (ABPM) according to renal function status.

Design and method: We conducted a cross-sectional analyses with data from 14 382 hypertensives included in the Spanish ABPM Registry. Performance of ABPM was standardized according to guideline recommendations. Kidney function was graded according to current KDIGO definitions for chronic kidney disease (CKD) staging. Estimated glomerular filtration rate was calculated by the CKD-EPI equation. Short-term (reading-to-reading) BP variability was assessed by standard deviation (SD) of mean daytime and nighttime systolic BP (SBP) and diastolic BP (DBP).

Results: Mean age of the population was 61.0 ± 13.9 years and 52.6% of patients were male. Distribution according to renal function status was: 8,689 (60.4%) with no CKD, 765 (5.3%) with stage 1 CKD, 494 (3.4%) with stage 2 CKD, 3893 (27.1%) with stage 3 CKD, 413 (2.9%) with stage 4 CKD, and 128 (0.9%) with stage 5 CKD. SD of daytime SBP was higher at more advanced CKD stage (13.6 in CKD-free patients, and 15.7, 16.7, 15.7, 17.5, and 19.0 mmHg in stage 1 to 5 CKD patients respectively, p-trend < 0.001). SD of nighttime SBP also increased with progressive CKD stage, with the change being proportionally higher than that observed for daytime SBP (15.1 in CKD-free patients, and 17.5, 18.8, 17.7, 20.1, and 23.8 mmHg in stage 1 to 5 CKD patients respectively, p-trend < 0.001). SD of daytime DBP and nighttime DBP also increased as renal function worsened but with only marginal statistical significance.

Conclusions: Increased short-term BP was significantly associated with progressive CKD stages in a large sample of hypertensive patients. This association was stronger for SBP than for DBP, and for nighttime than for daytime BP. We suggest that increased SBP variability, particularly at night, may partially explain the sharp elevation of cardiovascular risk with worsening renal function.

3D.03 INFLUENCE OF AORTIC ATHEROSCLEROSIS ON THE PROGNOSTIC VALUE OF POSTURAL BLOOD PRESSURE CHANGES

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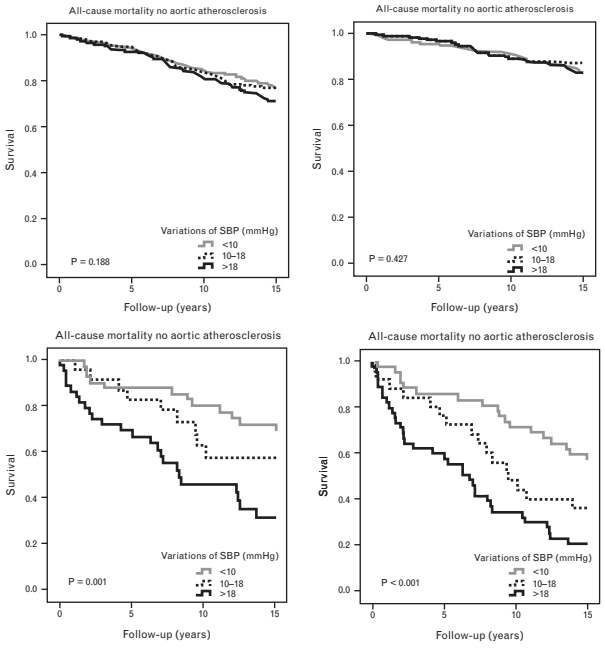
Objective: Orthostatic blood pressure (BP) variations have been related with cardiovascular events in hypertensive patients; they are associated with autonomic and neurohormonal abnormalities. Large vessels damages, i.e. aortic atherosclerosis (ATS), may exaggerate this BP deregulation and thus, amplify its prognostic consequence. This study aimed at investigating the interaction of ATS on the prognostic value of postural BP changes.

Design and method: In a cohort of 958 hypertensive patients with an aortography available (mean age 44 ± 11 years, 61% of men, 26.5% of secondary prevention), BP was measured with a manual sphygmomanometer after 10 minutes of rest in the supine position and in the standing position, one minute after assuming the upright position. Supine and standing SBP were each the average of six measurements. Postural BP change was recalculated as absolute value of the difference between mean supine SBP and mean standing SBP. ATS was assessed by a 2-modality score: absent or mild vs. moderate or severe. All-cause and cardiovascular deaths were assessed after 15 years of follow-up.

Results: BP was 182/110 mm Hg, on average. During the follow-up, 167 cardiovascular and 280 all-cause death occurred. As illustrated in the figure, an increased risk of death was observed across tertiles of increasing level of postural BP changes in the presence of moderate or severe ATS but not if ATS was absent or mild. In a multivariable Cox Regression analysis adjusted for major cardiovascular risk factors, postural BP change was statistically associated with all-cause and cardiovascular mortality only in the presence of moderate or severe ATS: tertile 2 vs. 1: 2.19 [1.10–4.39] and 2.02 [0.82–4.96] respectively; tertile 3 vs. 1: 3.21 [1.73–5.94] and 4.65 [2.20–9.80] respectively (P for interaction 0.006 for all-cause mortality and 0.002 for cardiovascular mortality). We did not observe such interaction with ECG left ventricular hypertrophy, history of heart failure and anti-hypertensive treatment.

Conclusions: The prognostic significance of postural BP changes is markedly influenced by aortic damage in hypertensive patients.



3D.04 BLUNTED NIGHTLY BLOOD PRESSURE REDUCTION IS ASSOCIATED WITH INCREASED ARTERIAL STIFFNESS IN ISCHEMIC STROKE PATIENTS: A NORWEGIAN STROKE IN THE YOUNG STUDY

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Objective: Lack of nightly blood pressure (BP) reduction is associated with increased cardiovascular risk. The aim of this study was to assess the association of nightly BP reduction with arterial stiffness in young and middle-aged ischemic stroke patients.

Table 1. Independent covariates of non-dipping BP pattern in multiple logistic regression analysis

Predictive variable	OR	95% CI	P value
High for age PWV	2.22	1.05-4.70	<0.05
Known hypertension	2.90	1.57-5.36	<0.01
Diabetes mellitus	0.97	0.39-2.42	0.94
Mean day BP, mmHg	0.97	0.94-1.00	0.05
Serum creatinine, µmol/L	1.02	1.00-1.04	<0.05

OR (odds ratio), CI (confidence interval), PWV (pulse wave velocity)

Design and method: Clinic and ambulatory BP measurements were performed 3 ± 1 month after the acute stroke in 261 patients (aged 15–60 years) included in the prospective Norwegian Stroke in the Young Study. The percent reduction in nocturnal BP was calculated from mean BP and defined as dipping if > =10%. Arterial stiffness was derived from carotid-femoral pulse wave velocity (PWV) using applanation tonometry with a Sphygmocor device.

Results: Non-dipping pattern was found in 38%. Non-dipping patients had higher PWV (8.2 ± 2.2 vs. 7.5 ± 1.7 m/s) and lower renal function, and included more patients with hypertension (51 vs. 26%) or diabetes (16 vs. 8%, all $p < 0.05$). Furthermore, 26% of the non-dippers had high for age PWV, reflecting early arterial stiffening. Age, anthropometric variables and the level of serum lipids did not differ significantly between the groups. In multivariate logistic regression analysis, non-dipping BP pattern was associated with high for age PWV (OR 2.22 [95% CI 1.05–4.70], $p < 0.05$) independent of higher creatinine, known hypertension, mean day BP or diabetes (Table 1). In multivariate linear regression analysis, non-dipping pattern was also associated with higher PWV (Beta = 0.18, p = 0.01).

Conclusions: In the Norwegian Stroke in the Young Study, blunted nightly BP reduction was common and associated with premature arterial stiffness.

3D.05 RELATIONSHIP BETWEEN 24-HOUR BLOOD PRESSURE VARIABILITY AND 24-HOUR AORTIC PRESSURE AND STIFFNESS IN HYPERTENSIVE PATIENTS

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Objective: 24-hour blood pressure variability (BPV) is a predictor of cardiovascular complications in hypertension, but its association with arterial stiffness is poorly understood. We recently showed that central aortic pressure and stiffness evaluated non-invasively over the 24-hours are increased in hypertensive patients. In the present analysis we report on the impact of 24-hour BPV on such estimates.

Design and method: Brachial BP was measured non-invasively over the 24-hours by an electronic, oscillometric, automated BP monitor in 661 uncomplicated, treated or untreated, hypertensive patients. Digitalized waveforms obtained during each brachial oscillometric BP measurement were stored in the device memory and analyzed by a validated transfer function algorithm (Vasotens technology) in order to obtain aortic systolic (S) BP, pulse wave velocity (PWV) and augmentation index (AI). BPV was calculated as weighted standard deviation (SD) of 24-hour SBP (average day-time and night-time SBP SD divided by the duration, in hours, of each time period). Patients were classified in two groups according to whether the 24-hour SD was below (n = 324) or above (n = 337) the median (12 mmHg) of the whole group.

Results: BPV showed a direct correlation with aortic SBP ($r = 0.40$ unadjusted, $r = 0.33$ after adjustment for age, gender, body mass index, antihypertensive treatment and 24-hour SBP; $p < 0.001$ for both), aortic PWV ($r = 0.21$ and $r = 0.18$, $p < 0.001$ for both) and aortic AI ($r = 0.27$, $p < 0.001$ and $r = 0.10$, $p < 0.05$). Aortic SBP, PWV and AI were larger in patients with high (122.6 mmHg,10.0 m/s and 25.9%) than in those with low BPV (116.0 mmHg, 9.3 m/s and 16.9%, $p < 0.001$ for all). Between-group differences were unchanged after adjustment for age, gender, body mass index, antihypertensive treatment and 24-hour SBP: the comparison was statistically significant for aortic SBP (121.6 vs. 117.0 mmHg, $p < 0.001$) and PWV (9.9 vs. 9.4 m/s, $p < 0.001$), but not for AI (22.6 vs. 20.4%, $p = 0.110$).

Conclusions: In hypertensive patients 24-hour BPV shows a strong relation to aortic BP and stiffness, which is independent from the absolute 24-hour BP level.

3D.06 BLOOD PRESSURE VARIABILITY AT REST AND DURING EXERCISE IN HEALTHY MEN: SEVEN DAY AMBULATORY BLOOD PRESSURE MONITORING

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Objective: The aim of the study was to compare 24-hour profile from the 7-day blood pressure monitoring at rest and during exercise. From the seven day ambulatory blood pressure monitoring we compared the blood pressure 24 h profile in the day with exercise (0–24 h) and in the day without exercise (25–48 h after exercise).

Design and method: We examined 21 men, healthy subjects, age 29 ± 4.9 years. For exercise training we used bicycle ergometer Kettler, type X7, Germany. The subjects were recruited for seven-day blood pressure monitoring (A and D, Japan). To made comparison among the 24-h profile of blood pressure in the days with exercises (0–24 h) and the days without exercise (25–48 h) we used Bland-Altman statistical method.

Results: The 24-hour mean SBP in the day with exercise (119 ± 2.1 mmHg) and in the day without exercise (119 ± 1.7 mmHg) and the 24-hour mean DBP in the day with exercise (69 ± 1.5 mmHg) and in the day without exercise (69 ± 1.5 mmHg) in 21 healthy subject was not different.
Comparisons between 7-days mean and 24-hour means SBP in the days with exercise using Bland-Altman plot showed the limits of agreement in the day with exercise (the ± 1.96 SD of the difference in 24-hour means of SBP was 6.85 mmHg and in the days without exercise the limits of the agreement (the ± 1.96 SD of the difference) was 8.59 mmHg. Bland-Altman plot comparisons between 7-days mean and 24-hour means DBP in the days with exercise the limits of the agreement (the ± 1.96 SD of the difference in DBP) was 4.95 mmHg and in the days without exercise (the ± 1.96 SD of the difference in DBP) was 6.06 mmHg.

Conclusions: Our results showed large variability of mean 24 h SBP in the days with exercise and also in the days without exercise and also in DBP the variability is similarly large. Bland –Altman plots comparing daily SBP and DBP in days with exercise and without exercise showed that the 24 h means of blood pressure were not affected by exercise, and also the blood pressure variability was not affected.

3D.07 CORRELATION BETWEEN THE ARTERIAL PRESSURE VARIABILITY ESTIMATED AT CLINICS, MAPA AND AMPA

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Objective: To measure the variability (VB) of the arterial pressure (AP) with the use of serial measurements at the clinics (VBCLIN), with 24 h ambulatory monitoring (MAPA) (VBMAPA) and home automonitoring -AMPA- (VBAMPA) and to estimate a relationship among each method.

Design and method: This is an observational, descriptive and transversal study assessed with 91 hypertensive patients in treatment and stable with AP < 160/100 mmHg for the last 3 months. Patients between 50–80 years old were included. The VB of the AP was defined as the standard deviation for both, diastolic and systolic pressures. The different VB were determined with the use of tensiometers and validated AP monitors. VBCLIN was estimated from 8 measurements per week in the clinics. A 24 h MAPA was assessed to all the patients included in the study in order to obtain the VBMAPA and an AMPA in two non-consecutive weeks to obtain the VBAMPA (total of 54 measurements).

Results: 91 patients with 66 ± 7.7 years old and 58.2% males were recruited. AP values were $134 \pm 14/82 \pm 10$ mmHg for systolic and diastolic APCLIN, respectively. AP values were $122 \pm 17 / 68 \pm 12$ mmHg for systolic and diastolic APMAPA, respectively. AP values were $125 \pm 13/75 \pm 7$ mmHg for systolic and diastolic APAMPA, respectively. The systolic VB for the three above methods was significantly correlated being maximal between VBCLIN and VBAMPA ($r = 0.45$; $0 < 0.001$) and lower for VBCLIN and VBMAPA ($r = 0.25$; $p = 0.015$) and VBMAPA and VBAMPA ($r = 0.32$; $p = 0.002$). Means of the systolic AP between each method were statistically different except for VBCLIN and VBAMPA. Corresponding to diastolic AP VB, we could only found a significant relationship between VBCLIN and VBAMPA ($r = 0.243$; $p = 0.021$).

Conclusions: The correlation between VB of AP measured in the clinics, with AMPA and MAPA methods is weak. This observation suggests that these are not interchangeable methodologies. Future studies focused on the relationship between VB —with different methods— and vascular target organ damage would be of great help in order to define the best analytical method.

3D.08 ARTERIAL STIFFNESS AND AUTONOMIC NERVOUS FUNCTION ON ORTHOSTATIC BLOOD PRESSURE-ELEVATION IN HYPERTENSIVE PATIENTS

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Objective: Using a simple standing-up test in hypertensive patients, we evaluated orthostatic upright postural blood pressure (BP) changes and autonomic nervous function, as well as the relationship between orthostatic BP-elevation and subclinical markers of atherosclerosis.

Design and method: A total of 351 hypertensive patients aged 35–75 years (60.4 ± 8.7 years) were enrolled. We measured body mass index (BMI), systolic BP (SBP) and diastolic BP (DBP) and subclinical markers of atherosclerosis. Brachial ankle pulse wave velocity (baPWV), late systolic peak of the pressure wave form (SBP2) and carotid mean IMT were measured. Participants underwent a simple standing-up test involving sitting then standing for 2 minutes each, followed again by sitting. To evaluate autonomic fluctuations, we calculated the coefficient of variation of the R-R interval, the ratio of low to high frequency heart rate variability (LF/HF), and the coefficient of component variance of high frequency.

Results: Orthostatic hypotension (OH: $\delta SBP < -20$ mmHg) and hypertension(OHT: $\delta SBP > 10$mmHg) was assessed with blood pressure measurements in sitting and standing position. OH was present in 30, normal response in 283, and OHT was 38 patients. OH was excluded in this study. Significant correlations were found between baPWV and resting SBP($r^2 = 0.462$, $P < 0.001$) and sympathetic α function($r^2 = 0.177$, $p < 0.01$). In OHT group, δSBP(15.0 vs-3.25mmHg;$p < 0.0001$), δDBP(3.3 vs -0.27mmHg;$p < 0.001$), baseline SBP(145.4 vs 138.7mmHg;p-0.02), SBP2(134.6 vs 125.9mmHg; $p = 0.001$), baPWV(1757 vs 1637 mm/s; $p = 0.014$), LF/HF at standing(6.17 vs 3.86; $p = 0.015$), CVRR at standing (2.95 vs 2.56; $p = 0.031$)were significantly higher than in OHT(-) group. Multiple regression analyses showed that an increase in SBP as well as baseline SBP, age, BMI, were independent determinants of PWV.

Conclusions: We have shown that increased arterial stiffness and autonomic nervous function in the hemodynamic response was associated with OHT during a standing-up test. Arterial stiffness may contribute to greater BP elevation to postural changes from standing.

3D.09 AGREEMENT BETWEEN AMBULATORY, HOME AND OFFICE BLOOD PRESSURE VARIABILITY

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Objective: Increased blood pressure (BP) variability is a possible independent risk factor for cardiovascular events. BP variability has been assessed with several methods of BP measurement in recent literature, although it is unclear whether these measurements of variability with varying timeframes reflect the same phenomenon. The aim of our study was to compare the agreement between ambulatory, home and office BP variability.

Design and method: The study population consisted of 509 participants randomly drawn from the population register or recruited by general practitioners on the basis of newly diagnosed untreated hypertension. Ambulatory 24-h blood pressure monitoring, 28 home BP measurements (twice every morning and evening during 7 consecutive days) and 8 office BP measurements (duplicate measurements on 4 visits) were performed in all participants. 3 log-transformed variability indices (SD, standard deviation; CV, coefficient of variation and ARV, average real variability) were calculated for all measurement methods and Pearson's correlations between them were calculated. The agreement of different methods on the diagnoses of extreme BP variability (participants with variability above the highest decile) was also assessed with kappa coefficients.

Results: Systolic/diastolic BP variability was greater in 24-h ambulatory (CV: 12.6 ± 2.8 /15.1 ± 3.4) than home (CV: 4.4 ± 1.8/4.7 ± 2.0, p < 0.001 versus ambulatory CV for both) and office (CV: 4.8 ± 2.6/5.3 ± 2.6, p < 0.001 versus ambulatory CV for both) measurements. Ambulatory daytime variability was greater than nighttime variability (CV: 11.0 ± 2.8/13.1 ± 3.5 vs. 9.5 ± 3.8/12.8 ± 4.6, p < = 0.001 for both). Pearson's correlation coefficients for systolic/diastolic variability indices between different measurement methods were 0.08–0.34/0.03–0.26, indicating only negligible to weak positive relationship (Table). The agreement of ambulatory, home and office BP variability measures on diagnoses of extreme systolic/diastolic BP variability was only slight, with the kappa coefficients varying between 0.00–0.20/0.03–0.16. Extreme variability was diagnosed in only two persons with all three methods.

Table. Pearson's correlations between systolic ambulatory, home and office blood pressure variability

Variability index		Ambulatory 24 h	Ambulatory day	Ambulatory night	Home
SD	Home	0.33**	0.34**	0.19**	-
	Office	0.24**	0.26**	0.19**	0.27**
CV	Home	0.18**	0.18**	0.083	-
	Office	0.13*	0.16**	0.13*	0.17**
ARV	Home	0.26**	0.24**	0.18**	-
	Office	0.23**	0.20**	0.19**	0.20**

* indicates p<0.01 and ** indicates p<0.001.

Conclusions: Shorter-term and longer-term BP variability assessed with different methods of BP measurement seem to correlate only weakly with each other. Our study suggests that BP variability assessed by different methods and timeframes reflects various phenomena, not a single entity.

ORAL SESSION

LATE-BREAKERS SESSION 1

LB01.01 ALLIED HEALTH PROFESSIONAL-LED INTERVENTIONS FOR IMPROVING CONTROL OF BLOOD PRESSURE IN PATIENTS WITH HYPERTENSION: A COCHRANE SYSTEMATIC REVIEW AND META-ANALYSIS

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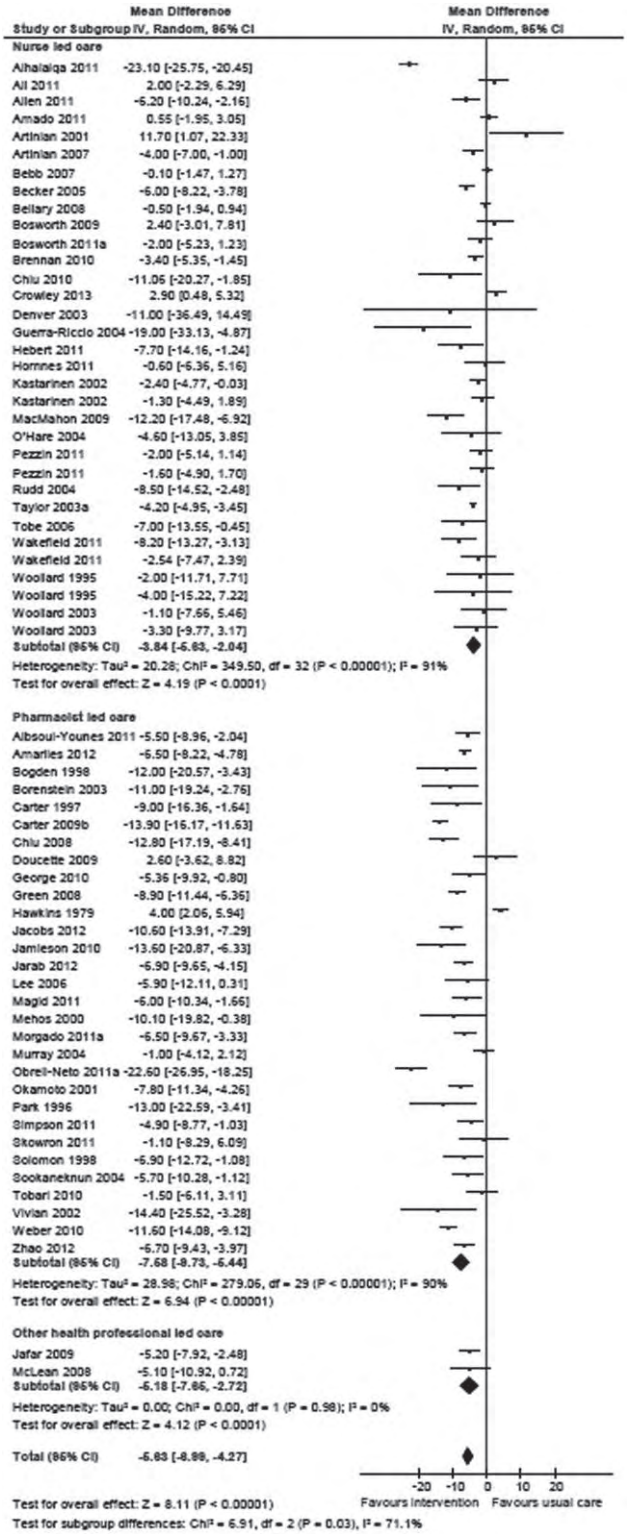
Objective: Nurse or pharmacist-led care may improve control of hypertension. We have undertaken a new Cochrane review of evidence for allied health professional led interventions in the management of hypertension.

Design and method: We searched multiple bibliographic databases to October 2013 for randomised controlled trials. We included any nursing, pharmacist, or allied health professional-led intervention designed to improve control of blood pressure (BP), compared to usual management of hypertension.
Primary outcome measures were change in systolic BP, achievement of study target BP and use of antihypertensive medication. Two authors independently assessed studies for inclusion, extracted data, and assessed risk of bias using Cochrane criteria. Intervention effects were pooled using odds ratios (OR) or mean differences (MD).

Results: We identified 579 potential unique citations; 234 full-texts were assessed, and 98 papers met the inclusion criteria. Overall, half the risk of bias judgments across studies were rated as low risk.
Compared to usual care, greater falls in systolic BP were seen for both nurse-led interventions (MD −3.8mmHg (95% CI: −5.6 to −2.0); 28 studies, 10573 participants) and pharmacist-led interventions (MD −7.6mmHg (−9.7 to −5.4); 30 studies, 6504 participants, $p < 0.01$ for difference; figure). Nurse-led interventions (OR 1.5 (1.3 to 1.7); 24 studies, 15833 participants) and pharmacist-led interventions (OR 3.5 (2.7 to 4.4); 24 studies, 4443 participants) attained higher achievement of study BP targets ($p < 0.001$ for difference between professions), and greater use of antihypertensive medication (nurse-led OR 1.4 (1.1 to 1.7) vs. pharmacist-led OR 2.2 (1.3 to 3.7); $p = 0.02$).
Interventions empowering nurses or pharmacists to prescribe or alter antihypertensive medication, compared to doctor-led medication management, achieved greater reductions in systolic BP (MD −6.7mmHg (−8.2 to −5.3) vs. −3.9mmHg (−6.7 to −1.1); $p = 0.08$) and greater achievement of study BP targets (OR 2.5 (2.0 to 3.2) vs. 1.7 (1.3 to 2.1); $p < 0.01$).

Conclusions: Nurse and pharmacist-led interventions are more likely to lower BP, achieve BP targets, and facilitate use of antihypertensives than usual care, and pharmacist-led interventions appear more effective than nurse-led interventions. Permitting nurses and pharmacists to alter or prescribe antihypertensive medications improves the impact of interventions.



LB01.02 MORNING HOME BLOOD PRESSURE IS A STRONG PREDICTOR OF CORONARY ARTERY DISEASE EVENTS AS WELL AS STROKE EVENTS IN HYPERTENSIVE PATIENTS ON ANTIHYPERTENSIVE TREATMENT. THE HONEST STUDY

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Objective: Previous studies indicated that clinic blood pressure (CBP) is a strong predictor of stroke events, but CBP does not predict coronary artery disease (CAD) events so strongly. Morning home blood pressure (HBP) is more closely associated with stroke risk than CBP. However, few studies have investigated the relationship between morning HBP and CAD risk. We investigated the relationship between morning HBP and incidence of stroke events and CAD events, respectively, using data from the HONEST study.

Design and method: HONEST was a prospective observational study of hypertensive outpatients on olmesartan-based antihypertensive treatment. All the ischemic and hemorrhagic cerebrovascular events expect transient ischemic attack were defined as stroke events, and myocardial infarction and angina pectoris with coronary revascularization procedure were defined as CAD events.

Results: In 21591 participants (mean age, 64.9 years; mean follow-up, 2.02 years), 127 (2.92/1000 patient years) stroke events and 121 (2.78/1000 patient years) CAD events occurred. The incidence of stroke events was significantly increased in morning HBP >=145 to <155 mmHg and >=155 mmHg compared with <125 mmHg; also in CBP >=150 to <160 mmHg and >=160 mmHg compared with <130 mmHg. The hazard ratio (HR) in morning HBP >155 mmHg was 6.01 (95% CI, 2.85–12.68) compared with <125 mmHg; in CBP >=160 mmHg, it was 5.82 (3.17–10.67) compared with <130 mmHg, indicating that morning HBP predicted stroke events similarly to CBP. The incidence of CAD events was significantly increased in morning HBP>=145 to <155 mmHg and >=155 mmHg compared with <125 mmHg; in CBP >=160 mmHg compared with <130 mmHg, but not in CBP >=150 to <160 mmHg. The HR in morning HBP >=155 mmHg was 6.24 (2.82–13.84). In contrast, the HR in CBP >=160 mmHg was 3.51 (1.71–7.20), indicating that CBP underestimated CAD risk compared to morning HBP.

Conclusions: Morning HBP predicted CAD events similarly to stroke events. In contrast, CBP is more likely to underestimate CAD risk than morning HBP. Morning SBP-guided approach for managing hypertension may be more effective in predicting future risk of CAD events than CBP-based one.

LB01.03 INCIDENCE AND PROGNOSIS OF CANCER ASSOCIATED WITH DIGOXIN AND COMMON ANTIHYPERTENSIVE DRUGS

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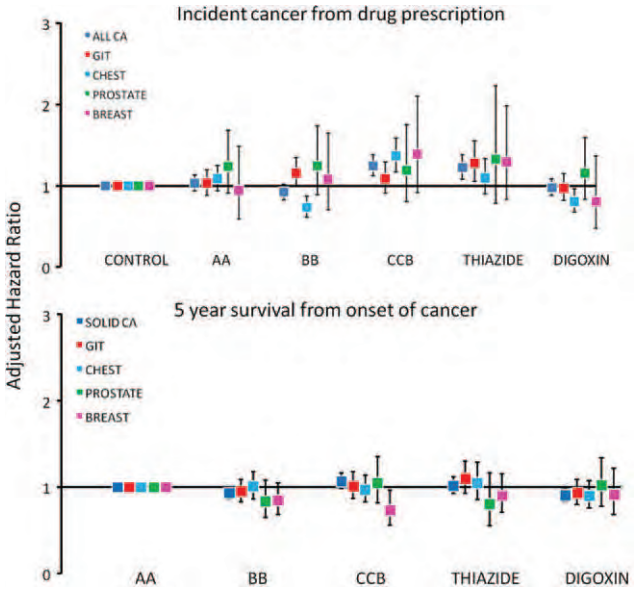
Objective: Recent observational studies have shown varied association between antihypertensive drugs and digoxin with either cancer risk or prognosis. We studied the time to incident cancer in two large patient cohorts in relation to four antihypertensive drugs and digoxin.

Design and method: We studied a hospital admission based cohort of 525,046 patients admitted at least once to the Western Infirmary and Gartnavel hospitals between 1980 and March 2013. Patients were classified into 6 mutually exclusive groups based on monotherapy with either ACEI/ARB(AA), beta-blockers(BB), calcium antagonist(CCB), thiazides, digoxin and a control group without exposure to these drugs. All control subjects were included if they were not on the any of the above drugs and were aged 60–80 years at 1/4/2004. The inclusion criteria for the drug groups included new prescription of the drug after 1/4/2004, no previous prescription of any of the study drug, at least 90 days of prescription, discontinuation of the drug no later than 1 year before onset of cancer. Each of the 4 antihypertensive drug groups were mutually exclusive for any prescription for the other drugs while the digoxin group included all subjects exposed to digoxin. Age and sex adjusted time to first cancer diagnosis and time to death from cancer diagnosis were performed.

Results: 34,634 subjects fulfilled the inclusion criteria and of them 6,153 had a new diagnosis of cancer after 1/4/2004. During 8-year period follow-up 6,557 patients were diagnosed with cancer in the hospital cohort (2,313 gastrointestinal, 2,439 lung, 464 prostate, 321 breast cancers). The results of the multivariate adjusted Cox model for incident cancer are presented in Figure 1.



Conclusions: Exposure to digoxin or beta-blocker therapy appears to be protective against incident respiratory cancers while CCB increased risk. Thiazides are associated with increased GIT cancers. CCB use at diagnosis of breast cancer improved survival.

LB01.04 IMPORTANCE OF DIETARY SALT INTAKE IN ANTI-ALBUMINURIC EFFECT OF AN ALDOSTERONE BLOCKER

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Objective: Excessive salt intake was reported to counteract the renoprotective effect by the blockade of renin-angiotensin system (RAS) on chronic kidney disease (CKD) of hypertensive patients. We have shown salt loading induces hypertension and renal damage via the ligand-independent activation of mineralocorticoid receptor (MR) through Rac1 activation in rodent kidneys (Nat Med 2008, J Clin Invest 2011). Therefore, we hypothesized that excessive salt intake activates Rac1-MR pathway also in the hypertensive patients, leading to the progression of CKD, despite of RAS blockade. To examine the hypothesis, we analyzed the participants of EVALUATE study, a double-blind, randomised, placebo-controlled trial that enrolled non-diabetic hypertensive patients with albuminuria, in which all participants were received the aldosterone blocker eplerenone or placebo depending on random assignment in addition to RAS blockade (Lancet Diabetes Endocrinol 2014).

Design and method: We analyzed 314 subjects who completed the study. They were divided into tertiles according to the estimated 24-h urinary sodium excretion at baseline (LOW / MIDDLE / HIGH) and evaluated the change in urinary albumin-to-creatinine ratio (UACR) from baseline.

Results: UACR and blood pressure (BP) were not significantly different among groups at baseline. The percent change in UACR were as follows: LOW: −0.84% vs. −10.2%, MIDDLE: +9.5% vs. −19.5%, HIGH: +21.8% vs. −22.5%, placebo vs. eplerenone, respectively. Eplerenone effectively suppressed albuminuria only in HIGH. The decrease in systolic BP with eplerenone was also greater in the HIGH than in the LOW.

Conclusions: Our result suggests that resistance to RAS blockade by excessive salt intake would be due to ligand-independent activation of MR. The antihypertensive effects of eplerenone is BP-dependent and independent. Eplerenone added on RAS blockade will be beneficial to treat CKD of hypertensive patients with excessive salt intake.

LB01.05 VASCULAR CONSEQUENCES OF PRE-ECLAMPSIA

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Objective: Women with a history of pre-eclampsia (PE) are at higher risk of cardiovascular disease later in life. We evaluated the cardiovascular health of women who had PE in comparison with women who had normotensive pregnancies.

Design and method: Women were recruited from the previous Proteomics in Pre-eclampsia (PIP) Study, the Generation Scotland Scottish Family Health Study and the Glasgow Blood Pressure Clinic (pregnancies 1–5, 10–30 and 1–30 years ago, respectively).We assessed heart rate-adjusted augmentation index (AIx; SphygmoCor), carotid-femoral pulse wave velocity (PWV; SphygmoCor), carotid intima-media thickness (CIMT; ultrasound) and brachial flow-mediated dilatation (FMD; ultrasound).

Results: A total of 166 women (86 cases, 80 controls) attended for vascular studies. Women with a history of PE had higher systolic blood pressure (SBP) (130 ± 14 vs 122 ± 10 mmHg; $P < 0.001$) and diastolic blood pressure (DBP) (82 ± 9 vs 78 ± 7 mmHg; $P = 0.001$) compared with controls. They also had a higher BMI (29.4 ± 6.1 vs 26.6 ± 4.5 kg/m^2; $P = 0.002$). We found impaired endothelial function (FMD 5.9 ± 3.3 vs 7.0 ± 3.3 %, $P = 0.017$) and greater PWV (7.8 ± 1.6 vs 7.1 ± 1.1 m/s, $P = 0.002$) and heart rate-adjusted AIx (25.7 ± 11.0 vs 22.5 ± 9.6 %, $P = 0.023$) in cases compared with controls. There was no difference in CIMT ($P = 0.110$). After adjustment for age, BMI and SBP the difference in endothelial function remained statistically significant ($P = 0.014$).

Conclusions: Women who had PE have higher blood pressure and BMI compared to women at similar age who had normotensive pregnancies. A history of PE is also associated with impaired endothelial function which could explain the higher cardiovascular risk in this group.

LB01.06 VISIT-TO-VISIT BLOOD PRESSURE VARIABILITY AND CARDIOVASCULAR OUTCOMES IN FELODIPINE EVENT REDUCTION STUDY

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Objective: Many antihypertensive outcome trials have shown that visit-to-visit blood pressure variability is correlated closely with clinical outcomes in hypertensive patients. The objective of the study was to investigate the relationship between visit-to-visit blood pressure variability (BPV) and the major cardiovascular outcomes in the Chinese hypertensive patients.

Design and method: Felodipine Event Reduction (FEVER) study was a double-blind, randomized trial on 9711 Chinese hypertensive patients, in whom cardiovascular outcomes were significantly reduced by more intense therapy achieving a mean of 138 mmHg SBP compared with less-intense therapy achieving a mean of 142 mmHg. Visit-to-visit BPV during the follow-up period [defined as standard deviation (SD), coefficient of variation (CV), and average real variability(ARV)] was derived from casual cuff BP measures after six months follow-up until the end of the study. Hazard ratios (HRs), for the incidence of CVD associated with SD, CV, and ARV of SBP and DBP were calculated using Cox proportional hazard models. Overall predictive power [area under receiver operating characteristic (AUC ROC) curve] of the level of blood pressure, blood pressure variability and other baseline characteristics was calculated.

Results: In FEVER study, visit-to-visit variability in SBP were significant predictors of subsequent stroke [eg, hazard ratios [HR] for ARV, SD and CV was 1.071 (95% CI: 1.025-1.118), 1.373 (95% CI: 1.159–1.626) and 0.572 (95% CI: 0.451–0,726)]. Visit-to-visit variability in DBP were also showed similar trend [eg, HR for ARV, SD and CV was 1.066 (95% CI: 0.992–1.145), 1.931 (95% CI: 1.435–2.598) and 0.558 (95% CI: 0.438–0,710)]. However, using the analysis of AUC ROC analysis, the risk importance sequence of the stroke events in this cohort was level of SBP, age, level of DBP ARV, SD, sex, CV and treatment.

Conclusions: Visit-to-visit blood pressure variability has some effects on the cardiovascular outcomes in the Chinese hypertensive patents in the cohort in FEVER Study. However, blood pressure per se is even more important for the development of stroke in this group of patients.

LB01.07 ELEVATED BLOOD PRESSURE WITHOUT HYPERTROPHY RAISES LEFT VENTRICULAR EJECTION FRACTION

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Objective: Hypertension remains a major cause of cardiovascular morbidity and mortality worldwide. Persistent blood pressure (BP) elevation may lead to left ventricular (LV) hypertrophy and heart failure. We wanted to assess the impact of high BP on LV function in an asymptomatic cohort, with no evidence of LV hypertrophy.

Design and method: We included all 96 asymptomatic volunteers scanned with cardiovascular magnetic resonance (CMR) as part of the HAPPY London primary prevention study. BP was taken sitting, from the left arm with at least 2 consistent measures. We compared those with elevated clinic BP (systolic >140mmHg and/or diastolic >90mmHg) to those with a 'normal' BP, regardless of whether on BP treatment. CMR at 1.5 Tesla was performed within 2 weeks of the clinic.

Results: Average age was 64.5 years and 74% were males, similar in both groups. Half were taking antihypertensive medication in both groups. 31 participants had elevated clinic BP and the remaining 65 had normal BP. Mean BPs were: 150mmHg $\pm$ 8 / 86mmHg $\pm$ 11 in high BP group and 127mmHg $\pm$ 8 / 77mmHg $\pm$ 7 in the normal (Table 1).

	BP>140/90 N=31	BP<140/90 N=65	P value
Males	23 (74%)	48 (74%)	NS
Age (years)	65	64	NS
Hypertension treatment	17 (55%)	33 (51%)	
BP systolic (mmHg)	150	127	<0.001
BP diastolic (mmHg)	86	77	<0.001
LVEF (%)	67.9%	63.8%	<0.05
LV myocardial mass	49.4	50.2	0.71

Table 1. Patient demographics, LV and PWV results in those with elevated vs. normal clinic BP.

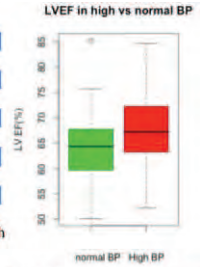

Figure 1. Boxplots comparing the LVEF in those with high vs. normal clinic BP.

LV ejection fraction (EF) was significantly elevated in the high BP group (68% vs. 64%, $p < 0.05$; Figure 1), despite similar indexed LV myocardial mass.
Systolic BP was correlated with LVEF (Cor coeffeicient = 0.26, $p = 0.01$, $t = 2.62$, CI 0.06 – 0.44). In a multiple regression model both systolic BP and BP treatment, but not diastolic BP, were predictors for LV EF ($r2 = 0.17$, $p < 0.001$), independent of diastolic BP, LV myocardial mass, BP treatment, age and heart rate.

Conclusions: We believe this is the first description of this relationship. Thus in the absence of LV hypertrophy, asymptomatic individuals who have elevated clinic BP have a higher EF compared to those with normal BP. Sustained hyperdynamic circulation may be a contributory mechanism for future hypertrophy, heart failure and other long-term complications.
Preliminary data suggests this increased EF may settle with improved BP control. It is possible that we may need to consider an EF correction factor based on BP.

LB01.08 TREATMENT OF HYPERTENSION USING TELEMEDICAL HOME BLOOD PRESSURE MEASUREMENTS

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Objective: Telemonitoring of home blood pressure measurements (TBPM) is a new and promising supplement to diagnosis, control and treatment of hypertension. We wanted to compare the outcome of antihypertensive treatment based on TBPM and conventional monitoring of blood pressure.

Design and method: Participants ($n = 356$) were recruited from a prevalence study among citizens aged 55–64 years in the municipality of Holstebro, Denmark. The study was a randomised, controlled, unblinded 3 months trial. In the intervention group, antihypertensive treatment was based on TBPM with transmission of the measurements and subsequent communication by telephone or E-mail. In the control group, patients received usual care. Primary outcome was reduction in daytime ambulatory blood pressure measurements (ABPM) from baseline to 3 months' follow-up.

Results: In both groups, daytime ABPM decreased significantly. The decrease in daytime ABPM in the intervention group was systolic/diastolic, $-8 \pm 12/-4 \pm 7$ mmHg. This did not differ significantly from the control group's $-8 \pm 13/-4 \pm 8$ mmHg. An equal number of participants obtained normal daytime ABPM, in the intervention group 17% (31/175) versus control 21% (37/181), p = 0.34. Blood pressure reduction in the TBPM group varied with the different practices.

Conclusions: No further reduction in ABPM or number of patients reaching blood pressure targets was observed when electronic transmission of TBPM was applied in the treatment of hypertension by GPs. Thus, as an isolated tool TBPM did not improve BP control during a 3 month period.

LB01.09 STUDY OF A LARGE COHORT OF CONNECTED DEVICES USERS TO ASSESS THE ASSOCIATION BETWEEN WALKING AND BLOOD PRESSURE

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Objective: Increase or decrease of blood pressure has recently been linked to active transportation, and represents a convenient prevention tool. However, there is a need of objective and longitudinal data to deliver tailored recommendations. The aim of the study is to assess this link on a large population using data from connected devices.

Design and method: Cross-sectional and longitudinal multivariate linear regressions were performed on data from a pool of 19,000 adult owners of Withings' Pulse activity trackers and Wireless Blood Pressure Monitors. These devices measure number of steps per day and systolic Blood Pressure (SBP) respectively. Analyses were adjusted according to age, sex and Body Mass Index (BMI) collected through Withings' HealthMate mobile application. Covariates also included the frequency of measurement of SBP and the wear time of activity trackers.

Results: The study population is characterized by a mean $\pm$ SD age of 50.2 ± 11.5 years, a BMI of 28.9 ± 5.2 kg/m^2, 28.3 ± 26.6 SBP measurement per month and 23.7 ± 8.4 days of activity tracker wear time. Multivariate cross-sectional analyses showed an inverse association between SBP and number of steps per day in both sexes ($p < 10^{-15}$ in men and $p < 10^{-5}$ in women), and between SBP and number of days in the month in which the tracker was worn ($p < 10^{-15}$ in both sex). In longitudinal bivariate analyses, a one-month increase of 1,000 steps a day was associated with a decrease of 0.13 mmHg of SBP in men ($p < 10^{-15}$) and 0.21 mmHg in women ($p < 10^{-3}$). These results remain significant in fully adjusted models for men ($p < 10^{-15}$) but not for women (p = 0.07).

Conclusions: There is an increasing number of connected devices in general population, and Public Health should not miss the opportunities to use data coming from these devices. In the Withings' population, daily walking was associated with a decrease of SBP in both sexes according to cross-sectional and longitudinal analyses. Our results show that physical activity improves physical health and helps lower blood pressure. These results provide new insights for additional tailored non-pharmacological measures using connected devices.

LB01.10 EFFECT OF XANTHINE OXIDASE INHIBITION ON ARTERIAL STIFFNESS IN PATIENTS WITH CHRONIC HEART FAILURE

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Objective: The Xanthine Oxidase inhibitor Allopurinol improves endothelial function in different populations. Its effect on arterial stiffness parameters is less clear. We investigated the effect of short-term low-dose Allopurinol therapy on arterial stiffness parameters in stable Saudi patients with mild-moderate chronic heart failure.

Design and method: A prospective, randomized, double-blind, placebo-controlled study was performed on 73 patients with mild-moderate chronic heart failure. 36 were randomized to Allopurinol 300 mg daily for 3 months, while 37 patients were randomized to placebo. Arterial stiffness parameters; augmentation index, aortic and brachial pulse wave velocity, were assessed at baseline and after 3 months. Serum uric acid concentration was measured at baseline and after 3 months.

Table 1: Baseline demographics and hemodynamic data of study patients

Parameters	Placebo group	Allopurinol group	P value
Number randomized	37	36	
Males	29 (78.3%)	29 (80.5%)	0.818
Age	55.3 ± 13	56.6 ± 10.1	0.632
Body mass index	31.47 ± 4.1	26.27 ± 5.3	< 0.001
NYHA functional class			
2	29 (78.4%)	28 (77.8%)	0.581
1	4	2	
3	4	6	
Fractional shortening %	26.6 ± 10.3	24.6 ± 11.8	0.438
Smoking			
Active/x-smoker/never	13/8/16	5/9/21	0.113
Uric acid (mg/dl)	6.09 ± 1.9	6.31 ± 1.4	0.580
Mean blood pressure (mmHg)	94.1 ± 12.3	94.6 ± 12.4	0.863
Heart rate/ min	67.9 ± 11.4	69.0 ± 13.2	0.713
Augmentation index (AI) %	25.9 ± 11.4	27.8 ± 12.7	0.505
Heart rate-corrected AI %	21.8 ± 10.5	24.6 ± 9.6	0.238
Aortic pulse wave velocity (m/s)	9.99 ± 3.0	9.57 ± 2.7	0.555
Brachial pulse wave velocity (m/s)	9.35 ± 1.4	9.33 ± 1.5	0.947

Table 2: Changes in uric acid and arterial stiffness parameters after 3 months

Parameters	Placebo group	Allopurinol group	P value
Uric acid (mg/dl)	- 0.10 ± 0.9	2.44 ± 1.6	< 0.001
Augmentation index %	1.38 ± 6.0	1.06 ± 6.4	0.835
Heart rate corrected-augmentation index %	0.28 ± 5.1	1.32 ± 5.8	0.443
Brachial pulse wave velocity (m/s)	0.45 ± 1.2	0.15 ± 1.2	0.350
Aortic pulse wave velocity (m/s)	-0.27 ± 1.6	-0.20 ± 1.8	0.865

Results: 66 patients completed the study. Both groups were matched for age and gender, and there was no difference in severity of heart failure between groups, 78% of all participants were NYHA class 2. Allopurinol recipients had a significant fall in their uric acid concentration from 6.31 ± 1.4 (SD) mg/dl to 3.81 ± 1.2, P < 0.001. Placebo group had no significant change in uric acid concentration. Comparing the change in uric acid between the two groups was significant with a mean drop of 2.44 ± 1.6 mg/dl in allopurinol group, vs -0.10 ± 0.9 in placebo group, P < 0.001. No significant difference in arterial stiffness parameters was observed between allopurinol and placebo groups. Heart rate corrected augmentation index in allopurinol group was 24.6 ± 9.6 % before treatment and 24.0 ± 9.1 after, P = 0.212. Aortic pulse wave velocity before treatment was 9.57 ± 2.7 m/s, and 9.85 ± 2.6 after, P = 0.563. Brachial pulse wave velocity before treatment was 9.33 ± 1.5 m/s, and 8.98 ± 1.1 after, P = 0.510.

Conclusions: We have shown that Allopurinol significantly reduced uric acid concentration in Saudi patients with chronic heart failure, yet it has not shown any significant improvement in their arterial stiffness parameters during the study period.

LB01.11 PREVALENCE OF SECONDARY HYPERTENSION IN YOUNG HYPERTENSIVE ADULTS

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Objective: Data from referral centers suggest that approximately 10% of hypertensive patients could have secondary hypertension (2HTN). It is commonly accepted that 2HTN is more frequent in younger subjects but its prevalence is not known.

Design and method: Retrospective analysis of the computerized medical records of consecutive hypertensive patients aged 18 to 40 years referred to the Georges Pompidou ESH hypertension center who underwent in-hospital work-up including renal artery duplex ultrasound or CT angiography, determination of plasma aldosterone/renin ratio and 24 h urinary metanephrine.

Results: Between January 2008 and December 2013, 843 patients (52.2% women) aged 26.9 ± 6.2 years were referred to our center. 509 patients (60.4%) had a family history of hypertension and 356 (42.4%) had a body mass index exceeding 27 kg/m^2. BP levels were 142.0/89.2 mmHg with a median number of 1 (range 0–7) antihypertensive drugs. 250 patients (29.6%) were diagnosed with 2HTN including primary aldosteronism in 62 patients (7.4 %), fibromuscular dysplasia in 49(5.8%) and pheochromocytoma in 33 (3.9%) patients.

Conclusions: Before the age of 40, the prevalence of 2HTN is close to 30%. This high prevalence confirms the necessity of a systematic work-up for 2HTN in younger adults. Further analysis will aim to identify the phenotype based on the cause of hypertension.

LB01.12 PREVALENCE OF METABOLIC SYNDROME AND ITS COMPONENTS IN SPANISH POSTMENOPAUSAL WOMEN

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Objective: This study aimed to estimate prevalence of metabolic syndrome and all its components to know the cardiovascular risk and metabolic control of the main risk factors in postmenopausal women aged over 45 years in the province of Cuenca (Castilla la Mancha, Spain).

Design and method: In this cross-sectional study, we randomly selected 716 postmenopausal women from 3,108 women aged over 45. Metabolic syndrome was identified according to the National Cholesterol Education Program Adult Treatment Panel III definition. Cardiovascular risk was calculated by the Systematic Coronary Risk Evaluation (< 65 years). The American Diabetes Associationś standards of medical care in diabetes were used to estimate metabolic control. The statistical analysis was done with SPPS.19

Results: Prevalence of metabolic syndrome was 61.7% (95%CI: 56.9–66.4). Prevalence of each component was: high blood pressure: 95.8% (95%CI: 95.7–95.8), abdominal obesity: 91% (95%CI: 90.9–91.0), low high-density lipoproteins cholesterol (HDLc) levels: 70% (95%CI: 69.8–69.9), high triglyceride levels: 56.9% (95%CI: 56.4–56.9), high glucose levels: 54.3% (95%CI: 54.2–54.3). Cardiovascular risk was moderate until 65 years, but was high after this age. Metabolic control in postmenopausal women was very good for glucose, bad for systolic blood pressure and worse for lipid levels. Bad blood pressure control was associated with being over 65 years, being hypertensive and taking treatment for diabetes, but it reduced when being physically limited to do moderate exercise and anxiety increased.

Conclusions: Prevalence of metabolic syndrome in postmenopausal women in the province of Cuenca is the highest in Spain. High blood pressure and abdominal obesity are the commonest components. Cardiovascular risk was moderate-high in postmenopausal women, but systolic blood pressure and lipid profile were unsatisfactorily controlled. Early intervention is necessary to achieve a better risk profile.

ORAL SESSION

ORAL SESSION 4A
RESISTANT HYPERTENSION

4A.01 LONG-TERM EFFECTS OF RENAL ARTERY DENERVATION IN REAL WORLD PATIENTS WITH UNCONTROLLED HYPERTENSION FROM THE GLOBAL SYMPLICITY REGISTRY

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Objective: The Global SYMPLICITY Registry (GSR) provides real world experience regarding the effects of radiofrequency denervation of the renal artery nerves in patients with uncontrolled hypertension. These data in hypertensive patients with a high proportion of concomitant conditions also characterized by sympathetic nervous system will further characterize the effects of renal denervation across a diverse patient population.

Design and method: The GSR is a prospective, open-label, registry being conducted at 245 international sites. Office and 24-hour ambulatory blood pressure (BP) change, laboratory values and protocol-defined safety events are collected. One year results in the first 1000 enrolled patients are now available and two-year results in 600 patients will be available in the spring for presentation.

Results: In the first 1000 consecutive patients enrolled, the mean age was 61 ± 12 years, 61% were male and mean body mass index was 30 ± 6 kg/m2. Comorbidities included diabetes mellitus (42%), renal dysfunction (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73m2; 23%), obstructive sleep apnea (11%) and history of cardiac disease (51%). Baseline office BP was 165/89 ± 24/16 mm Hg and baseline 24-hour BP was 154/86 ± 18/14 mm Hg. 1 year office systolic BP change in 740 patients was -13.0 ± 26.3 mmHg ($p < 0.001$) and 24-hr systolic BP change ($n = 390$) was -8.3 ± 17.8 mmHg ($p < 0.001$). In patients with more severe hypertension (baseline office systolic blood pressure of at least 160 mm Hg plus an ambulatory 24-hour systolic blood pressure at least 135 mm Hg while taking 3 or more antihypertensive medications) the office systolic BP change was -21.5 ± 25.6 mmHg ($p < 0.001$) and the 24-hr systolic BP change was -11.4 ± 17.9 mmHg ($p < 0.001$). At 1 year post-denervation there were 7 cardiovascular deaths, new renal artery stenosis >70% occurred in 2 patients, and new onset end-stage renal disease occurred in 3 patients.

Conclusions: Renal denervation in a large real world population resulted in significant blood pressure reductions 1 year post-procedure. There were no long-term safety concerns following the denervation procedure. These data, including analysis of the BP-lowering effects of RDN in select subgroups, will be updated with two year follow-up of approximately 600 patients in June.

4A.02 STENTING OF ATHEROSCLEROTIC RENAL ARTERY STENOSIS DOES NOT IMPROVE CLINICAL OUTCOMES IN PATIENTS PRESENTING WITH CONGESTIVE HEART FAILURE, AN ANALYSIS OF THE CORAL TRIAL

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Objective: In some guidelines congestive heart failure is an indication for renal artery stenting. We sought to determine, in patients enrolled with a history of congestive heart failure (CHF), the effect of renal artery stenting on clinical outcomes in the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial.

Design and method: The CORAL trial is a prospective, international, multicenter clinical trial that randomized participants with atherosclerotic renal artery stenosis, who received optimal medical therapy, to stenting versus no stenting. Optimal medical therapy included treating blood pressure and diabetes to goal, use of an angiotensin receptor-blocking drug, a statin, and anti-platelet therapy. Clinical data from patients with a history of CHF were analyzed using SAS and R software. Glomerular filtration (eGFR) was estimated using the serum creatinine-cystatin-C-CKD-EPI equation. Patients were followed for a median of 43 months (IQR, 31 to 55). Blood pressure was measured in triplicate, after 5 minutes seated quietly, with an oscillometric device.

Results: A history of CHF was present at enrollment in 123 of 931 subjects, 69 in the medical therapy group and 54 in the medical therapy + stenting group. Neither the composite event rate (41% vs. 48%, $p = 0.51$), rate of CHF admission (20% vs. 26%. $p = 0.112$) nor the rate of cardiovascular death (16% vs. 17%, $p > 0.99$) differed between medical therapy only and the stent + medical therapy groups. At 2-years follow-up no differences were observed between medical therapy and medical therapy + stent for systolic blood pressure (SBP) (136 ± 26 vs. 136 ± 18 mmHg, $p = 0.94$) or eGFR (56 ± 23 vs. 56 ± 23 ml/min, $p = 0.96$). In the longitudinal analysis of eGFR and SBP, neither stent treatment ($p = 0.212$ and $p = 0.9801$, respectively) nor the interaction between stent treatment and time ($p = 0.429$ and $p = 0.551$, respectively) were significant.

Conclusions: Renal artery stenting and optimal medical therapy, when compared to optimal medical therapy only, did not reduce the risk of fatal and nonfatal cardiorenal events in patients that were enrolled with history of congestive heart failure in the CORAL trial. Furthermore, stent treatment of CHF patients did not affect kidney disease progression or blood pressure control.

4A.03 CATHETER-BASED RENAL DENERVATION FOR RESISTANT HYPERTENSION: 24 MONTH RESULTS OF THE ENLIGHTN I STUDY USING A MULTIELECTRODE ABLATION SYSTEM

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Objective: The EnligHTN I, the first-in-human study using a multielectrode ablation system for renal denervation (RDN) in patients with drug resistant hypertension (dRHT) demonstrated efficacy and safety at 6 and 12 months. The aim of this study was to report the complete set of 24 month data on office, ambulatory and home blood pressure (BP) changes as well as long term safety.

Design and method: We studied 46 patients (age: 60±10 years, 4.7 ± 1.0 antihypertensive drugs, body mass index: 32 ± 5 kg/m^2) with dRHT on >or=3 antihypertensive medications who had a systolic BP>or=160 mmHg (>or=150 mmHg for diabetics). At baseline, the average office BP, 24-hour ambulatory BP and home BP were 176 ± 16/96 ± 14 mmHg, 150 ± 14/83 ± 13 mmHg and 158 ± 16/90 ± 12 mmHg respectively. Bilateral RDN was performed using percutaneous femoral approach and standardized techniques.

Results: Reduction in office BP at 18 and 24 months from baseline were -24/-10 mmHg and -29/-13 mmHg, while the reduction in 24-hour ambulatory BP and in home BP at 24 months were -13/-7 mmHg and -11/-6 mmHg respectively ($p < 0.05$ for all). Apart from higher body mass index (33.3 ± 4.7 vs 29.5 ± 6.2 kg/m^2, $p < 0.05$), there were no differences in age, baseline office BP, heart rate, diabetes mellitus and baseline antihypertensive drug therapy in patients that were RDN responders at 24 months [defined as 10 mmHg decline in office BP compared to baseline (74%, n = 34)]. Stepwise logistic regression analysis revealed no prognosticators of RDN response (p = NS for all). At 24 months apart from a trend for renal function decrease, there were no new serious or life-threatening adverse events related with the procedure.

Conclusions: The EnligHTN I study provides evidence that the multielectrode ablation system constitutes a safe method of RDN in patients with dRHT and is accompanied by a sustained reduction of office, ambulatory and home BP at 24 months after the procedure. However, no predictors of RDN response were identified at long term follow-up.

4A.04 EFFECTS OF RENAL DENERVATION ON ASYMMETRIC DIMETHYLARGININE AND SYMPATHETIC NERVE TRAFFIC IN RESISTANT HYPERTENSIVE PATIENTS

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Objective: Plasma concentrations of the endogenous inhibitor of nitric oxide synthase asymmetric dimethyl arginine (ADMA) are associated with sympathetic activity in patients with chronic disease. The driver of this association remains unknown. To solve the question it has been used the renal denervation of resistant hypertensive patients due to the marked reduction in whole-body norepinephrine spillover and sustained decrease in sympathetic nerve traffic (MSNA), thus representing an unique model to examine the hypothesis that sympathetic activity modulates circulating ADMA and its symmetric enantiomer (SDMA).

Design and method: 14 true resistant hypertensives (ESH/ESC guidelines definition) were evaluated at baseline and 15, 30, 90, 180 days after renal denervation. In each session blood samples were taken and then we measured beat-to-beat finger blood pressure (BP, Finapres), heart rate (HR), MSNA (microneurography). The global relationship between MSNA vs ADMA and SDMA was based on the calculation of the areas under the curves of these variables after renal denervation. Regression analyses were then performed.

Results: After renal denervation we observed a reduction in MSNA of -17% (range: from -66% to +10%). Changes in MSNA were strongly associated with the corrisponding changes in plasma ADMA ($r = 0.69$, $p = 0.005$) and SDMA ($r = 0.87$, $p < 0.001$). Furthermore, changes in MSNA went along with simultaneous changes in systolic ($r = 0.79$, $p = 0.001$) and diastolic BP ($r = 0.82$, $p < 0.001$) and HR ($r = 0.68$, $p < 0.01$). All these relationships were largerly independent of renal dysfunction.

Conclusions: These observations are compatible with the hypothesis that the sympathetic nervous system exerts an important role in modulating circulating levels of ADMA and SDMA in this condition.

4A.05 CIRCULATING FGF-23 AS AN INDEPENDENT CORRELATE OF HYPERTENSION AND ATHEROSCLEROSIS IN EARLY STAGES OF CKD

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Objective: Clinical and experimental evidence support a role for fibroblast growth factor (FGF-23) in promoting osteoclastic bone resorption, but the precise molecular mechanisms are not yet fully understood. FGF-23 has been implicated in chronic kidney disease (CKD) and is important in humans for osteogenesis. However, to date the possible role of FGF-23 in secondary hyperparathyroidism (SHP) is still unclear. The aim of this study was to investigate the serum levels of FGF-23 and its potential correlation with blood pressure, atherosclerotic markers and albuminuria in patients with early stages of CKD.

Design and method: CKD patients (n = 50) of stages 1 and 2 with type 2 diabetic nephropathy (DN, n = 25) and chronic glomerulonephritis, (CG, n = 25) were included. As controls, there were two groups, patients with diabetes type 2 without CKD (n = 40) and healthy individuals (n = 40). FGF-23 levels were measured by an ELISA method. Blood pressure (BP) was taken using a manual sphygmomanometer. Intima media thickness (IMT) of carotid arteries as a sub-atherosclerotic marker and presence of atherosclerotic plaque were evaluated by a high resolution ultrasonography. Statistical analysis was performed with the use of a SPSS system.

Results: The levels of FGF-23 were significantly higher in patients than in the control groups (0.5 ± 0.1, $p < 0.004$). IMT was also significantly higher in patients than in the control groups (0.35 ± 0.15, $p < 0.001$) and albuminuria (300 ± 150, $p < 0.0001$). There was negative strong correlation between FGF-23 and GFR ($r = -0.75$, $p < 0.005$), and positive strong correlation between FGF-23 and BP (0.7, $p < 0.0001$), between FGF-23 and IMT ($r = 0.85$, $p < 0.0001$) and FGF-23 and albuminuria ($r = 0.75$, $p < 0.0001$). Further, FGF-23 levels were independent correlates of BP, IMT and albuminuria.

Conclusions: This study suggests that serum levels of FGF-23 were strongly correlated with BP, IMT, atheromatic plaque as well as with albuminuria, attributing a role for FGF-23 in atherosclerosis of CKD patients. FGF-23 might present an independent correlate of atherosclerosis in early stages of CKD.

4A.06 ARTERIAL AND RENAL HEMODYNAMICS AND BARORECEPTOR FUNCTION IN NORMOTENSIVE AND HYPERTENSIVE RATS DURING FIELD STIMULATION OF CAROTID BARORECEPTORS

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Objective: Field stimulation of the carotid baroreceptors has been used successfully to induce long-term reduction in blood pressure. However, the effect of baroreceptor stimulation on short-term blood pressure regulation and circulatory hemodynamics in normotensive and hypertensive rat models is not well established.

Design and method: Male, Wistar Kyoto (WKY, n = 19) and spontaneously hypertensive rats (SHR, n = 19) (age: 13–58 weeks) were anaesthetised (urethane, 1.3 g/kg) and unilaterally vagotomised. Thoracic and aortic pressures, aortic pulse wave velocity (PWV), abdominal aortic flow and renal artery flow were measured. The left carotid artery was exposed and electrical field stimulation was applied to baroreceptors in the proximity of the carotid bifurcation (stimulation frequency: 100 Hz, pulse width: 0.53ms, signal amplitude: 3–5 v). A bolus of phenylephrine (1.5 μg) was delivered during baseline (no stimulation) conditions and during carotid baroreceptor stimulation to characterize baroreceptor function. Baroreceptor gain was computed as the absolute change in heart rate (HR) with respect to change in mean blood pressure (MAP).

Results: Field stimulation caused a significant reduction ($p < 0.001$) in HR and MAP in both WKY and SHR, indicative of sympathetic inhibition. Mean aortic flow reduced significantly in SHR ($p < 0.05$) but did not change in WKY. However, mean renal flow decreased significantly in both WKY ($p < 0.001$) and SHR ($p < 0.05$). Pulse pressure showed a significant reduction in WKY ($p < 0.05$) as compared to SHR ($p > 0.05$). There was a significant reduction in PVW ($p < 0.001$) with

stimulation in both WKY and SHR. There was no change in aortic or renal resistance. No change in baroreceptor gain (bpm/mmHg) was observed in both groups. WKY: gain (no stimulation), -0.54 ± 0.07; gain (stimulation), -0.48 ± 0.06. SHR: gain (no stimulation), -0.45 ± 0.07; gain (stimulation), -0.29 ± 0.03 mm/mmHg. There was a reduction in gain in SHR compared to WKY in both baseline ($p > 0.05$) and stimulation ($p < 0.05$) conditions.

Conclusions: Unilateral field stimulation of carotid baroreceptor nerves reduced MAP, HR and mean renal flow in WKY and SHR while it preserved baroreflex function in both groups. There was a significant reduction in SHR baroreceptor gain compared to WKY during stimulation.

4A.07 PREVALENCE AND RISK FACTORS FOR REFRACTORY HYPERTENSION IN THE DENERHTN STUDY

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Objective: The French DENERHTN trial has shown that renal denervation (RDN, Symplicity Catheter) in addition to standardized optimal medical treatment (SOMT) decreases ambulatory BP more (6 mmHg) than the same SOMT alone at 6 months in patients (pts) with resistant hypertension (RH). However, some pts did not respond to RDN or SOMT at 6 months. The aim of the study was to determine the prevalence and characteristics of refractory hypertension (RFH) to more than 5 antihypertensive treatments at 6 months in the 2 groups.

Design and method: Pts with RH to > = 3 antihypertensive drugs, including a diuretic, entered a 4-week standardised triple treatment with indapamide 1.5 mg/day, ramipril 10 mg/day (or irbesartan 300 mg/day if cough), and amlodipine (10 mg/day). After 4 weeks, pts with daytime ambulatory SBP/DBP (dASBP/dADBP) > = 135 or 85 mmHg were randomised to the RDN or control group. After randomisation, the SOMT included: spironolactone (25 mg/day), bisoprolol (10 mg/day), prazosin (5 mg/day), and rilmenidine (1 mg/day) sequentially added if home BP (HBP) was > = 135 or 85 mmHg at month 2, 3, 4 and 5.

Results: 49/97 pts (50.5%) had RFH at 6 months (RDN: 20/44, 45.5% vs. control: 28/53, 52.8%; $p = 0.157$). RFH pts were more frequently women, had more frequently OSA, had higher baseline BP values, responded less to any intervention (RDN + SOMT or SOMT alone) despite receiving more antihypertensive treatments, had lower plasma creatinine at baseline. The Morisky adherence score was lower ($p = 0.085$) at baseline than at 6 months in the RFH group.

	RFH (n=49)	No RHF (n=48)	P
Age (years)	56·3±11·2	53·5±9·8	0·1795
Women, N (%)	25 (50·0)	13 (28·6)	0·0306
Caucasian, N (%)	31 (64·6)	32 (65·3)	0·2696
Type 2 diabetes, N (%)	12 (25·0)	10 (20·4)	0·5892
Prior cardiovascular event, N (%)	4 (8·3)	4 (8·2)	0·9757
Obstructive sleep apnea, N (%)	17 (35·4)	10 (20·4)	0.0992
BMI (kg/m^2)	30.7±4·7	29.7±4·9	0·3254
Baseline Plasma creatinine (µmol/l)	78±23	88±24	0·0402
Baseline dASBP (mmHg)	159·5±18·2	146·8±11·5	<0·001
Baseline dA DBP (mmHg)	95·1±15·8	89.9±8.9	0·0500
Baseline Moryski score	7·26±1·07	7·59±0·83	0·0859
Change in dASBP (mmHg)	-7·9±15·9	-16·9±12	0·0022
Change in dADBP (mmHg)	-5·5±9·5	-10.6±9.4	0·0090
6-month Moryski score	7·65±0·78	7·46±1·16	0·3551
Treatment score at 6 months	6·10±0·86	4·57±1·41	<0·001
Plasma creatinine at 6 months (µmol/l)	86±25	91±27	0.314

Data are mean±SD or median [IQR]

Conclusions: In conclusion, despite following strictly ESH guidelines for treating patients with RH to a triple therapy, around 50% of the pts have RFH after 6 months follow-up in the DENERHTN trial. Female gender, high BP, low plasma creatinine, and lower adherence at baseline were associated with RFH.

4A.08 ASSESSING MODULATIONS IN SYMPATHETIC NERVE ACTIVITY AFTER RENAL SYMPATHETIC DENERVATION USING RENAL 123I-MIBG SCINTIGRAPHY

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Objective: Over recent years moderation of renal sympathetic nerve activity by catheter-based renal sympathetic denervation (RDN) has received a considerable amount of attention as a treatment potential for therapy-resistant hypertension. However, incomplete nerve disruption is a possible factor that causes the wide inter-individual variety of blood pressure (BP) response. ^{123}I-meta-iodobenzylguanidine (^{123}I-mIBG) scintigraphy enables assessment of organ specific sympathetic activity. We hypothesized that renal ^{123}I-mIBG scintigraphy could be used as a measure of denervation following RDN. In addition, we explored its association with BP and plasma renin activity before and after denervation.

Design and method: In patients with treatment resistant hypertension (median age 60.0 years, average 24 h BP measurement (ABPM) 160/93 mmHg), we prospectively studied ^{123}I-mIBG scintigraphy, ABPM plasma- and urine-catecholamines before and 6 weeks after RDN.
Planar scintigrams of the base of the skull to the upper thighs were performed at 15 min and 4 h after administration of ^{123}I-mIBG. In these scintigrams, regions of interest of the kidney (specific) and muscle (non-specific) were drawn. The ratio of specific counts vs. non-specific counts represents ^{123}I-mIBG uptake and washout of ^{123}I-mIBG was calculated between 15 min and 4 h. Data of ^{123}I-mIBG scintigraphies from six patients receiving complete denervation following renal transplantation served as control.

Results: In 21 treatment resistant hypertensive patients no significant alterations were observed in ^{123}I-mIBG readouts: uptake at 15 min before RDN was 3.08 (IQR 2.79–4.95) and 3.47 (IQR 2.26–5.53) after RDN ($p = 0.289$) pre-RDN washout was 41.5% and 42.7% post-RDN ($p = 0.230$). ABPM did not change significantly after denervation: 160/93 mmHg before RDN (IQR 151–173/84–100) to 157/92 mmHg (IQR 139–174/80–95) after RDN ($p = 0.602$). Post-RDN, office-based systolic BP decreased from 172 to 153 mmHg ($p = 0.036$) but office-based diastolic BP changed non-significantly from 97 to 90 mmHg, $p = 0.531$). In neither the catecholamines in plasma and urine or renin were statistical differences observed.

Conclusions: We observed no modifications in renal sympathetic nerve activity using renal ^{123}I-mIBG scintigraphy. No changes in ABPM or catecholamines were found at six weeks after RDN, which is consistent with incomplete denervation.

4A.09 SAFETY AND PERFORMANCE OF THE ENLIGHTN RENAL DENERVATION SYSTEM IN PATIENTS WITH SEVERE UNCONTROLLED HYPERTENSION: 12 MONTH RESULTS FROM THE ENLIGHTN II STUDY

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Objective: Percutaneous sympathetic renal artery denervation is available for the treatment of patients with resistant hypertension. We further investigated the safety and efficacy of a multi-electrode renal denervation system (EnligHTN^{TM}) in patients with severe uncontrolled hypertension.

Design and method: The EnligHTN-II study is a post-market clinical investigation in which patients were assigned to one of three groups; Group A, office systolic BP (OSBP) >/=160 mmHg and estimated glomerular filtration rate (eGFR) >/=45 mL/min per 1.73 m2, Group B, OSBP >/=140–159 mmHg and eGFR >/=45 mL/min per 1.73 m2 and Group C, OSBP >/=140 mmHg and eGFR >/=15 mL/min per 1.73 m2. For all three groups subjects were required to be on at least 3 anti-hypertensive medications (including 1 diuretic), or to have documented drug intolerance such that they are unable to take 3 anti-hypertensive drugs.

Results: 129 patients from Group A (average age 62 ± 9.5 yrs taking on average 4.22 ± 2.21 anti-hypertensive medications) were included. Bilateral renal nerve ablation was performed using a percutaneous femoral approach. Baseline average OSBP was 181.9 ± 16.2 mmHg, average office diastolic BP (ODBP) was 97.6 ± 16 mmHg, average daytime ambulatory SBP (ASBP) was 163.3 ± 17.5 mmHg, and average daytime ambulatory DBP (ADBP) was 91.6 ± 13.8 mmHg.
At present, 103 6-month and 64 12-month follow-up visits are completed. The average reduction in OSBP/ODBP was 18.2/8.5 mmHg (SD 21.5/14.3) and 17.2/9.9 mmHg (20.9/13.3) at 6- and 12-month follow up respectively ($p < 0.0001$ for all). The average reduction in daytime ASBP/ADBP was 7.9 (17.0) /4.8 (9.0) mmHg ($p < 0.0001$ for both) and 7.6 (17.1) /4.0 (9.7) mmHg ($p = 0.0024/0.0049$) at 6 and 12 M follow up respectively. Significant changes in nocturnal and 24 hour ambulatory BP were also observed. Neither eGFR nor serum creatinine changed significantly from baseline at either 6 or 12-months follow up.

Conclusions: In this real world, post-marketing study we demonstrate that multi-electrode renal denervation results in durable, highly significant and safe lowering of both office BP and ambulatory BP parameters in patients with severe uncontrolled hypertension up to 12 months following treatment.

4A.10 PREFERENTIAL REDUCTION IN MORNING/NOCTURNAL HYPERTENSION BY RENAL DENERVATION FOR DRUG-RESISTANT HYPERTENSION: A NEW ABPM ANALYSIS OF SYMPLICITY HTN-3 AND HTN-JAPAN

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Objective: To study the impact of catheter-based renal artery denervation (RDN) on change in morning and night systolic BP (SBP) defined by ambulatory BP measurements (ABPM) 6 months post-randomization.

Design and method: SYMPLICITY HTN-3 and SYMPLICITY HTN-Japan are prospective, randomized, controlled trials of RDN for treatment of resistant hypertension. However, SYMPLICITY HTN-3 included a blinded, sham control and HTN-Japan control patients were not blinded and continued medical management alone. Patients in both trials were on a stable antihypertensive regimen of at least 3 drugs including a diuretic before randomization. Average morning SBP (7 am to 9 am), maximum morning SBP (between 6 am and 10 am), average nocturnal SBP (1 am to 6 am), average peak nocturnal SBP (average of 3 highest SBPs between 1 am and 6 am) and average daytime SBP were calculated using pooled patient-level ABPM data. Six-month change in SBP parameters were compared between RDN and control patients.

Results: A total of 386 patients (364 from HTN-3 and 22 from Japan) received RDN and 190 patients were in the control group (171 from HTN-3 and 19 from Japan). The average morning SBP was reduced -8.0 ± 22.3 mmHg in the RDN group which was significantly more than the change in the control group (-3.5 ± 22.2 mmHg, p = 0.023). The maximum morning SBP change was -8.6 ± 22.3 mmHg for RDN patients and -4.8 ± 23.8mmHg for controls (p = 0.072). Furthermore, the change in average nocturnal and average peak nocturnal SBP was significantly greater in the RDN patients compared with the control patients; -6.3 ± 18.1 vs -1.7 ± 19.2 mmHg, p = 0.008 for average nocturnal SBP and -6.7 ± 20.0 vs -1.3 ± 20.5 mmHg, p = 0.004 for average peak nocturnal SBP. Average daytime SBP change was not significantly between the RDN and control groups (-7.1 ± 16.0 vs -5.7 ± 18.0 mmHg, p = 0.349).

Conclusions: This analysis demonstrated that RDN significantly reduced morning and nighttime SBP compared with control patients suggesting potential benefit of this device approach on cardiovascular protection in drug-resistant hypertension when measurements are captured during higher risk time periods.

ORAL SESSION

ORAL SESSION 4B
DIABETES

4B.01 CONTRASTING INFLUENCES OF RENAL FUNCTION ON BLOOD PRESSURE AND HBA1C REDUCTIONS WITH EMPAGLIFLOZIN IN PATIENTS WITH TYPE 2 DIABETES AND HYPERTENSION

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Objective: To determine if impaired renal function attenuates antihypertensive effects of empagliflozin.

Design and method: In a Phase III randomised placebo-controlled trial (EMPA-REG BP^{TM}), patients with type 2 diabetes and hypertension (defined as mean seated office systolic blood pressure [SBP] 130–159 mmHg and diastolic BP 80–99 mmHg at screening) received empagliflozin 10 mg, empagliflozin 25 mg or placebo for 12 weeks (mean [SD] age 60.2 [9.0] years, HbA1c 7.90 [0.74] %, 24-hour SBP 131.4 [12.3] mmHg). We assessed changes from baseline in mean ambulatory 24-hour SBP and HbA1c in subgroups by baseline eGFR (MDRD equation).

Results: In patients with normal renal function, stage 2 or 3 chronic kidney disease (CKD; eGFR >=90 [n = 261], 60 to <90 [n = 516], 30 to <60 [n = 45] ml/min/1.73m^2, respectively), empagliflozin significantly reduced HbA1c and mean 24-hour SBP versus placebo. As expected, placebo-corrected HbA1c reductions with empagliflozin appeared to decrease with decreasing eGFR. Differences versus placebo in changes from baseline in mean 24-hour SBP were −3.8 (−6.3,−1.4) and −3.4 (−5.7,−1.1) mmHg with empagliflozin 10 mg and 25 mg, respectively, in patients with normal renal function, −2.7 (−4.4, −1.1) and −4.5 (−6.2,−2.8) mmHg, respectively, in patients with stage 2 CKD, and −11.0 (−17.4,−4.6) and −6.8 (−12.6,−1.0) mmHg, respectively, in patients with stage 3 CKD (all p < 0.05).

Conclusions: Unlike HbA1c, reductions in mean 24-hour SBP with empagliflozin in patients with type 2 diabetes and hypertension appear to be greater in patients with lower eGFR, indicating that SBP modulation with empagliflozin may involve pathways other than urinary glucose excretion.

4B.02 THE SODIUM GLUCOSE COTRANSPORTER 2 INHIBITOR EMPAGLIFLOZIN REDUCES BLOOD PRESSURE AND MARKERS OF ARTERIAL STIFFNESS AND VASCULAR RESISTANCE IN TYPE 2 DIABETES

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Objective: To assess the vascular effects of empagliflozin, beyond reducing systolic blood pressure (SBP) and diastolic BP (DBP) in patients with type 2 diabetes.

Design and method: Using pooled data from patients with type 2 diabetes (n = 2477) who participated in four 24-week phase III randomised trials of empagliflozin 10 mg or 25 mg (n = 1652) versus placebo (n = 825) as monotherapy or add-on therapy (mean [SD] age 55.6 [10.2] years, HbA1c 8.0 [0.9]%, BMI 28.7 [5.5] kg/m^2), we assessed changes in HbA1c, SBP, DBP, pulse pressure (PP; SBP -DBP), a validated surrogate marker of the stiffening of the conduit vessels, mean arterial pressure (MAP), reflecting cardiac output multiplied by vascular resistance (MAP = ([2 x DBP] + SBP)/3) and heart rate (HR).

Results: In placebo and empagliflozin groups, respectively, baseline mean SBP was 128.6 and 129.3 mmHg, DBP was 78.0 and 78.5 mmHg, PP was 50.5 and 50.8 mmHg, MAP was 94.9 and 95.4 mmHg and HR was 74.3 and 74.1 bpm. At week 24, compared with placebo, empagliflozin significantly reduced HbA1c (mean [SE] difference: -0.65% [0.03]; p < 0.001), SBP (mean [SE]: -3.6 [0.5] mmHg; p < 0.001), DBP (mean [SE]: -1.3 [0.3] mmHg; p < 0.001), PP (mean [SE]: -2.3 [0.4] mmHg; p < 0.001) and MAP (mean [SE]: -2.1 [0.3] mmHg; p < 0.001). Adjusted mean (SE) change in HR with empagliflozin compared to placebo was -0.8 (0.3); p < 0.05.

Conclusions: Empagliflozin had favourable effects on BP, arterial stiffness and vascular resistance, which are intermediate markers of cardiovascular risk. The EMPA-REG OUTCOME^{TM} trial (NCT01131676) will evaluate whether these benefits will translate into cardiovascular risk reduction.

4B.03 EMPAGLIFLOZIN REDUCES SYSTOLIC BLOOD PRESSURE IN DIPPER AND NON-DIPPER PATIENTS WITH TYPE 2 DIABETES AND HYPERTENSION

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Objective: To assess changes in systolic blood pressure (SBP) with empagliflozin in patients with type 2 diabetes and hypertension (defined as mean seated office SBP 130–159 mmHg and diastolic BP 80–99 mmHg) categorised as dippers or non-dippers.

Design and method: In a subgroup analysis of patients who received empagliflozin 10 mg, empagliflozin 25 mg or placebo in a Phase III randomised trial (EMPA-REG BP^{TM}), we assessed changes from baseline in SBP (mean 24-h, awake-time, sleep-time) via ambulatory BP monitoring at week 12 in patients categorised as dippers (sleep-time mean SBP <=90% of awake-time mean; n = 417) or non-dippers (sleep-time mean SBP > 90% of awake-time mean; n = 350).

Results: Baseline mean (SD) 24-h SBP (mmHg) was 129.9 (11.6) in dippers and 133.1 (12.4) in non-dippers. Adjusted mean (SE) changes from baseline in mean 24-h SBP (mmHg) in dippers were -0.2 (0.7) with placebo versus -3.8 (0.6) and -3.9 (0.7) with empagliflozin 10 and 25 mg, respectively (both p < 0.001), and in non-dippers were 1.0 (0.7) with placebo versus -1.6 (0.7) with empagliflozin 10 mg (p = 0.013) and -3.8 (0.7) with empagliflozin 25 mg (p < 0.001). Hourly mean SBP patterns over 24 h for dippers and non-dippers were maintained with empagliflozin 10 mg and 25 mg. Compared with placebo, changes from baseline in awake-time and sleep-time SBP were significantly greater with empagliflozin 10 mg or 25 mg, except for sleep-time SBP with empagliflozin 10 mg.

Conclusions: In patients with type 2 diabetes and hypertension, empagliflozin 10 mg and 25 mg significantly reduced SBP versus placebo in dippers and non-dippers.

4B.04 COST-UTILITY OF ANGIOTENSIN-CONVERTING ENZYME INHIBITOR COMPARED TO THIAZIDE DIURETIC BASED TREATMENT FOR HYPERTENSION IN ELDERLY AUSTRALIANS CONSIDERING DIABETES AS COMORBIDITY

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Objective: To examine the cost-effectiveness of angiotensin-converting enzyme inhibitor-based (ACEI) treatment compared to thiazide diuretic-based treatment

for hypertension in elderly Australians considering diabetes as an outcome along with cardiovascular outcomes from the Australian government perspective.

Design and method: We used a cost-utility analysis to estimate the incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) gained. Data on cardiovascular events and new-onset of diabetes were used from the Second Australian National Blood Pressure Study, a randomized clinical trial comparing diuretic-based (hydrochlorothiazide) versus ACEI-based (enalapril) treatment in 6083 elderly (age 65yrs or more) hypertensive patients over a median 4.1-year period. For this economic analysis, the total study population was stratified into two groups. Group A was restricted to participants diabetes-free at baseline (n = 5,642); and Group B was restricted to participants with pre-existing diabetes mellitus (Type I or Type II) at baseline (n = 441). Data on utility scores for different events were used from available published literatures; whereas, treatment and adverse event management cost were calculated from direct health care costs available from Australian Government reimbursement data. Quality of life and costs were discounted at 5% per annum. One-way and probabilistic sensitivity analyses were performed to assess the uncertainty around utilities and cost data.

Results: After a treatment period of five years, for Group A the ICER was AUD 27,698 (Euro 18,004; AUD 1∼ € 0.65) per QALY gained comparing ACEI-based with diuretic-based treatment (sensitive to the utility value for new-onset diabetes). In Group B, ACEI-based treatment was a dominant strategy (both more effective and cost-saving). On probabilistic sensitivity analysis, the ICERs per QALY gained were always below AUD 50,000 for Group B; whereas for Group A the probability of being below AUD 50,000 was 85%.

Conclusions: Although the dispensed price of diuretic-based treatment of hypertension in the elderly is lower, upon considering the potential enhanced likelihood of the development of diabetes in addition to the costs of treating cardiovascular disease, ACEI-based treatment may be a more cost-effective strategy in this population.

4B.05 PLASMA COPEPTIN IS ASSOCIATED WITH INSULIN RESISTANCE IN A SWISS POPULATION-BASED STUDY

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Objective: Previous studies suggest that arginine vasopressin may have a role in metabolic syndrome (MetS) and diabetes by altering liver glycogenolysis, insulin, and glucagon secretion and pituitary ACTH release. We tested whether plasma copeptin, the stable C-terminal fragment of arginine vasopressin prohormone, was associated with insulin resistance and MetS in a Swiss population-based study.

Design and method: We analyzed data from the population-based Swiss Kidney Project on Genes in Hypertension. Copeptin was assessed by an immunoluminometric assay. Insulin resistance was derived from the HOMA model and calculated as follows: (FPI x FPG)/22.5, where FPI is fasting plasma insulin concentration (mU/L) and FPG fasting plasma glucose (mmol/L). Subjects were classified as having the MetS according to the National Cholesterol Education Program Adult Treatment Panel III criteria. Mixed multivariate linear regression models were built to explore the association of insulin resistance with copeptin. In addition, multivariate logistic regression models were built to explore the association between MetS and copeptin. In the two analyses, adjustment was done for age, gender, center, tobacco and alcohol consumption, socioeconomic status, physical activity, intake of fruits and vegetables and 24 h urine flow rate. Copeptin was log-transformed for the analyses.

Results: Among the 1,089 subjects included in this analysis, 47% were male. Mean (SD) age and body mass index were 47.4 (17.6) years 25.0 (4.5) kg/m2. The prevalence of MetS was 10.5%. HOMA-IR was higher in men (median 1.3, IQR 0.7–2.1) than in women (median 1.0, IQR 0.5–1.6,P < 0.0001). Plasma copeptin was higher in men (median 5.2, IQR 3.7–7.8 pmol/L) than in women (median 3.0, IQR 2.2–4.3 pmol/L), P < 0.0001. HOMA-IR was positively associated with log-copeptin after full adjustment (β (95% CI) 0.19 (0.09–0.29), P < 0.001). MetS was not associated with copeptin after full adjustment (P = 0.92).

Conclusions: Insulin resistance, but not MetS, was associated with higher copeptin levels. Further studies should examine whether modifying pharmacologically the arginine vasopressin system might improve insulin resistance, thereby providing insight into the causal nature of this association.

4B.06 EFFECT OF CHRONIC KIDNEY DISEASE, DYSLIPIDEMIA AND HYPERTENSION ON CAROTID ATHEROSCLEROSIS IN ELDERLY PATIENTS WITH TYPE 2 DIABETES

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Objective: To assess the possible role of dyslipidemia, hypertension and chronic kidney diseases on the characteristics of carotid atherosclerosis in elderly patients with type 2 diabetes (DT2).

Design and method: We investigated 76 patients both sexes with DT2 aged 65.54 ± 4.37 years (from 60 to 75 years). Control group included 24 healthy subjects the same age. The intima-media thickness (IMT) was measured as the distance between the lumen-intima interface and the media-adventitia interface. Atherosclerotic plaque was defined as a focal structure encroaching into the arterial lumen of 0.5 mm or 50% of the surrounding IMT value. Total plaque area (TPA) was calculated as the sum of all plaque areas.

Results: The mean blood glucose and HbA1c level were 8.52 ± 3.10 mmol/L and 6.59 ± 1.88%, respectively. We divided all patients into 3 groups: Group 1 (n = 24) – patients did not have any additional atherosclerosis risk factor, Group 2 (n = 25) – patients had one additional atherosclerosis risk factor, and Group 3 (n = 43) – patients had two or three additional atherosclerosis risk factors. Using multiple linear regression analysis adjusted for confounding factors, IMT and TPA were significantly correlated with age > 60 years (p < 0.0001; p < 0.0001), hypertension (p = 0.003; p < 0.0001), dyslipidemia (p = 0.0001; p < 0.0001) and CKD (p = 0.003; p < 0.0001), respectively. However, gender (men) was not significantly correlated with IMT (p = 0.171) and TPA (p = 0.112). We found a significant difference in carotid IMT between left and right carotid artery (0.70 ± 0.16 mm versus 0.66 ± 0.13 mm, p < 0,001, respectively). There were no significant difference in carotid IMT between patients with plague and without plague (p = 0.171).

Conclusions: We showed the role of additional atherosclerosis risk factors to carotid atherosclerosis in elderly patients with DT2. In these patients, the presence of dyslipidemia, hypertension, and different CKD status were predictors of carotid plaque.

4B.07 BASELINE CARDIAC TROPONIN T LEVELS ARE ELEVATED IN SUBJECTS WITH UNTREATED DIABETES MELLITUS: A CROSS-SECTIONAL STUDY

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Objective: Cardiac troponins are biomarkers of myocardial injury and serve both diagnostic and prognostic purposes. Even mild elevations represent subclinical myocardial damage in the general population. The objective of this study was to investigate the relationship between glucometabolic status and cardiac troponin T in middle-aged or older apparently healthy subjects.

Design and method: We examined cross-sectional associations between high-sensitivity cardiac troponin T (hsTnT) and FPG categorized as normal fasting glucose (NFG: FPG</=6.0mmol/L), impaired fasting glucose (IFG: FPG 6.1–6.9mmol/L), and diabetes mellitus (DM: FPG>/=7.0mmol/L), in 535 men and 226 women aged 56–79 years without overt cardiovascular disease who received no cardiovascular, antidiabetic or lipid lowering drugs, using multiple linear regression analysis.

Results: FPG category (r = 0.159; p < 0.001) was positively correlated with hsTnT. Mean hsTnT levels increased significantly with worsening glucometabolic status (NFG: 7.55 ng/L +/- standard deviation 3.99 ng/L; IFG: 8.09 ng/L +/- 6.81 ng/L; DM: 10.28 ng/L +/- 7.55 ng/L; p < 0.001). Levels were significantly higher in subjects with DM compared to NFG (p < 0.001) and IFG (p = 0.005), but there was no significant difference between subjects with NFG and IFG (p = 0.26). After adjusting for age and sex, FPG category remained significantly predictive of hsTnT (B = 1.08 [95% confidence interval (CI), 0.56–1.59]; p < 0.001). After further adjusting for traditional cardiovascular risk factors, cystatin C levels, and electrocardiographic left ventricular hypertrophy (LVH) defined by the Sokolow-Lyon index and/or Cornell voltage-duration product, FPG category remained significantly

associated with hsTnT (B = 0.87 [95% CI, 0.35–1.39]; p = 0.001), independently of age (B = 0.29 [95% CI, 0.22–0.36]; p < 0.001), sex (B = 2.08 [95% CI, 1.20–2.95]; p < 0.001), systolic blood pressure (B = 0.032 [95% CI, 0.012–0.051]; p = 0.001), and cystatin C (B = 3.69 [95% CI, 1.60–5.79]; p = 0.001). There was a significant interaction between FPG category and age (NFG: B = 0.22 [95% CI, 0.16–0.29]; IFG: B = 0.33 [95% CI, 0.18–0.48]; DM: B = 0.41 [95% CI, 0.20–0.62]; p = 0.03).

Conclusions: In middle-aged or older apparently healthy subjects, untreated DM was associated with higher levels of hsTnT, independently of traditional cardiovascular risk factors. The importance of age increased with worsening glucometabolic status.

4B.08 SERUM LEVELS OF TIMP-1 AND IL-6 ARE ASSOCIATED WITH HYPERTENSION AND ATHEROSCLEROSIS IN PATIENTS WITH EARLY STAGES OF CHRONIC KIDNEY DISEASE AND TYPE 2 DIABETIC NEPHROPATHY

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Objective: Tissue inhibitor of metalloproteinase -1 (TIMP-1) has been identified in humans and its expression is regulated during development and tissue remodeling. TIMP-1 overexpression in a mouse model of atherosclerosis showed a lesion reduction. Interleukine-6 (IL-6) is considered to be pro-inflammatory lipocytokine. The aim of the present study was to determine the serum levels of TIMP-1 and IL-6 and to investigate their potential correlation with hypertension, atherosclerotic markers and albuminuria in early stages of type 2 diabetic nephropathy (DN).

Design and method: CKD patients of stages 1 and 2 with type II DN (n = 50) were included. As controls, there were two groups, patients with diabetes type II without CKD (n = 40) and healthy individuals (n = 40). Clearance of creatinine (Clcr) and albumin excretion were examined in the 24 h urine. TIMP-1 and IL-6 levels were measured by an ELISA method. Blood pressure (BP) was taken using a manual sphygmomanometer. Intima media thickness (IMT) of carotid and femoral arteries and atheromatic plaque were evaluated by a high resolution ultrasonography. Statistical analysis was performed with the use of a SPSS system.

Results: There was a statistically significant difference between TIMP-1 (400 ± 20, $p < 0.0001$), IL-6 (4 ± 0.5, $p < 0.0001$), BP (20 ± 5, $p < 0.0001$) and IMT (0.3 ± 0.09, $p < 0.0001$) between patients and controls. There was a statistically significant negative strong correlation between levels of TIMP-1 and IL-6 ($r = -0.7$, $p < 0.0001$), such as between TIMP-1 and IMT ($r = -0.65$, $p < 0.0001$) in the patient group. There was also a statistically positive correlation between IL-6 and IMT ($r = 0.7$, $p < 0.0001$) in the patient group. Further, TIMP-1 and IL-6 levels were independently correlated with IMT and atheromatic plaque.

Conclusions: Our study suggests that serum levels of TIMP-1 and IL-6 might present independent risk factors of blood pressure, atherosclerosis and albuminuria, at least in the early stages of type II diabetic nephropathy to the progression of CKD.

4B.09 DIABETES MELLITUS AND ORGAN DAMAGE, CARDIOVASCULAR DISEASE AND MORTALITY IN HYPERTENSIVE PATIENTS: FOLLOW-UP STUDY

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Objective: Diabetes mellitus is an important contributor to a vascular damage inducing a high risk of macro-and microvascular complications. In this study, we tried to evaluate the proposed correlation of diabetes with target organ damage and cardiovascular disease and mortality in hypertensive patients.

Design and method: We studied 134 participants (91 females, 43 males). Each participant underwent asymptomatic organ damage: 12-lead electrocardiogram examination, two-dimensional and Doppler echocardiography, colour Doppler sonography of the carotid arteries, laboratory investigations were prospectively followed for total and cardiovascular mortality and disease over a median of 6 years.

Results: They had a mean age of 62.9 ± 8.5 years, body mass index of 28.9 ± 3.68 kg/m^2, office blood pressure of $158 \pm 16.7/91 \pm 10.8$ mmHg, index left ventricular mass (LVM) of 139.1 ± 3.99 g/m2, carotid intima-medial thickness (IMT) of 0.94 ± 0.25 mm and presence of a plaque in 69 (51.5%) participants.
Diabetes mellitus was found in 41 (30.6%) participants (group I). The mean value of blood pressure (144 vs. 145.9 mmHg), visit-to-visit blood pressure variability (16.8 vs. 16.9 mmHg), serum total cholesterol (5.25 vs. 5.4 mmol/l), and fasting serum triglycerides (1.83 vs. 1.77 mmol/l) did not differ between the groups in the end of the study.
In group I, 27(66%) participants presence of a plaques in carotids, vs. 43(46%) participants in group II ($p < 0.04$). Mean Carotid IMT of 1.01 ± 0.22 in group I, vs. 0.91 ± 0.26 mm in group II ($p < 0.04$). Echocardiographic mean LVM index of 140.4 ± 30.1 in group I and 138.5 ± 31.66 g/m2 in group II (ns).
A total of 5 (3.7%) participants died from cardiovascular disease, 4 patients from group I and 1 patients from group II ($p < 0.02$). Major CV events were observed in 13 participants (31.7%) from group I, while there were 13 (14%)(group II) ($p < 0.02$). In group I, 6 (14.6%) participants developed a malignant disease vs. 9(9.7%) participant in group II (ns).

Conclusions: Diabetes mellitus in hypertensive patients is associated with higher incidences of asymptomatic carotid disease and major cardiovascular events.

4B.10 24 HOUR URINE FREE CORTISOL TO CORTISONE RATIO IS A NOVEL BIOMARKER FOR INCREASED LEFT VENTRICULAR MASS IN DIABETIC HYPERTENSIVES

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Objective: Renal 11 beta hydroxysteroid dehydrogenase type 2 (11BHSD2) is a key molecular player in the renin- angiotensin- aldosterone system (RAAS). We hypothesize that decreased renal 11BHSD2 activity, as measured by increased urinary free cortisol to cortisone (UFF/UFE) ratio using gas chromatography-mass spectrometry (GCMS), may be an important biomarker in identifying diabetic patients with increased left ventricular mass.

Design and method: We studied insulin-naive male patients with type 2 diabetes and stage 1 hypertension (blood pressure of 140–160/90–100 mmHg) in this study. 24-hour urine was collected and UFF/UFE ratio was determined using GCMS. All patients underwent 2D-echocardiogram (2DE) for measurement of left ventricular mass index (LVMI).

Results: A total of 43 diabetic male patients with hypertension were evaluated in this study. As per current hypertension guidelines, all subjects were already taking either an angiotensin converting enzyme inhibitor (ACE) or angiotensin receptor blocker (ARB) for their hypertension control. The mean 24 hour UFF/UFE ratio was 0.77+/- 0.05 (interquartile range 0.52 to 1.00), with higher UFF/UFE ratios reflecting lower renal 11BHSD2 activity. Higher UFF/UFE ratio correlated with higher LVMI ($r = 0.46$, $p = 0.003$). Among the subjects in the highest quartile (UFF/UFE ratio > 1.00), the left ventricular mass index was significantly higher (113.8 g/m2 vs 89.1 g/m2, $p = 0.03$; difference between means 23.7 +/- 9.8 g/m2) when compared to the rest of the cohort. This association was independent of age, blood pressure, duration of diabetes, medications, glycated hemoglobin (HBA1C), body mass index (BMI), ethnicity or serum creatinine.

Conclusions: In diabetics with stage 1 hypertension, a 24 hour urine free cortisol to cortisone ratio >1.00 as measured by gas chromatography-mass spectrometry, independently identifies patients with a significantly higher left ventricular mass, a subset of patients known to be at a higher risk of developing cardiovascular complications.

ORAL SESSION

ORAL SESSION 4C

CEREBROVASCULAR DISEASES, STROKE, DEMENTIA AND COGNITIVE DYSFUNCTION

4C.01 LIFETIME OBESITY, CARDIOVASCULAR DISEASE AND COGNITIVE FUNCTION: A LONGITUDINAL STUDY FROM THE 1946 BIRTH COHORT

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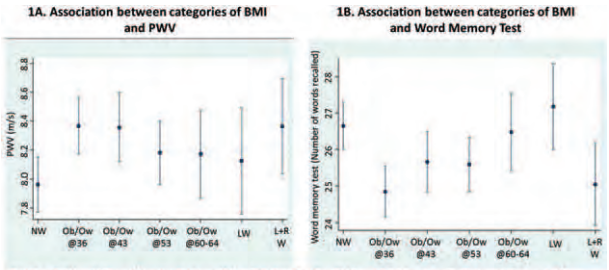
Objective: Obesity is a major risk factor for cognitive impairment and increases risk of cardiovascular disease (CVD). As CVD in itself is a risk factor for cognitive impairment, we assessed the influence of cardiovascular (CV) phenotypes on the association between lifetime exposure to obesity and midlife memory function.



Ob/Ow@36 = Obese or overweight at 36 years old; Ob/Ow@43 = Obese or overweight at 43 years old; Ob/Ow@53 = Obese or overweight at 53 years old; Ob/Ow@60-64 = Obese or overweight at 60-64 years old; LW = lost weight at any point during follow up; L+RW = Lost and re-gained weight during follow up. See text for P values of the differences between groups. Figure 1A is adjusted for sex.

Design and method: 233 participants of the National Survey of Health and Development (NSHD) Study, with lifetime measures of BMI (36, 43, 53, and 60–64 years) and CV risk factors, vascular phenotypes (carotid intima-media thickness, cIMT, aortic pulse wave velocity, aPWV, and aortic calcification score, AAC-8) and cognitive data (word memory test, WMT) at 60–64 years were included in this study. Patterns of BMI change over 30 years were identified. Multivariable linear regression models (with adjustments for sex, heart rate, education and CV risk factors) were used to establish the associations between cross-sectional and lifetime measures of adiposity with memory function as well as the influence of vascular phenotypes on these associations.

Results: At 60-64 years old, obese participants had lower WMT performance ($P < 0.001$), higher cIMT ($P < 0.001$), aPWV ($P < 0.002$) and AAC-8 ($P = 0.012$) compared to their normal weight peers. aPWV and AAC-8 ($P < 0.001$ for both) but not cIMT were negatively associated with performance at the WMT. The association between BMI with WMT remained significant following adjustments for aPWV and CV risk factors ($P < 0.001$). Similarly, adjustment for BMI and CV risk factors did not affect the association between aPWV and WMT ($P = 0.009$). Longer exposure to adiposity was associated with lower memory function (P-trend < 0.001) and higher aPWV (P-trend = 0.043) at 60–64 years. Individuals who, at any point, dropped one BMI category had memory function and vascular phenotypes similar to normal weight subjects ($P = 0.431$ and $P = 0.914$, respectively). The beneficial effect of wieght loss on memory function was lost if people re-gained weight (Figures 1A and 1B).

Conclusions: Lifetime exposure to adiposity increases aortic stiffness and reduces memory function. These impacts are potentially reversible with weight loss. However, once vascular damage is established, its impact on memory function is likely to be independent from current BMI and CV risk factors levels.

4C.02 PROLONGED ANGIOTENSIN II-INDUCED HYPERTENSION IMPAIRS SHORT-TERM MEMORY IN ADULT MICE

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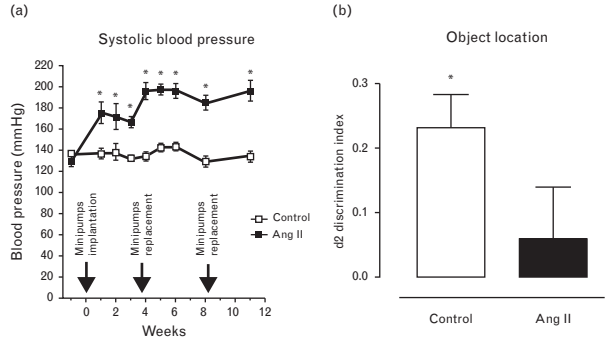
Objective: Cognitive impairment is a major disability increasing due to population ageing. Hypertension is a major risk factor for the development of vascular cognitive impairment. However the contribution of hypertension in the pathological cascade of vascular cognitive impairment remains elusive. Although few cardiovascular models have shown to be relevant for the study of vascular cognitive impairment, chronic hypertensive models with established cognitive impairment are lacking. In particular working and short-term memories have never been investigated. The aim of this study was therefore to evaluate the impact of prolonged Angiotensin II-induced hypertension on working and short-term memories in adult mice.

Design and method: 3–4 months old male C57BL/6 mice were infused during 3 months with Angiotensin II at a dose of 2000 ng/kg/min (Ang II, n = 10) or saline (Control, n = 10) via osmotic minipumps. Blood pressure was measured weekly by the tail-cuff method. Garcia neurological test was used to assess motor and behavioural functions to detect eventual stroke signs. Working memory was assessed in a Y-maze during an alternation task over 3 months. Finally, evaluation of short-term memory was performed during an object location task (1 h intertrial). The resulting discrimination index d2 calculated is an indication of recognition of the novel location of the objects.

Results: Systolic blood pressure increased and reached a plateau after 4 weeks (Figure, panel A). Neurological score was unchanged in both groups, suggesting absence of stroke. The percentage of alternations was significantly higher in both groups than the chance level of 50% ($p < 0.05$) indicating a functional working memory in both groups. While the alternation rate did not differ between Ang II and Control (pint 0.14, pAngII 0.93, ptime 0.51), the discrimination index d2 was different from zero (no discrimination) in Control ($p < 0.001$) but not in Ang II ($p = 0.48$) and tended to differ between both groups ($p = 0.06$) (Figure, panel B).



Conclusions: In conclusion, we show for the first time that prolonged Angiotensin II-induced hypertension impairs short-term memory in adult mice. Immunohistochemical investigations of brain sections are being done to identify the structural damage involved in this hypertensive model of short-term memory impairment.

4C.03 SHORT-TERM HEART RATE VARIABILITY AND COGNITIVE FUNCTION IN OLDER SUBJECTS AT RISK OF CARDIOVASCULAR DISEASE

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Objective: To test the cross-sectional and longitudinal association of heart rate variability measured from 10-second electrocardiogram recordings with cognitive function in older subjects at high risk of cardiovascular disease.

Design and method: We studied 3,583 men and women, mean age 75.0 years, who were enrolled in PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) study. From baseline 10-second electrocardiograms the standard deviation of normal-to-normal RR intervals was calculated as the index of heart rate variability. Four domains of cognitive function testing reaction time, processing speed and immediate and delayed memory were assessed at baseline and repeated during a mean follow-up of 3.2 years. Using analyses of covariance, we calculated the adjusted mean values of baseline and annual changes of cognitive scores in thirds of heart rate variability.

Results: Participants with lower heart rate variability had worse cognitive function at baseline including reaction time, processing speed and immediate and delayed memory (all p-values < 0.05). In longitudinal analysis, participants with lower heart rate variability had a steeper cognitive decline in reaction time (mean annual change of: 1.49 seconds in the lowest tertile, 0.84 seconds in the middle tertile and 1.06 seconds in the highest tertile, p-value = 0.05) and processing speed (mean annual change of: -0.51 digits coded in the lowest tertile, -0.45 digits coded in the middle tertile and -0.35 digits coded in the highest tertile, p-value = 0.009). There was no significant difference in annual changes of immediate and delayed memory between heart rate variability groups. All these associations remained unchanged after adjustment for medications, cardiovascular risk factors and co-morbidities.

Conclusions: The present study indicates that lower heart rate variability measured from 10-second electrocardiogram recording is associated with worse executive function at baseline as well as future decline in executive function independent of cardiovascular risk factors and co-morbidities.

4C.04 TRENDS IN ADMISSION BLOOD PRESSURE IN PATIENTS WITH ACUTE STROKE AND TRANSIENT ISCHEMIC ATTACK: THE NATIONAL ACUTE STROKE ISRAELI SURVEY (NASIS)

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Objective: Elevated blood pressure (BP) is commonly observed during an acute stroke and is often higher in patients with a history of hypertension. Several studies have shown that elevated admission systolic BP during acute stroke is associated with unfavorable outcome. Management of hypertension has been improved in recent years leading to a higher rate of BP control. Our aim was to evaluate trends in admission BP levels in patients admitted with acute stroke and transient ischemic attack (TIA) over the past decade.

Design and method: Data were based on the triennial 2-month period (February to March 2004, March to April 2007, April to May 2010) National Acute Stroke Israeli Registry. The study population comprised 6177 patients, aged above 18 years who were hospitalized with acute stroke or TIA and had data on BP levels on admission. Among those who were included in the study, 4382 had ischemic stroke, 1227 had TIA and 476 had intracerebral hemorrhage. We compared patients' characteristics and temporal trends of admission BP and antihypertensive therapy before admission.

Results: Admission systolic BP (SBP) decreased from161 ± 29 mm Hg in 2004 to 153 ± 28 mm Hg in 2010 (p < 0.001). This trend was observed in patients with hypertension (164 ± 29 to 156 ± 28) and in those without hypertension (148 ± 26 to 140 ± 21). Similar tredns were observed for patients with TIA. The use of three or more antihypertensive agents increased from 16.9% in 2004 to 20% in 2010 (p = 0.02). In patients with acute stroke, admission SBP was associated with stroke severity (p < 0.001). Rate of disability at discharge or in-hospital death decreased from 71.3% in 2004 to 64.8% in 2010 (p < .0001). Admission SBP was associated with in-hospital death or short-term disability with an adjusted OR, for 10 mmHg change in SBP, of 1.040 (95% CI; 1.011–1.071).

Conclusions: Admission SBP in patients with acute stroke and TIA decreased over the years and may contribute to the improved outcome in these patients.

4C.05 PWV IS AN INDEPENDENT DETERMINANT OF COGNITIVE DYSFUNCTION IN CKD PATIENTS

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Objective: Cognitive dysfunction has long been recognized as a complication of chronic kidney disease (CKD), through several putative mechanisms, including high BP, large and small artery damage. Our study tests the hypothesis that large artery stiffness and microvascular damage are related to brain microcirculation changes as reflected by impaired cognitive function in CKD patients.

Parameters	Stage 1 (n=50)	Stage 2 (n=67)	Stage 3 (n=53)	Stage 4 (n=47)	p value
Age(years)	49.6±1.29	57.1±12.3	61.4±11.7	66.4±11.2	<0.001
bSBP(mmHg)	137.1±14.9	139.4±14.3	139.0±11.6	140±21.5	ns
aSBP(mmHg)	128.1±14.8	130.1±16.1	130.0±12.3	131±20.5	ns
cSBP, (mmHg)	138.2±16.2	144.9±18.6	145.3±14.8	152.1±24.2	ns
cfPWV(m/sec)	7.8±1.8	8.9±2.4	9.07±2.4	9.08±2.9	ns
AIx	26.3±12.1	24.1±11.2	22.6±11.5	23.6±12.7	ns
MMSE	21.4±3.8	20.2±4.7	20.6±4.4	18.4±6.5	<0.01

Design and method: Two hundred seventeen patients (50 with CKD stage 1; 67 stage 2; 53 stage 3; 47 stage 4), with mean age 58.4 years (64.5% males), were enrolled in a cross-sectional study. Cognitive function was assessed using Mini Mental State Examination (MMSE). Full score on the MMSE is 30; cognitive impairment was defined as <26 and cognitive dysfunction as <19. Educational level was categorized as lower versus higher education. Using the Sphygmocor system and an oscillometric device, we directly measured brachial SBP (bSBP) and pulse pressure (bPP), carotid SBP (cSBP) and pulse pressure (cPP) and estimated aortic SBP (aSBP) and pulse pressure (aPP) from the radial pressure waveform. Pulse Pressure Amplification (PPA), augmentation index (AIx) and carotid-femoral pulse wave velocity (cfPWV) were calculated.

Results: The risk of cognitive dysfunction increased significantly from CKD stage 3 to 4 (p < 0.01). Table.In univariate analysis, age (p < 0.001), education level (p < 0.001) stages of CKD (p < 0.004), cfPWV (p < 0.029), AIx (p < 0.03), bSBP (p < 0.002), aSBP (p < 0.012), cSBP (p < 0.015) and cPP (p < 0.002) were significantly and negatively associated with MMSE. In multivariate regression analysis, adjusted for CKD stages, the remaining independent factor significantly (p < 0.02) associated with cognitive dysfunction was cfPWV.

Conclusions: Carotid-femoral PWV may be a more sensitive marker of cognitive dysfunction than other parameters of central blood pressure. Since high cfPWV is associated with high pressure pulsatility at the cerebrovascular level, these data suggest that the later could play a pathophysiological role in cognitive dysfunction. In clinical practice, measuring aortic stiffness may help predicting the cognitive decline. Whether, the reduction in aortic stiffness following treatment translates into improved cognitive outcomes remains to be determined.

4C.06 COGNITIVE STATUS IN HYPERTENSIVE PATIENTS. HEART AND BRAIN STUDY IN ARGENTINE

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Objective: Know the cognitive status of hypertensive patients, the prevalence of the cognitive impairment and its association with different parameters of hypertensive disease.

Design and method: Multicenter study (18 centers) distributed in 5 regions of the Argentine. Epidemiological, cross and observational study. In the Heart and Brain Study, 1281 hypertensive patients, >/ = 21 years, both sexes were included. The sample was obtained by patients attending cardiology clinic. A validated survey with closed answers was used. Blood pressure (BP) was obtained according to international norms. The hypertensives patients were divided in two groups: treated/controlled (</ = 140 and </ = 90 mm Hg) and treated/no-controlled (>140 y >90 mm Hg). The education levels was registered. Cognition was assessed by Mini-Mental Statement Examination (MMSE) (global cognition), Clock drawing test (executive function), mini-Boston Naming Test (mBNT)(semantic memory). The cut-off of the test were: 1) MMSE </ = 24 pts., CDT </ = 5 pts., mBNT </ = 9 pts. (applied in patients >/ = 60 years with >/ = 7 years education).

Results: Average age was $60,2 \pm 13,5$ yrs, 71% female (n = 881). In the treated /controlled group (n = 570; 46,0%) the BP (SBP 125.8 ± 9.7 mm Hg and DBP 75.9 ± 8.4 mm Hg) was lower than treated/no-controlled group (SBP 155.5 ± 18.4 mm Hg and DBP 88.7 ± 11.6 mm Hg) (p <0.001). In the treated/

no-controlled group, higher OR for poor outcomes in mini-BNT was observed (OR = 1.36; CI 95%, 1.04–1.75, p = 0.021), ajusting for age, sex and education level in the logistic regression model. The 22.1% presented impairment in global cognition, 36.2% executive dysfunction and 48.9% impairment semantic memory. In the one way analysis of variance, high pulse pressure was associated with poor outcomes in CDT (<0.0036) and mini-BNT (<0.001), whereas that SBP was associated with poor outcomes in mini-BNT (<0.001). But, after ajusting (age, sex, education) in the linear regression model the miniBNT was the only test associated with high BP (p 0.05).

Conclusions: In this sample of hypertensive patients impairment of the semantic memory (cortical function) was more prevalent than executive dysfunction (subcortical). The miniBNT was the only test associated with high BP in treated/no-controlled group. Hypertension could impact negatively on cortical structures as well as the known subcortical.

4C.07 RELATIONSHIPS BETWEEN COGNITIVE DYSFUNCTION, CLINIC AND AMBULATORY BLOOD PRESSURE AND BLOOD PRESSURE VARIABILITY: RESULTS FROM THE PAMELA STUDY

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Objective: The relation between blood pressure (BP) and cognitive function has received growing interest in recent years. Some cross-sectional studies have shown an inverse association between BP and cognitive dysfunction, while longitudinal studies yield mixed results.

Design and method: In the PAMELA study cognitive function was assessed via minimental test at the evaluation performed in 2001–2002, taking as reference clinic data collected at the 1st PAMELA examination carried out 10 yrs before. 471 subjects participated at this substudy. Measurements included clinic and 24-hour BP (Spacelabs 90207). BP variability was obtained by calculating 1) the SD of 24-hour, day, and night mean values, 2) the day/night BP difference and (3) the residual or erratic BP variability (Fourier spectral analysis).

Results: Mean age of the subjects enrolled was 63.0 ± 5.7 yrs (mean ± SD) at the 1St examination. At the 2nd evaluation performed 10 yrs later 26 subjects had a minimental score < 23, indicative of a cognitive dysfunction (CD), the remaining 445 showing normal scores (C, 24–30). For similar heart rate, office and home systolic (but not diastolic) BP were, although not significantly, greater in CD than in C (148.0 ± 22.5 vs 143.5 ± 19.9 and 139.5 ± 15.14 vs 133.3 ± 17.9 mmHg, P = NS). 24hour BP was similar in CD and C, this being the case also for 24 hour BP variability, expressed as SD systolic (15.3 ± 4.1 vs 14.8 ± 3.7 mmHg, P = NS) and diastolic (12.9 ± 3.47 vs 12.2 ± 2.9 mmHg, P = NS) or day/night BP difference. In contrast, residual BP variability was significantly greater in CD than in C for both systolic (11.2 ± 2.2 vs 10.6 ± 2.5 mmHg, P < 0.05) and diastolic (9.3 ± 2.1 vs 8.7 ± 2.3 mmHg, P < 0.05), the difference between groups being greater when the grading of minimental responses was based on 3 score categories (0–20,21–24 and >24). This was particularly the case in males.

Conclusions: Our data show that the most sensitive prognostic variable for the development of cognitive alterations does not appear to be absolute BP load or absolute BP variability but rather its short-term erratic component, which has been previously shown to represent the part of BP variability with major impact on cardiovascular mortality.

4C.08 AORTIC STIFFNESS IS AN INDEPENDENT BIOMARKER OF SUBCLINICAL BRAIN DAMAGE IN ACUTE ISCHEMIC STROKE

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Objective: Ischemic stroke may be the first manifestation of cerebrovascular disease. However, subclinical organ complications of underlying arterial stiffness and hypertension may coexist and stratify outcome. The study aimed to examine measures of arterial stiffness and blood pressure (BP) on subclinical brain damage in acute ischemic stroke patients.

Design and method: In a prospective study, we enrolled 132 (68,6% males) patients with acute ischemic stroke, AIS (age 62.2 ± 12.2 years, admission National Institutes of Health Stroke Scale score 7.1 ± 6.5, mean ± SD). Carotid-femoral pulse wave velocity (CF-PWV), central augmentation index (cAIx), as well as central and peripheral BPs were measured (SphygmoCor, Omron, respectively) one week after stroke onset. The presence of brain subclinical lesions was graded on admission computed tomography scans using van Swieten criteria with any relevant cerebral small vessel disease considered as brain microvascular damage.

Results: In univariate analysis, high carotid-femoral PWV (p = 0.00005), and high cAIx (p = 0.02) were significantly associated with brain microvascular damage. Age, presence of hypertension, diabetes mellitus, previous ischemic stroke, but not BP values, also predicted brain outcome. In multivariate analysis, the predictive value of carotid-femoral PWV remained significant (OR, 1.30; 95% CI, 1.04–1.62; p = 0.02). By contrast, cAIx had no significant predictive value after adjustment.

Conclusions: Increased aortic stiffness is associated with brain microvascular disease in patients with acute ischemic stroke, beyond and above classical risk factors. PWV provides a useful new tool for identification of subclinical brain damage in AIS.

4C.09 EFFECT OF ANGII-INDUCED HYPERTENSION AND ANTIHYPERTENSIVE TREATMENT ON PATHOLOGICAL CHANGES IN A MOUSE MODEL FOR ALZHEIMER'S DISEASE

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Objective: Hypertension is a risk factor for Alzheimer's disease (AD). It is a treatable condition which opens important avenues for prevention of AD. Elevated angiotensin II (AngII) is an important cause of essential hypertension and has deleterious effects on endothelial function and cerebral blood flow (CBF). In this study we therefore investigated the interaction between AngII, systolic blood pressure (SBP), and MRI-measurements in the APPswe/PS1[Delta]E9 (APP/PS1) mouse model of AD.

Design and method: We studied the effect of 2 months of induced hypertension (AngII-infusion using osmotic micropumps, vs saline (sal) as control) and, subsequently (after 1 month of induced hypertension) the effect of treatment (vs placebo) with antihypertensive (eprosartan mesylate (EM), 0.35 mg/Kg vs water) on SBP and metabolite levels, functional and neuronal connectivity and CBF in 10 months-old wildtype C57bl6/j (WT) and APP/PS1 mice. SBP was monitored twice a month via tail cuff plethysmography. RsfMRI, DTI, MRS, FAIR-ASL were measured on the 11.7T magnet (Bruker BioSpec).

Results: In this study, chronic AngII-infusion increased BP in both transgenic and WT mice, while at 12-Month under AngII-infusion APP/PS1 mice had a higher SBP than WT mice. Furthermore, only in hypertensive AD mice cortical CBF was lowered compared to hypertensive WT mice. Additional data will be presented on the impact of AngII-induced hypertension and subsequent treatment with EM on Aβ-pathology, cognition, metabolite levels, structural and functional connectivity.

Conclusions: Together, these data suggest an interaction between APP/PS1 induced pathologies, SBP, and antihypertensive treatment. Our results also reveal an association between hypertension (AngII), APP/PS1 and CBF.

4C.10 LOWER COGNITIVE PERFORMANCE IS NOT CORRELATED WITH VASCULAR STIFFNESS IN ELDERLY TREATED HYPERTENSIVES

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Objective: To correlate cognitive performance with vascular stiffness in elderly normotensives and hypertensives.

Design and method: Cognitive performance was assessed by CAMCOG-R in elderly normotensives [NTN; n = 20 (7 women); 68 ± 1yo; 131 ± 3mmHg; education = 11 ± 1y] and pharmacologically treated hypertensives [HTN; n = 42 (26 women); 68 ± 1yo; 149 ± 3mmHg; education = 8 ± 1y]. Subjects treated with beta-blockers were excluded. Depression was assessed by Beck Depression Inventory. We measured carotid-femoral pulse wave velocity (PWV) with Complior and central aortic systolic pressure (CASP) with SphygmoCor. Augmentation pressure (AP) was derived from central aortic pressure waveform.

Results: CAMCOG-R global score was larger in NTN (87 ± 2 vs. 77 ± 1, p < 0.001). While CASP was higher in HTN (137 ± 5 vs. 123 ± 2mmHg, p = 0.001), PWV and AP were similar in NTN and HTN (PWV 11.6 ± 0.5 vs. 11.6 ± 0.4m/s,

p = 0.9; AP 15 ± 1 vs. 18 ± 1mmHg, p = 0.1). In a linear multiple regression model controlled for sex and depression, both hypertension and less education, but not PWV and AP, were independent adverse predictors of CAMCOG-R global score (Table; adjusted R-squared of model = 0.56; p-value of model < 0.001).

Conclusions: As expected, normotensives exhibited better cognitive performance than hypertensives. Importantly, hypertension and less education, but not indices of vascular stiffness, were associated with lower cognitive performance. These results suggest that vascular stiffness is not correlated with lower cognitive performance in elderly treated hypertensives.

Model	B (SE)	P-value of B
Education	1.1 (0.2)	<0.001
Hypertension	-4.6 (1.9)	0.02
Sex	-1.9 (1.6)	0.3
Depression	-0.5 (0.4)	0.3
PWV	-0.1 (0.3)	0.9
AP	-0.1 (0.1)	0.7

B, unstandardized regression coefficient; SE, standard error

ORAL SESSION

ORAL SESSION 4D
LARGE ARTERIES

4D.01 A SIMPLE CALCULATOR FOR THE ASSESSMENT OF MEASUREMENTS OF CAROTID-FEMORAL PULSE WAVE VELOCITY AND LOCAL ARTERIAL STIFFNESS RELATIVE TO THE REFERENCE VALUES DATABASE

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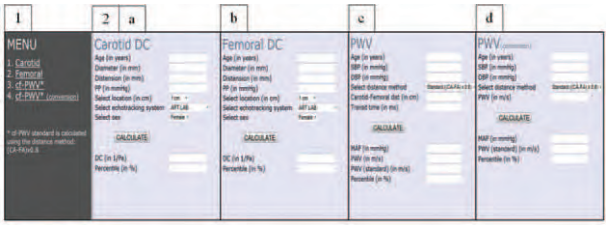
Objective: Arterial stiffness has been demonstrated to predict and be related to cardiovascular disease (CVD). Reference values of carotid-femoral pulse wave velocity (cf-PWV), the gold standard measure of arterial stiffness, and local carotid and femoral arterial stiffness, derived from the distensibility coefficient (DC), have been established. The use of different devices and methods, however, still hampers the widespread clinical use of these reference values. The aim of this work was therefore to create a web-based application that allows easy assessment - for different methodological approaches - of a given measured value of arterial stiffness, with the application providing the percentile reference associated with that specific value.

Design and method: Reference values of cf-PWV (11,092 individuals; age range: 15–97 years, 49.8% men) and local carotid (22,708 individuals; age range 15–99 years; 54% men) and femoral (5,069 individuals; age range: 15–87 years; 49.5% men) arterial stiffness were obtained from literature (The Reference Values for Arterial Stiffness' Collaboration 2010) and the database of The Reference Values for Arterial Stiffness' Collaboration. Individuals without CVD and established cardiovascular risk factors (CV-RFs) constituted a healthy subpopulation and were used to establish equations for percentiles of cf-PWV and sex-specific percentiles of carotid and femoral DC across age. Using these established equations, an application was created (in JavaScript) to provide the percentile reference value from routine parameters obtained in clinical practice.

Results: The tool can be found at: http://users.ugent.be/~flondono/ and consists of two panels (see figure). The first panel (1) presents a menu, where the user selects the parameter to be determined (or standardized). Then an application is displayed in the second panel (2): a. Carotid DC; b. Femoral DC; c. cf-PWV, or d. cf-PWV conversion. Subsequently, the user provides a number of inputs which are used to calculate the selected parameter, the percentile and, when relevant, additional information.

Conclusions: An easy and intuitive interface was created to assess a given measurement of arterial stiffness relative to know reference values.



4D.02 ACCELERATED VASCULAR AGING: RESULTS FROM THE CARDIOVASCULAR RISK FACTORS AFFECTING VASCULAR AGE (CRAVE) STUDY

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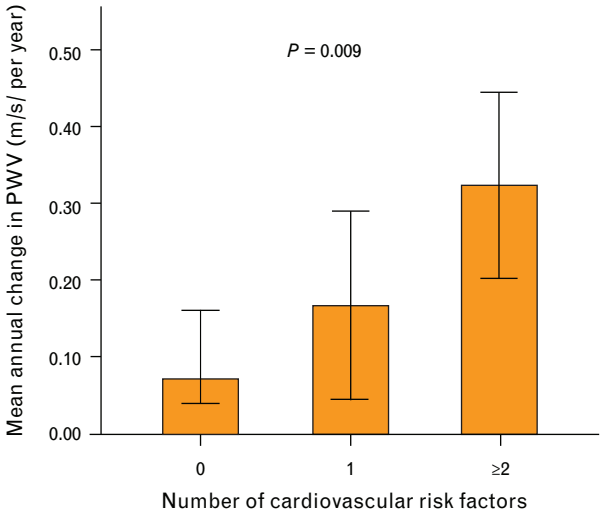
Objective: Vascular aging, as assessed by structural and functional properties of the arteries, is an independent indicator of cardiovascular risk. We investigated the effect of cardiovascular risk factors (RFs) on the progression of vascular aging.

Design and method: One hundred and forty-two subjects (mean age 51.9 ± 10.8 years, 94 men) attending the Peripheral Vessels Unit with no established cardiovascular disease were investigated in two examinations over a 2-year period (mean follow-up visit 1.84 years). Subjects were classified at baseline according to their number of cardiovascular RFs (from zero to two and more). The RFs were hypertension, dyslipidemia, smoking and diabetes. Subjects had at the beginning and end of the study determinations of carotid-femoral pulse wave velocity (cfPWV), aortic augmentation index corrected for heart rate (AIx75), brachial flow-mediated dilatation (FMD) and carotid intima-media thickness (cIMT). Based on these measurements the annual absolute changes were calculated.

Results: Subjects with more RFs had a gradual higher annual progression of cfPWV (0.092 m/s for no RF, 0.153 m/s for 1 RF and 0.316 for more than 2 RFs; p = 0.03) after adjusting for age, gender, baseline waist circumference and annual change of mean blood pressure heart rate and renal function. (Figure) Subjects with more RFs had a trend for a gradual higher annual deterioration of FMD (-0.04% for no RF, -0.14% for 1 RF and -0.51% for more than 2 RFs; p = 0.11) after adjusting for age, gender and baseline FMD. Annual progression of AIx75 between groups was not statistically significant. However, when only subjects <55 years where considered the progression rate was significantly higher in subjects with more RFs (1.04% vs. 1.52% vs. 3.15%, respectively, p = 0.02). Subjects with more RFs did not show an association with a gradual higher annual deterioration of cIMT. There was also a trend for a statistical association between the annual rate of PWV and FMD (P = 0.07).



Conclusions: The presence of more RFs is associated with accelerated progression of vascular aging.

4D.03 INTRAFAMILIAL AGGREGATION AND HERITABILITY OF AORTIC REFLECTED (BACKWARD) WAVES DERIVED FROM WAVE-SEPARATION ANALYSIS

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Objective: Although aortic augmentation index (AIx) and pressure (Pa) are inherited, AIx and Pa are poor measures of reflected (backward) wave function. As wave reflection predicts outcomes beyond brachial BP, we aimed to determine the intra-familial aggregation and heritability of indices of aortic wave reflection derived from wave separation analysis (reflected [backward] wave index [RI] and pressure [Pb]) and compare these with the intra-familial aggregation and heritability of AIx and Pa.

Design and method: Aortic Pb, RI, Pa and AIx were determined using radial applanation tonometry and SphygmoCor software in 1152 participants of 315 families (111 father-mother pairs, 705 parent-child pairs and 301 sibling-sibling pairs) with 24 families including three generations from an urban developing community of black African ancestry. Aortic Pb was determined using wave separation analysis where the aortic forward and backward waves were separated using a triangular aortic flow wave. Heritability estimates (h2) were determined from S.A.G.E software.

Results: With adjustments for age, sex, pulse rate, mean arterial pressure, body weight, body height, regular smoking, regular alcohol intake and diabetes mellitus or an HbA1c > 6.1%, significant correlations were noted between parent-child pairs for Pb, RI and Pa ($p < 0.05$ for all), but not for AIx ($p = 0.90$) and between sibling-sibling pairs for Pb and Pa ($p < 0.05$), but not for RI ($p = 0.06$) or AIx ($p = 0.14$). No correlations for indices of wave reflection were noted between fathers and mothers ($p > 0.57$). After the aforementioned adjustments, Pb ($h2 = 0.24 \pm 0.07$), RI ($h2 = 0.26 \pm 0.07$) and Pa ($h2 = 0.23 \pm 0.07$)($p < 0.001$ for all) but not AIx ($h2 = 0.10 \pm 0.07$, $p = 0.07$) showed significant heritability. Intra-familial correlations and heritability estimates for Pa remained significant despite further adjustments for either Pb ($h2 = 0.13 \pm 0.06$, $p < 0.05$) or RI ($h2 = 0.14 \pm 0.06$, $p < 0.05$). The intra-familial aggregation and heritability of aortic pulse pressure was accounted for by both Pb and forward wave pressures.

Conclusions: Aortic reflected (backward) waves derived from wave separation analysis show intra-familial aggregation and heritability, but these effects are poorly characterized by measures of aortic pressure augmentation.

4D.04 TIMING OF THE CAROTID PRESSURE WAVE INFLECTION POINT IS COUPLED TO SYSTOLIC MYOCARDIAL MOTION IN OLDER PATIENTS WITH CARDIOVASCULAR RISK FACTORS

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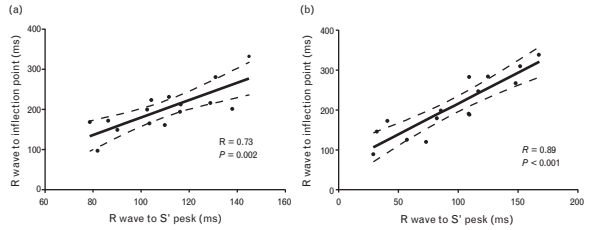
Objective: Cardiac motion during systole has been shown to be closely associated with carotid pressure wave inflection point timing in young, healthy volunteers. In these individuals the inflection point occurred following the systolic pressure peak (Murgo Type C). The relationship between myocardial motion and the timing of inflection point in older patients with cardiovascular risk factors where the inflection point precedes peak systolic pressure remains unknown.

Design and method: 15 patients with cardiovascular risk factors were prospected enrolled and underwent simultaneous carotid tonometry and TDI tracking of medial mitral annular motion. Measurements were obtained in the resting state and following the administration of either intravenous dobutamine (10mcg/kg/min) or GTN (400mcg sub-lingual). The ECG R-wave was used as the fiducial marker to determine the timing of both peak systolic mitral annular motion (S') and the carotid pressure wave inlection point.

Results: 30 paired measurements were obtained. Dobutamine increased SBP, HR and PP whereas GTN decreased these parameters. Augmentation index decreased following both agents. The left ventricular outflow tract velocity time integral (indicative of stroke volume) increased with dobutamine and decreased with GTN. Despite these changes, the timing of peak S' was significantly correlated with the timing of the carotid inflection point both at rest and with pharmacological intervention ($R = 0.73$, $P = 0.002$ and $R = 0.89$, $P < 0.001$ respectively).



Peak medial mitral annular velocity (S') timing and carotid pressure waveform inflection point timing at rest (A) and following dobutamine / GTN (B). R = Spearman's Rank Correlation coefficient

Conclusions: Peak systolic mitral annular motion timing (representing the commencement of myocardial deceleration in systole) always precedes and remains coupled to carotid pressure wave inflection point timing in older patients with established cardiovascular risk factors. This data suggests that the morphology of the central blood pressure waveform may relate more strongly to local ventricular-vascular interactions, rather than wave reflections.

4D.05 RECOVERY OF VASCULAR HEALTH AFTER KIDNEY TRANSPLANTATION

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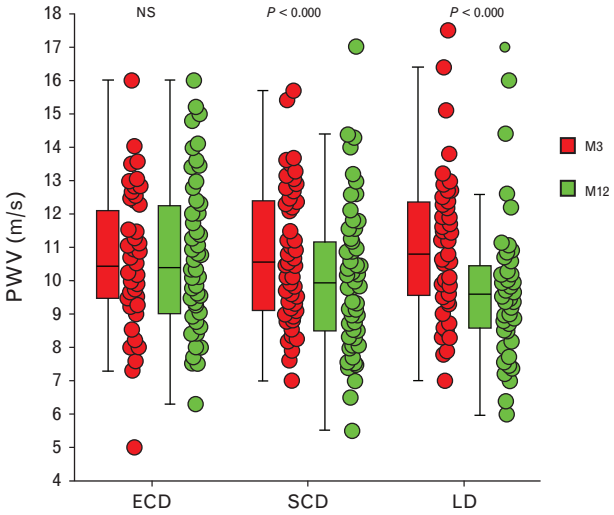
Objective: Chronic kidney disease (CKD) is characterized by stiffening, thinning and dilatation of large arteries, leading to a deleterious increase in circumferential wall stress (CWS) and accelerated vascular ageing. Transplantation reverses many pathological features of CKD and improves life expectancy; however, longitudinal studies exploring the impact of kidney transplantation (KT) upon recipient large artery structure and function are scarce. This study was designed to appraise changes in vascular health following kidney allograft transplantation, in particular comparing live with deceased donors.



Design and method: Carotid-femoral pulse wave velocity (PWV), and carotid remodelling (CWS and carotid internal diameter, CID) and stiffness were measured at three months (M3) and one year (M12) after KT, in 161 consecutive recipients receiving either a live (LD, n = 49) or a deceased donor (DD, n = 112) allograft.

Results: PWV decreased from 10.8 ± 0.2 m/s at M3 to 10.1 ± 0.3 m/s at M12 ($p < 0.001$). After multivariate adjustment, the PWV reduction was independently associated with LD KT, initial PWV (M3), and change in mean arterial pressure

(M3 to M12), $p < 0.001$ for all. CWS decreased (70 ± 1 vs 64 ± 1 kPa) due mainly to a reduction in CID (6.4 ± 0.1 vs 6.1 ± 0.1 mm) and stiffness (6.6 ± 0.1 vs 6.4 ± 0.1 m/s), $p < 0.001$ for all. Reductions in CWS were independently associated with live allograft donation ($p < 0.001$) and with initial CWS ($p < 0.001$). For DD, changes in both PWV and CWS showed progressively less improvement compared to LD when further classified into standard and extended criteria donors, with minimal improvement observed in the latter group. Importantly, all changes were independent of renal function.

Conclusions: The large artery stiffness and maladaptive carotid artery remodelling of CKD is reversed within 12 months of transplantation and appears unrelated to renal function. Improvements are independently associated with live organ donation, severity of initial pathology, and reduction in mean arterial blood pressure. Data also suggest that extended criteria donors may prejudice vascular recovery.

4D.06 PROGRESSION OF CAROTID ARTERY REMODELING AND STIFFNESS IN HYPERTENSIVE PATIENTS: A PROSPECTIVE COHORT STUDY

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Objective: To evaluate the rate progression over time of carotid and aortic stiffness and carotid remodeling in hypertensive patients in real-life and explore determinants of stiffness changes over time.

Design and method: In this prospective observational study, 153 hypertensive patients were evaluated at Visit 0 (V0) and after a 3.6 ± 1.2-year follow-up (V1). Carotid-femoral pulse wave velocity (PWV), carotid intima-media thickness (cIMT) and carotid stiffness (CS) were assessed.

Results: Diastolic BP was reduced during follow-up, (from $142.4 \pm 15.6/82.2 \pm 8.8$ to $141.2 \pm 17.2/79.7 \pm 10.9$ mmHg, p = ns for systolic BP, $p = 0.026$ for diastolic BP), due to increased number of antihypertensive drugs (1.2 ± 1.0 to 1.8 ± 1.0, $p < 0.001$). PWV, cIMT, CS were unchanged from V0 to V1. Conversely a significant increase in carotid diameter was observed (from $7,49 \pm 0,85$ to $7,80 \pm 0,81$ mm, $p = 0,002$).
The study population was divided in tertiles according to reduction (delta V1-V0 < -0.5 m/s), stability or increase (delta V1-V0 > 0.5 m/s) in PWV or CS. Patients with reduced PWV during follow-up showed at V0 greater values of systolic BP (146.3 ± 14.4, 139.8 ± 13.6, 141.0 ± 17.4mmHg, $p = 0.077$), PWV (10.1 ± 2.1, 8.7 ± 1.8, 8.9 ± 1.8m/s, $p < 0.05$) and mean carotid diameter (7.82 ± 0.93, 7.26 ± 0.75, 7.41 ± 0.72 mm, $p < 0.05$) than those with stable or increased PWV. They also experienced an increased systolic BP reduction over time (-7.9 ± 17.0, -2.0 ± 15.1, $+3.5 \pm 18.2$ mmHg, $p < 0.0001$) and no further carotid enlargement ($+0.16 \pm 0.58$, $+0.40 \pm 0.53$, $+0.39 \pm 0.47$ mm, $p = 0.046$).
Patients with reduced CS over time showed at V0 higher systolic BP values (146.9 ± 15.3, 144.6 ± 13.0, 135.8 ± 16.3 mmHg, $p = 0,0008$) than those with stable or increased CS, a greated BP reduction over time (-10.6 ± 18.1, -4.5 ± 16.3, $+7.6 \pm 12.8$ mmHg, $p < 0.0001$) and no further carotid enlargement over time ($+0.13 \pm 0.57$, $+0.35 \pm 0.50$,$+0.45 \pm 0.50$ mm, $p = 0,016$). Patients with increased CS over time had a lower rate of BP-lowering grug uptitration (54.7, 51.1, 31.9%, $p = 0.05$).

Conclusions: In a cohort of hypertensive patients, followed-up for about 3 years in a real-life setting, aortic and carotid stiffness, as well as cIMT did not change over time, but there was a progression of carotid artery maladaptive remodeling. Patients with reduced PWV and CS over time showed higher BP values at baseline, greater BP reduction over time and no further carotid enlargement, possibly due to more intensive drug treatment.

4D.07 ENDOTHELIN A RECEPTOR BLOCKADE REDUCES VASCULAR CALCIFICATION IN RATS WITH CHRONIC KIDNEY DISEASE AND MINERAL DISORDERS

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Objective: Increased risk of cardiovascular disease in patients with chronic kidney disease (CKD) has been related to vascular stiffness and isolated systolic hypertension as a result of vascular calcification due to mineral metabolism abnormalities. Using a rat model of CKD with vascular calcification, we found a marked increase in endothelin-1 (ET-1) production in the media of calcified vessels suggesting a role for ET-1. This study was designed to investigate the effect of the ETA receptor antagonist atrasentan on vascular calcification and hemodynamic parameters in CKD rats with mineral metabolism abnormalities.

Design and method: CKD was induced in Wistar rats by renal mass ablation and mineral metabolism abnormalities by a calcium/phosphate-rich diet and vitamin D supplementation (Ca/P/VitD) that lead to vascular calcification. A group of CKD rats given Ca/P/VitD was treated with the ETA receptor antagonist atrasentan (10 mg/kg/day) for 6 weeks. Hemodynamic parameters were determined by vessels catheterisation in anesthetised animals and the thoracic aorta was harvested for the assessment of calcification.

Results: Treatment of CKD + Ca/P/VitD rats with the ETA antagonist atrasentan significantly reduced systolic blood pressure (109 ± 12 vs. 156 ± 8 mmHg, $p < 0.05$), pulse pressure (23 ± 3 vs. 60 ± 9 mmHg, $p < 0.05$) and carotid-femoral pulse wave velocity (481 ± 43 vs. 690 ± 28 cm/s, $p < 0.01$). These hemodynamic effects of ETA receptor blockade were associated with reduced vascular calcification assessed both by Micro-CT scanning (0.12 ± 0.03 vs. 0.24 ± 0.04 AU, $p < 0.05$) and von Kossa staining (1.9 ± 1.1 vs. 10.6 ± 2.5 AU, $p < 0.05$).

Conclusions: Our study shows for the first time that ETA receptor blockade reduces vascular calcification and the associated hemodynamic abnormalities in this model of CKD-related vascular calcification.

4D.08 INDEPENDENT ASSOCIATIONS OF GALECTIN-3 CONCENTRATIONS WITH AORTIC PULSE WAVE VELOCITY AND WAVE REFLECTION IN A COMMUNITY SAMPLE

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Objective: Although the pro-fibrotic inflammatory substance galectin-3 predicts outcomes in the general population, the mechanisms responsible for this effect are uncertain. As galectin-3 expression contributes to aortic stiffness in preclinical studies, we aimed to determine whether circulating galectin-3 concentrations are associated with carotid femoral (aortic) pulse wave velocity (PWV) and aortic reflective wave index (RI) in a community sample.

Design and method: Aortic PWV and RI were determined using applanation tonometry and SphygmoCor software in 966 randomly selected participants older than 16 years of age from a community sample of the South West Township (SOWETO) of Johannesburg. 661 participants had 24-hour ambulatory blood pressure (BP) monitoring that met with pre-specified quality control criteria.

Results: Galectin-3 concentrations were not independently associated with office or 24-hour systolic (SBP) ($p = 0.88$–0.92), or diastolic ($p = 0.65$–0.94) BP. In contrast, with adjustments for age, sex, office or 24-hour mean arterial pressure (or SBP and pulse pressure), pulse rate, body mass index, regular smoking, regular alcohol intake, total cholesterol concentrations, diabetes mellitus or an HbA1c > 6.1%, treatment for hypertension and estimated glomerular filtration rate, galectin-3 was independently associated with aortic PWV (partial $r = 0.15$, $p < 0.0001$) and RI (partial $r = 0.10$, $p < 0.005$). In 745 participants that had never received antihypertensive therapy, galectin-3 concentrations were similarly independently associated with PWV (partial = 0.16, $p < 0.0001$), and RI (partial $r = 0.11$, $p < 0.005$). With adjustments for all confounders, markedly higher PWV and RI values were noted in the highest 3–4 octiles as compared to the lowest 3 octiles of galectin-3 concentrations. The BP-independent relations between galectin-3 concentrations and aortic haemodynamics persisted with further adjustments for C-reactive protein concentrations (PWV: partial $r = 0.14$, $p < 0.0001$, RI: partial $r = 0.10$, $p = 0.002$).

Conclusions: Despite a lack of independent association with brachial BP, the pro-fibrotic inflammatory substance galectin-3 may contribute toward adverse outcomes through an impact on aortic stiffness and the magnitude of aortic reflected waves, effects that cannot be attributed to general inflammatory changes.

4D.09 DIFFERENT WAVE FORM CALIBRATION OF CENTRAL AORTIC PRESSURE AFFECTS THE ASSOCIATION TO OUTCOME

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Objective: The impact of different calibration methods on the prognostic power of aortic systolic pressure (aSBP) is only poorly reported in literature. The aim of this work was therefore the prospective investigation of the association of brachial (bSBP) and aortic systolic blood pressures to all cause mortality with special emphasis on different calibration methods for central pressure estimates, in particular brachial systolic and diastolic as well as brachial mean and diastolic pressures.

Design and method: 135 Patients were enrolled in a longitudinal, prospective study of arterial stiffness and cardiovascular risk in a cohort suffering from chronic kidney disease stages 2 to 4. Office measurements of bSBP and aSBP were assessed by a validated oscillometric device. Prognostic factors of survival were identified by use of Cox proportional hazards regression models.

Results: After a mean follow up duration of 42 months (range: 30 to 50 months) 13 patients died. In univariate Cox analysis, bSBP and aSBP (calibrated using brachial systolic and diastolic pressures) did not significantly predict mortality, only aSBP assessed using measured mean and diastolic pressure calibration was significantly associated with mortality ($HR = 1.027$, $p = 0.008$). This remained significant in

multivariate analysis after adjustment for age, sex and anthropometric measures and brachial pressure.

Conclusions: Within our cohort, only aSBP assessed with measured mean and diastolic pressure predicted mortality and provided highly significant prognostic value.

4D.10 CHANGES IN PWV IN PREVIOUSLY UNTREATED MILD HYPERTENSIVES ARE RELATED TO REDUCTION OF BLOOD PRESSURE BY TREATMENT

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Objective: Changes in target organ lesions, even beyond reduction of blood pressure, have been shown to have predictive value. Destiffening of arterial damage seems to be possible but the mechanisms are still elusive. We report changes in pulse wave velocity (PWV) after one year of treatment in new diagnosed previously untreated, hypertensive patients.

Design and method: We included in this longitudinal study 356 consecutive, never-treated patients with suspected hypertension. After standard clinical assessment, including ambulatory blood pressure monitoring (ABPM), pulse wave analysis and PWV (Sphygmocor§, AtcorMedical), 231 showed elevated office and/or ambulatory blood pressure (BP) and received monotherapy treatment accordingly. 125 patients who showed to be normotensive, served as control group. Clinical assessment was repeated after a median of 1.1 years in the whole cohort. PWV was adjusted to BP.

Results: In the whole group, 179 patients were female (50.3%), mean age was 48.8±12years. The hypertensive diagnosed group tended to be older (50 vs. 46 years, p<0,001) and had higher PWV even after mean BP adjustment (8.6±2.0 vs. 8.0±1.4 m/s, p<0.001), higher baseline office, ambulatory and central BP (145/86, 136/86 and 138/87 mmHg vs. 125/75, 120/76 and 120/79, respectively, p<0,001). After 1 year of treatment, BP was significantly improved only in the hypertensive group (follow-up office, ambulatory and central BP 128/75, 124/78, 121/79 mmHg, pintragroup<0.001) and remained constant in the control group (126/74, 120/76, 120/80, pintragroup=ns). The reduction of central and peripheral systolic BP in the hypertensive group was of the same magnitude (-17 vs -17 mmHg, p=ns). PWV was significantly reduced in both groups even after BP adjustment, at follow-up they were similar between groups (7.8 vs. 7.7, p=ns). The reduction of adjusted PWV was significantly higher in the hypertensive group (?=0.86 vs. 0,20 m/s, p=0.001). There was no differential effect in PWV reduction depending on antihypertensive class, except for patients treated with nebivolol.

Conclusions: Blood pressure reduction in newly diagnosed stage 1 hypertensive patients improves PWV within a year of treatment, confirming that rapid tight control of BP is important even in mild hypertensives. Of note, arterial destiffening seems to go beyond BP reductions.

4D.11 ARTERIAL STIFFNESS IN PATIENTS WITH ENDEMIC NEPHROPATHY UNDERGOING HEMODIALYSIS

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Objective: Arterial stiffness (AS) is an independent risk factor of cardiovascular mortality in general and haemodialysis (HD) population. Endemic (Balkan) nephropathy (EN) is a chronic tubulointerstitial salt wasting nephropathy characterized with later onset of arterial hypertension (AH) which could also affect AS. Thus our aim was to analyse AS in EN patients compared with other end-stage renal disease patients undergoing HD.

Design and method: A total of 186 HD patients (90 m, 96 w; 67.35 + 13.07 years) from 3 dialytic units and 2 endemic areas were enrolled. The exclusion criteria were: duration of dialysis < 3 months, atrium fibrillation, myocardial infarction or stroke in last 3 months, heart failure, arteriovenous anastomosis besides functional arteriovenous fistula. EN was diagnosed by modified WHO criteria. All patients were dialysed by European and KDIGO guidelines. Brachial blood pressure (BP) was measured with Omron M6 device and AS markers; pulse wave velocity (PWV) and aortic augmentation index (AIx) were measured by Arteriograph before mid-week dialysis.

Results: There were no differences in sex, smoking status, type of vascular access, phosphate binder doses, vitamin D, hypertension and brachial BP between two groups. Non-EN patients had more antihypertensives drugs (p < 0.001), higher body mass index, waist circumference and diabetes. There were no differences in dialysis modalities except lower ultrafiltration in EN patients (p < 0.001). EN were significantly older (p < 0.001) with later start of dialysis. EN had lower values of phosphates (p < 0.001), CaxP (p < 0.001) and iPTH (p < 0.001), and significantly lower PWV (9.2 ± 1.6 vs.10.5 ± 1.9; p < 0.001). Using multiple linear regression models EN was the most significant independent negative predictor for PWV (p < 0.001) and AIx (p = 0.002). Using logistic regression non-EN patients had odds ratio for increased AS (PWV > 10 m/s OR 3.12; 1.72–5.82; p < 0.00001).

Conclusions: EN patients despite being older had lower PWV and AIx values. Even more, EN is an independent predictor of lower arterial stiffness. This could be explained with later onset of AH in pre-dialytic clinical course and probably with lower phosphate values due to tubulopathy. Better control of Ca and P during dialysis also contributes to observed lower AS in EN patients undergoing HD.

4D.12 AORTIC STIFFNESS IS MODESTLY BUT EQUALLY ASSOCIATED WITH BOTH CENTRAL AND BRACHIAL PULSE PRESSURE IN ELDERLY SUBJECTS. THE MALMÖ DIET CANCER STUDY

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Objective: Arterial stiffness (AS) in the aorta is a well-documented and independent risk marker of cardiovascular disease risk and total mortality according to meta-analyses. Aortic AS can be measured by carotid-femoral pulse wave velocity (c-f PWV) as the "golden standard" method. A surrogate marker is pulse pressure (PP) during resting conditions, reflecting isolated systolic hypertension. During ageing the amplification of central blood pressure (cBP) in relation to brachial BP (bBP) is reduced. Our aim was to investigate cross-sectional associations between c-f PWV and cPP as well as bPP in an elderly population.

Design and method: We examined a total of 3001 subjects (mean age 72 years, 38% men) from MDCS by use of Sphygmocor® for determination of c-f PWV and pulse wave analysis (PWA) in arteria radialis after an additional mean 30 minutes (range: 15-40 min) of supine rest in a quiet room and well standardized procedures. PWA derived data were used for estimation of central hemodynamics by a transfer function in the device after addition of data on resting brachial BP. Finally, the difference (delta) in bBP during 30 minutes of rest between PWV and PWA measurements was calculated. Adjustment was made for age and sex.

Results: Mean values (SD) were for bBP: 131.0/73.4 (17.1/8.8) mmHg and for cBP: 122.3/74.4 (16.8/9.0) mmHg, with corresponding bPP: 57.5 (12.9) mmHg and cPP: 48.0 (12.3) mmHg, respectively. The pulse pressure amplification (bPP/cPP) was 21.2 (10.5) percentage. The mean c-f PWV was 10.5 (2.5) m/s. In multiple regression analysis after adjustment for age and sex, c-f PWV correlated significantly (p<0.001) and separately with both bPP (r= 0.37) and cPP (r= 0.29).: Mean c-f PWV levels in cPP quartiles ranged from 9.4 to 11.7 m/s, and in bPP quartiles from 9.2 to 12.1 m/s. c-f PWV was inversely correlated with delta bBP (r= -0.09; p<0.001) after full adjustment.

Conclusions: In elderly subjects c-f PWV (as a marker of AS) is modestly associated with both central and brachial PP, but not more closely with central PP as was expected. Selective survival bias may have influenced the findings.

ORAL SESSION

ORAL SESSION 5A
ATRIAL FIBRILLATION

5A.01 CORONARY ATHEROSCLEROSIS AND ADVERSE OUTCOME IN HYPERTENSIVE PATIENTS WITH RECENT-ONSET ATRIAL FIBRILLATION AND TROPONIN RISE

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Objective: Atrial fibrillation (AF), the most common cardiac-arrhythmia in critical-care, has reached a high prevalence in hypertensive patients. Prevention of systemic-embolism is mandatory; unfortunately, evidence to support the treatment of comorbidities as coronary artery disease (CAD) that contribute to excess mortality is lacking, and the mechanism underlying the troponin-rise during AF without acute coronary syndrome (ACS) is unclear. This study investigates the relationship between CAD, stroke and outcomes in patients with troponin-rise and AF.

Design and method: Patients with a recent-onset AF and without severe comorbidities were enrolled. Baseline characteristics in those with troponin-rise versus those without were adjusted with propensity-score-matching for possible confounders. SPSS-software allowed estimation of the propensity-score using logistic-regression and specifying nearest-neighbor matching in prior-stroke, heart-rate, hypertension, TIMI-risk-score, GRACE-score, CHA2DS2Vasc-score. Patients with a troponin-rise or cardiovascular event (CVE) were considered for angiography. The primary endpoint was the composite of ACS, revascularization (with critical CAD>/ = 70%) and cardiac-death at the follow-up; the secondary endpoint was stroke.

Results: Out of 6203 AF patients without severe comorbidities, 3541 with recent-onset AF completed the study; 202(6%) showed a troponin-rise, 91(3%) a CVE. After matching no difference existed in baseline characteristics. On multivariate analysis, in the entire cohort, troponin-rise, know-CAD and hypertension were predictors of the endpoint, whereas only troponin-rise (Odd Ratio, OR: 10, Confidence Interval 95%, CI: 4–22, $p < 0.001$) and TIMI-score > 2 (OR 4, CI 2–9, $p < 0.001$) in the matching cohort, suggesting the role of CAD in poor outcomes. Patients with or without troponin-rise achieved the endpoint in 38(19%) and 43(1%), respectively ($p < 0.001$). Stroke occurred in 4(2%) and 20 (1%), respectively ($p = 0.018$). Critical CAD account for 23(12%) and 15(1%), respectively ($p < 0,001$). In the matching cohort, only stroke did not reach the statistical significance. Interestingly, the best cut/off troponin level for decision-making was 0.30 ng/L which, on Receiver Operator Curve analysis, was associated with 68% of sensitivity and 60% specificity; the value > 0.50 ng/L with 55% and 75%, respectively.

Conclusions: Patients with a recent-onset AF and troponin-rise showed a high prevalence of CVE but not stroke, thus CAD might have a role in poor outcomes.

5A.02 FITNESS STATUS AND RISK FOR ATRIAL FIBRILLATION

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Objective: Chronic, high-intensity physical activity has been associated with increased risk of developing atrial fibrillation (AF). Limited reports also suggest that even moderate levels of physical activity increase the risk for AF.

Design and method: We performed a symptom-limited exercise tolerance test (ETT) in 6,390 veterans (4,401 blacks and 1,989 whites), at the VAMCs in Washington, DC, between 1986 and 2012. All had no evidence of ischemia, AF or atrial flutter at the time or prior to ETT. We established four fitness categories based on age-stratified quartiles of peak metabolic equivalents (MET) achieved: Least-Fit category (4.9 ± 1.13 METs; n = 1,578); Low-Fit (6.7 ± 1.0; n = 1,613); Moderate-Fit (7.9 ± 1.0 METs; n = 1,683) and High-Fit (9.3 ± 1.2 METs n = 1,516). Multivariable Cox models were used to estimate hazard ratios and 95% confidence interval [CI] for AF across fitness categories.

Results: During follow-up (median = 8.0 years), 838 developed AF. For every 1-MET increase in exercise capacity, the AF risk was 21% lower (hazard ratio, 0.79, 95% CI, 0.76–0.82, $p < 0.001$). AF risk was 23% lower for the Low-Fit (hazard ratio, 0.77; 95% CI, 0.65–0.91; $p < 0.001$); 46% for Moderate-Fit (hazard ratio, 0.54; 95% CI, 0.45–0.65; $p < 0.001$); and 64% (hazard ratio, 0.36; 95% CI, 0.29–0.45; $p < 0.001$) for High-Fit individuals.

Conclusions: We observed an inverse, independent and graded association between exercise capacity and AF risk. The decline in risk was precipitous with only modest increases in exercise capacity. These findings support that increased fitness status achievable with moderate increases in physical activity as recommended by National and International guidelines lowers the risk for AF.

5A.03 IMPACT OF MAIN RISK FACTORS OF THROMBOEMBOLIC EVENTS CHA2DS2-VASC SCORE ON THE EFFICACY OF CATHETER ABLATION OF ATRIAL FIBRILLATION IN PATIENTS WITH IMPLANTABLE ECG MONITOR

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Objective: Arterial hypertension (AH), especially not controlled, has a pivotal role in the pathogenesis and persistence of atrial fibrillation (AF). AH is included in each risk stratification of thromboembolic events (CHADS2 and CHADS2-VASC2 scores). Catheter ablation of atrial fibrillation (CA AF) has proved as an effective intervention method for cure highly symptomatic patients with AF.
This study aimed to determine the impact of AH and other risk factors from CHADS2-VASC2 score on the outcome CA AF. The outcome was evaluated as the overall AF burden (defined as the amount of time spent in AF). This parameter could be exactly quantified with an implantable ECG monitor, values are 0–100 % (100% = long persistent AF).

Design and method: We retrospectively analysed 133 patients (108 males - 81%), mean age 55 ± 9 years with paroxysmal/persistent AF. Patients underwent CA AF in the period of 9 years (2005–2013) and were monitored with an implatable ECG monitor (REVEAL XT, Medtronic). CA substrate of AF was was realised with mapping system application of radiofrequency energy by cooling catheter with the aim to achieve permanent electrical isolation of pulmonary veins.

Results: Arterial hypertension was presented in 104 (78.2%) patients. Averall AF burden was before CA AF 21.70 ± 17.9 %, 12 -15 months after CA AF 5.14 ± 12.5, AF burden drop was 16.56. We recorded statistically significant reduction AF burden after CA AF, with maximal drop at the 9 month after CA AF. AF burden reduction was not dependent on the CHA2DS2-VASc score.

Conclusions: Accumulation of the risk factors expressed in the CHA2DS2-VASc score, especially AH, is a certain parameter of overall morbidity of the patient. For the efficacy of CA AF is important to obtain pre- and post- procedural blood pressure control. Our analysis suggest that higher level CHA2DS2-VASc score did not influenced long term efficacy of CA AF. It can therefore be considered CA AF also in patients with paroxysmal/persitent AF with higher incidence of cardiovascular comorbidities.

5A.04 AN INCREASED VAGAL TONUS IS CRITICAL FOR THE INDUCTION AND MAINTENANCE OF ATRIAL FIBRILLATION IN A SYMPATHOEXCITATORY BACKGROUND AS METABOLIC SYNDROME

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Objective: Evaluate the effects of acute vagal stimulation on atrial conduction, atria and pulmonary veins (PV) refractoriness and AFib inducibility in a MetS rabbit model.

Design and method: MetS was induced in male NZW rabbits, 8 weeks, by a high sucrose diet given for 6 months, after which, under anaesthesia, a thoracotomy was performed to expose the heart. An array of 5 microelectrodes was placed in PV vicinity and in the atrial epicardium to record cardiac electrograms. The right vagus nerve was prepared for electrical stimulation (1ms, 50 Hz, ~100 μA). ECG electrodes were placed in 3 of the 4 limbs. The epicardial recordings were made in sinus rhythm. Stimulation bursts (10 s, 50 Hz) were used, alone or combined with vagal stimulation, in the right atrial appendage, left atrial appendage and PV to evaluate AFib inducibility. The effective refractory periods (ERP) and conduction times from the high-lateral right atrium to the high-lateral left atrium and PV were quantified before and after vagal stimulation. Heart rate variability using Fast Fourier Transform (FFT) was applied on autonomic evaluation. A control group matching age and sex was used.

Results: AFib inducibility was greater in MetS-rabbits with a 50 Hz pacing ($38 \pm 7\%$ vs $21 \pm 7\%$) and after vagal stimulation ($53 \pm 6\%$ vs $33 \pm 4\%$). The evoked AFib duration was longer in MetS rabbits than in controls and increased significantly after vagal stimulation. ERPs were lower in MetS rabbits and decreased at all evaluated sites during vagal stimulation. MetS-rabbits had an higher interatrial conduction time than controls (22 ± 1 vs 11 ± 1ms, $p < 0.05$). FFT analysis confirmed a sympathoexcitatory condition in MetS comparing to controls (0.40 ± 0.09 vs 0.11 ± 0.06mmHg2, $p < 0.05$).

Conclusions: Despite MetS-rabbits have an increased basal sympathetic activity which favoured AFib induction, a simultaneous increased vagal tonus seems to be critical not only for the inducibility but also for the maintenance of AFib in this animal model of MetS.

5A.05 INCREASED ARTERIAL STIFFNESS IS AN INDEPENDENT PREDICTOR OF FUTURE ATRIAL FIBRILLATION IN HYPERTENSIVE PATIENTS

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Objective: Atrial fibrillation (AF) is certainly the most common arrhythmia and confers a high risk of stroke and cardiac failure. Hypertension and ageing are two important risk factors of incident AF and are both associated with increased arterial stiffness (AS). The possible relationship between AS and AF are insufficiently documented and probably complex. We tested these relations in hypertensive patients.

Design and method: The patients included in this study belong to the Bordeaux cohort of hypertensive, a registry started in 1984 in which are included patients referred to our centre before administration of antihypertensive treatment and fulfilling the following criteria: Office BP > 140/90 on at least 2 occasions, Essential hypertension, no cardiovascular events or pathology likely to affect the prognosis, no type 1 diabetes. no history of AF, 24 h ambulatory measurement of BP coupled with the measurement of QKD interval inversely linked to AS (QKD100–60 (value for a systolic BP 100 mmHg and heart rate 60 bpm, corrected for patient's height and QRS duration and expressed as % of normal value = QKDh). An echocardiography was also performed at baseline in the majority of patients. AF free survival was analyzed according to the Cox model including sex, diabetes, smoking, hypercholesterolemia, QKDh, average 24 h PP and mean BP, mean 24 h HR, body mass index and left ventricular mass index (LVMI) and Left atrial Diameter (LAD) when available.

Results: 853 have been recruited 67 new on-set of AF have been noticed with a mean follow up of 102 ± 62 months. Cox analysis found 3 variables significantly and independently linked to the occurrence of AF: age, QKDh and 24 h average HR Results remained unchanged when LVMI was introduced. When LAD was introduced (n = 480, 35 incident AF), 3 variables were significantly and independently linked to the occurrence of AF: age, QKDh and LAD.

Conclusions: Arterial stiffness is a strong predictor of future AF in hypertensive patients, independently of age, 24 h pulse pressure, LVMI and LAD.

	Whole population n=853, 67AF			Subgroup with LVMI n=573, 41AF			Subgroup with LAD n=480, 35AF		
	HaRa	CI	P	HaRa	CI	p	HaRa	CI	p
Age (1 year)	1.073	1.049-1.098	0.001	1.077	1.046-1.109	0.001	1.094	1.056-1.133	0.001
QKDh (1%)	0.953	0.93-0.976	0.001	0.949	0.920-0.978	0.001	0.950	0.920-0.980	0.001
24h HR(1 bpm)	0.967	0.944-0.99	0.005	0.968	0.939-0.997	0.03	NS	NS	NS
LVMI ($1g/m^{2.7}$)	NA	NA	NA	NS	NS	NS	NS	NS	NS
LAD (1mm)	NA	NA	NA	NA	NA	NA	1.078	1.026-1.133	0.003

HaRa: Hazard ratio, CI: 95% confidence interval

5A.06 CORRELATION OF THROMBOEMBOLIC RISK WITH GLOBAL LEFT ATRIAL STRAIN IN HYPERTENSIVE PATIENTS WITH ATRIAL FIBRILLATION

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Objective: Multiple risk stratification schemes for prediction of thromboembolic (TE) events are mostly validated in patients (pts) with permanent atrial fibrillation (AF). The acceptable data on TE risk in paroxysmal and persistent AF are limited, and more extensive evaluation is needed.

Design and method: Sixty hypertensive pts [mean age 65 (60; 72) yrs, 45% men] with paroxysmal (n = 26) and persistent (n = 34) AF were included in study comparing echocardiographic measurements in the sinus rhythm period. AF duration was 28 (20; 59) months. Seven (12%) pts had previous stroke, 16 (27%) pts had history of prior MI, 14 (23%) pts had diabetes mellitus. Apical four- and two-chamber views images of 6 myocardial segments in the filling phase were obtained to assess global peak left atrial longitudinal strain (PALS) and strain rate (PALSR) in the reservoir (r) and contractile (c) phase.

Results: Pts with paroxysmal AF had significantly higher PALSr to compare with pts with persistent AF [15,1 (12,2; 16,4) vs 11,2% (8,0; 12,9), p = 0.0002] and PALSc [-15,0 (-16,2; -12,7) vs -12,0% (-13,0; -9,4), p = 0.0002]. PALSRr significantly differed in paroxysmal and persistent AF groups [2,16 (1,95; 2,34) vs 1,65 s-1(1,35; 1,90), p = 0.0003] as well as PALSRc [-2,02 (-2,25; -1,95) vs -1,56 s-1(-1,85; -1,38), p = 0.0008]. Higher CHA2DS2-VASc scores were significantly ($p < 0.05$) related with LVMI (r = 0,31), PALSr (r = -0,39), PALSRr (r = -0,44) and PALSRc (r = 0,47).

Conclusions: Thromboembolic risk was positivly correlated to LVMI and PALSRc, and negatively correlated to PALSr and PALSRr in hypertensive pts with paroxysmal and persistent AF.

5A.07 PREVALENCE OF ARTERIAL HYPERTENSION IN PATIENTS WITH ATRIAL FIBRILLATION UNDERGOING ABLATION. A PROSPECTIVE, COHORT STUDY

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Objective: Arterial hypertension (AF) is one of the major cofounders in the development of atrial fibrillation. Hemodynamic overload causes atrial wall stretch and promotes the arrhythmia. Therefore hypertension is commonly found in AF patients. The aim of the study was to establish the prevalence of arterial hypertension in patients undergoing ablation, who are relatively young and healthy group of AF patients.

Design and method: Two hundred sixty six consecutive patients admitted for AF ablation were screened for arterial hypertension. All patients had their blood pressure measured on admission by, prior to the ablation procedure by a qualified physician, according to the current guidelines. Also, medical records of patients were reviewed for the previous diagnosis of hypertension or taking hypotensive agents.

Results: The study group was predominantly male (173 patients, 65.0%) with a mean age of 57.6 ± 10.1 years. Mean body mass index was 29.7 ± 5.0 kg/m^2. Paroxysmal AF was present in the majority of patients (185 patients, 69.5%). In 194 (72.9%) patients hypertension was diagnosed previously. On admission, mean systolic and diastolic blood pressure values were 131.7 ± 16.7 and 80.7 ± 11.1 mmHg. 123 (46.2%) patients had systolic and/or diastolic blood pressure values respectively > 140 and/or > 90 mmHg. Patients with previously diagnosed hypertension were older (58.7 ± 8.7 vs. 54.6 ± 12.7 years; p = 0.003), had higher BMI (30.3 ± 5.0 vs. 28.1 ± 4.8 kg/m^2; p = 0.002), and more often had history of diabetes (10.8% vs. 1.4%; p = 0.03) compared to those without diagnosed hypertension. There were no differences between the groups in terms of dyslipidemia (p = 0.62), family history of cardiovascular disease (p = 0.89), history of stroke (p = 0.47) or myocardial infarction (p = 0.46).

Conclusions: In patients with AF qualified for ablation procedure, prevalence of diagnosed arterial hypertension is very high, much higher than in the general population. Nevertheless, majority of patients meet the criteria for proper blood pressure control.

ORAL SESSION

ORAL SESSION 5B
HEART AND HAEMODYNAMICS

5B.01 LONGITUDINAL AND RADIAL LEFT VENTRICLE SYSTOLIC FUNCTION ASSESSMENT IN HYPERTENSIVE PATIENTS

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Objective: Few data are available on the relationship between left ventricular (LV) circumferential and longitudinal systolic function in hypertensive patients with preserved LV ejection fraction (EF). The aim of this study is to analyze LV circumferential and longitudinal systolic function and their main determinants in a group of hypertensive patients.

Design and method: In 1285 hypertensive patients (547 female, mean age 57 ± 13 yrs, 77% treated) a standard echocardiographic examination was performed, to assess LV anatomy and systolic function parameters, including EF, Midwall fractional shortening (MidFS) and MidFS adjusted for endsystolic stress (ESS_MidFS). In addition longitudinal systolic function was evaluated by the measurement of tissue Doppler peak systolic velocity of the mitral annulus (Sm). A reduced systolic function was defined in the presence of ESS_MidFS lower than 89% or Sm lower than 8 cm/sec.

Results: A modest but statistically significant relationship between MidFS or ESS_MidFS and Sm ($r = 0{,}08$, $p < 0{,}001$) was observed. MidFS was independently related to age, body mass index (BMI), LV mass index, relative wall thickness (RWT) and hear rate, while the main determinants of Sm were age, heart rate, systolic blood pressure and LV mass index. According to previously defined criteria a reduction of Sm and ESS_MidFS was observed in 47% and 26% of patients, respectively.

Conclusions: Longitudinal systolic function is impaired in a high percentage of hypertensive patients with preserved EF and identifies a higher number of patients with impaired systolic function. The determinants of longitudinal and circumferential systolic function are, at least in part, different.

5B.02 LONGITUDINAL CHANGES IN LEFT VENTRICULAR DIASTOLIC FUNCTION IN A GENERAL POPULATION

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Objective: Data on changes in left ventricular diastolic function (LVDF) over time in the general population are sparse. We, therefore, investigated in the population cohort clinical correlates of longitudinal changes in Doppler diastolic indexes analyzed as continuous measures and assessed factors predictive of the changes in LVDF grades over time.

Design and method: We measured early and late diastolic peak velocities of mitral inflow (E and A) by conventional Doppler, and the mitral annular velocities (e' and a') by Tissue Doppler Imaging (TDI) in 650 participants (mean age 50.7 years) at baseline and after 4.7 years (5th to 95th percentile, 3.7—5.4).

Results: In stepwise regression, the multivariable-adjusted correlates of the change in the transmitral and TDI diastolic indexes included sex, age, baseline serum insulin, blood pressure (BP) and heart rate. Over follow-up, LVDF grades remained unchanged in 87.2% (95% CI, 84.6% to 89.8%), improved in 3.7% (95% CI, 2.25% to 5.15%) and worsened in 9.1% (95% CI, 6.9% to 11.3%). Baseline age was a strong predictor of worsening of LVDF from normal/mild grade to more advanced grade (OR = 3.22; $P < 0.0001$). A doubling of baseline insulin was associated with a 184% increase in the odds of worsening of LVDF ($P < 0.0001$). Moreover, baseline diastolic BP and the change in systolic BP over time predicted worsening of LVDF ($P < 0.014$).

Conclusions: The key findings of this study are that LVDF tended to worsen over time and was associated with advanced age, higher baseline insulin level and hemodynamic parameters such as heart rate and BP.

5B.03 ARTERIAL-VENTRICULAR COUPLING AND PARAMETERS OF VASCULAR STIFFNESS IN HYPERTENSIVE PATIENTS: ROLE OF GENDER

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Objective: The present study was designed to investigate the relationship between left ventricular elastance (ELV), arterial elastance (EA), parameters of vascular stiffness and the influence of gender in a population of hypertensive individuals at high cardiovascular (CV) risk.

Design and method: Seventy eight subjects participated in the study. Trans-thoracic cardiac ultrasound exam and parameters of aortic stiffness (carotid-femoral pulse wave velocity, PWV) wave reflection (augmentation index, AIx), aortic and carotid pulse pressure (PP) were obtained. Ultrasound images of the common carotid artery were acquired for the assessment of intima-media thickness (IMT) as well as carotid compliance (CC) and distensibility coefficient (DC).

Results: The mean age of subjects was 62,5 years old, 37,2% had diabetes, 48,7% dyslipidemia, 7,7% previous CV events. Women (43%) and men were superimposable for CV risk factors except for older age (63.3 ± 9.2 vs 57.5 ± 10.4 years, $p < 0.001$) and greater prevalence of dyslipidemia (66% vs 35%, $p = 0.04$).
In the overall population ELV was significantly correlated with EA ($r = 0.79, p < 0.001$), age, gender and BMI ($r = 0.30, p = 0.07, r = -0.64, p < 0.001, r = -0.32, p = 0.004$ respectively), AIx ($r = 0.53, p < 0.001$), aortic PP ($r = 0.39, p < 0.001$) CC ($r = -0.44$, $p < 0.001$) and DC ($r = -0.27$, $p = 0.02$), but not with PWV ($r = 0.13, p = 0.28$). In the multiple regression model including EA, ELV was still significantly correlated with EA, BMI, gender (all $p < 0.001$) and aortic PP ($p = 0.004$). Conversely, DC and PWV were not.
DC, CC, PWV and IMT were similar in men and women. ELV ($p < 0.0001$) and EA ($p = 0.0002$) were higher in women than in men, while EA/ELV was lower ($p = 0.0003$). While EA and BMI were significantly correlated with ELV both in men ($r = 0.74, p < 0.0001$) and women ($r = 0.77, p < 0.0001$), DC was correlated with ELV only in women (women $r = 0.04, p = 0.03$, men $r = -0.21, p = 0.17$), and aortic PP (men $r = 0.44, p = 0.002$, women $r = 0.44$, $p = 0.01$) and AIX (men $r = 0.37, p = 0.002$, women $r = 0.33$, $p = 0.06$) only in men.

Conclusions: In hypertensive individuals, main determinants of ventricular elastance are arterial elastance as an integrated index of arterial vascular load, central PP, gender and BMI. However, large artery stiffness in women and pressure augmentation in men might play an additional role.

5B.04 TIME TO PEAK SYSTOLIC MYOCARDIAL WALL STRESS IS INDEPENDENTLY ASSOCIATED WITH DIASTOLIC FUNCTION

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Objective: Diastolic dysfunction in hypertensive patients with preserved left ventricular (LV) ejection fraction (EF) (>40%) could be associated with prolonged systolic contraction and delayed systolic relaxation. We therefore examined whether time to peak systolic myocardial wall stress (MWS) relates to diastolic dysfunction.

Design and method: We studied 178 subjects, evaluated for hypertension but otherwise free of clinically apparent cardiovascular disease aged 45.8 ± 16.3 (mean $\pm$ SD) years with mean systolic blood pressure (SBP) of 139 ± 23 mmHg and EF of $57.9 \pm 7.5\%$. The E/E' ratio was calculated from Doppler echocardiography mitral valve inflow and tissue Doppler of the basal lateral segment and used as a surrogate of diastolic function. MWS, a function of left ventricle (LV) pressure and geometry was obtained using carotid tonometry to estimate LV pressure during systole and 2D transthoracic echocardiographic wall tracking analysis (Tomtec) to derive cavity and myocardial wall volume. Subjects were divided into three

groups (Group one (n = 64): SBP < 130mmHg and E/E' < 10; Group two (n = 92): SBP > = 130mmHg and E/E' < 10; Group three (n = 22): SBP > = 130mmHg and E/E' > = 10).

Results: EF was preserved and not significantly different between groups (p = 0.44). Time to peak systolic MWS (Group one: 81.4 ± 3.9ms (mean ± SE), Group two 91.8 ± 4.2ms and Group three 116.4 ± 12.2ms) was significantly higher in group three with or without adjustment for age, body surface area (BSA) and HR compared to group one and two (p = 0.001). Across all groups, time to peak MWS was positively associated (standardized β = 0.24, p = 0.001) with E/E' ratio.

Conclusions: In hypertensive patients with preserved EF, impaired diastolic relaxation is associated with prolonged ventricular contraction independent of age, BSA and HR.

5B.05 MARFAN SYNDROME: ASSESSMENT OF AORTIC DISSECTION RISK BY ANALYSIS OF AORTIC VISCOELASTIC PROPERTIES

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Objective: Marfan syndrome is an autosomal dominant genetic disorder characterized by an abnormal fibrillin-1 synthesis. Aortic root dilation and dissection are the main problems affecting patients prognosis in these patients. Their pharmacological prophylaxis with losartan or with a beta-blocker counteracts the aortic root dilation, but a close follow-up is required to assess therapeutic response rate and to identify non-responders. Unfortunately genotype-phenotype studies do not allow to determine the exact risk profile in these patients and there is no reliable method to accurately predict their risk of aortic dissection. Aim of this study was to evaluate non-invasive markers for identification of Marfan patients at higher risk of aortic complications.

Design and method: We studied 187 Marfan patients (identified according to 2010 Revised Ghent Criteria and positive genetic analysis), age 32.3 ± 16.5 yrs (mean ± SD). 52 patients (27.8%) had undergone surgical ascending aorta replacement (David or Bentall procedure). Central pressure curves were recorded by PulsePen tonometer, and the aortic viscoelastic aortic properties were studied by determination of carotid-femoral pulse wave velocity (PWV).

Results: With reference to the age related distribution of PWV values in a normal population, defined according to Arterial-Stiffness-Collaboration, PWV mean values in Marfan patients corresponded to 60th percentile in non- operated patients and to the 67th percentile in those operated. Adult Marfan patients (n = 146) generally displayed a low blood pressure, because of the pharmacological prophylaxis, and were compared with a population of 189 adult healthy subjects (81 males), matched by age (38 ± 13 vs 38 ± 16 yrs.), heart rate (64 ± 9 bpm vs 64 ± 11 bpm) and blood pressure (mean BP = 78 ± 9 mmHg vs 79 ± 4 mmHg) values. Average PWV value was higher than in healthy controls (PWV = 7.0 ± 1.7) both in not operated (PWV = 7.6 ± 1.6; p = 0.0003) and in operated (PWV = 9.5 ± 3.2; p < 0.0001) Marfan patients. Among non operated patients, PWV was significantly correlated to aortic root diameters (Aortic annulus: $R^2 = 0.14$; Valsalva sinuses: $R^2 = 0.22$; Sinotubular junction: $R^2 = 0.28$).

Conclusions: A significant reduction of the distensibility of the aorta was found in Marfan syndrome. Further analyses are needed to assess the prognostic significance of PWV changes seen in these in these patients.

5B.06 ASSOCIATION OF PLASMA TESTOSTERONE WITH CENTRAL HAEMODYNAMICS IN HYPERTENSIVE MEN

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Objective: There is evidence for an inverse association between plasma testosterone and blood pressure. Recently, low plasma testosterone was associated with increased risk of major cardiovascular events in middle-aged hypertensive men. Central (aortic) blood pressures predict cardiovascular mortality with equal ability compared to peripheral (brachial) blood pressures. The aim of the present study was to assess the relationship of plasma total testosterone (TT) with peripheral and central haemodynamics in hypertensive men.

Design and method: We studied 70 non-diabetic, hypertensive men (mean age = 60 years old). Office brachial systolic (bSBP) and diastolic (bDBP) blood pressures were measured according to the ESH guidelines. Pulse pressure (bPP) was calculated as SBP minus DBP. All patients were subject to measurement of aortic systolic (aoSBP), diastolic (aoDBP) and pulse pressures (aoPP) by pulse wave analysis using the Sphygmocor device. Wave reflections were assessed by the measurement of heart-rate corrected augmentation index (AIx75). Plasma TT was measured in all subjects by enzyme immunoassay.

Results: The mean value of TT in the whole population was 4.6 ng/ml (hypogonadism was defined as TT < 3.4 ng/ml). Plasma TT was inversely and significantly related to aoSBP (r = -0.26, p = 0.03), aoPP (r = -0.30, p = 0.01) and AIx75 (r = -0.31, p = 0.01) but only marginally related to bSBP (r = -0.22, p = 0.07) and bPP (r = -0.23, p = 0.06). In linear regression analysis, after adjustment for age, smoking, BMI, plasma glucose, total cholesterol and presence of antihypertensive treatment, aoSBP (b = -0.29, p = 0.03), aoPP (b = -0.31, p = 0.02) and AIx75 (b = -0.30, p = 0.03) were independently associated with TT but the relationship of TT with bSBP (b = -0.25, p = 0.06) and bPP (b = -0.23, p = 0.07) remained weak.

Conclusions: In hypertensive men, plasma TT is independently and inversely associated with central blood pressures and wave reflections. Considering the adverse prognostic role of central blood pressures on cardiovascular outcomes, the present finding might explain part of the increased cardiovascular risk associated with low testosterone. Whether measurement of central haemodynamics may improve risk stratification in men with low testosterone, warrants further investigation.

5B.07 HEMODYNAMIC AND GLUCOMETABOLIC FACTORS IN THE PREDICTION OF LEFT VENTRICULAR FILLING PRESSURES

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Objective: To explore possible hemodynamic and glucometabolic determinants of left ventricular filling pressures as assessed by the non-invasive surrogate marker, averaged E/é, in otherwise healthy, middle-aged male survivors from a random population sample.

Design and methods: Prospective population-based cohort study examining associations between hemodynamic factors (systolic blood pressure (SBP), heart rate (HR)), glucometabolic factors (fasting blood glucose, fasting plasma insulin, Homeostatic Model Assessment (HOMA) derived indices of beta-cell function (HOMA-2B) and insulin sensitivity (HOMA-2S)), other traditional cardiovascular risk factors (age, smoking status, body mass index (BMI), total serum cholesterol, serum creatinine) assessed at baseline, and values of E/é assessed at follow-up examination, using multivariable linear regression analysis (significance level 0.05, p-stay 0.20 on multivariable analysis). Subjects with prevalent cardiovascular disease and/or diabetes mellitus were excluded. E/é was positively skewed and, therefore, naturally log-transformed, as was fasting plasma insulin. HOMA-indices were assessed as continuous variables, both non-transformed and after natural log-transformation, as well as categorically, using quartiles. Study subjects were included 1974-1992, whilst the follow-up with echocardiography was performed 2002-2006.

Results: The final study population comprised 246 men with a median (IQR) age of 47 (47-48) years. Median (IQR) follow-up time was 28 (27-28) years, and median (IQR) E/é was 10 (8-12). In univariable analyses, E/é was associated positively with higher age, BMI, and serum creatinine, and negatively with shorter follow-up time. The multivariable model (adjusted r2 = 0.15) included all of these variables, i.e. age (beta = 0.016 per year (95% confidence interval (CI), 0.006 to 0.027); p = 0.002), BMI (beta = 0.03 per kg/m2 (95% CI, 0.02 to 0.04); p < 0.0001), serum creatinine (beta = 0.002 per micromole/l (95% CI, -0.001 to 0.005); p = 0.18), and time elapsed between baseline examination and echocardiography (beta = -0.03 per year (-0.06 to -0.01); p = 0.01). We did not find any significant interactions in the prediction of E/é.

Conclusion: In a prospective population-based cohort study including apparently healthy, middle-aged male subjects, higher age, BMI, and creatinine, but not SBP or HR, were significantly associated with higher left ventricular filling pressures as assessed by averaged E/é.

ORAL SESSION

ORAL SESSION 5C

EPIDEMIOLOGY OF HYPERTENSION AND BLOOD PRESSURE CONTROL

5C.01 LITTLE DIFFERENCE IN SALT INTAKE CRUCIALLY AFFECTS FUTURE BLOOD PRESSURE LEVELS IN THE GENERAL POPULATION

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Objective: A causal relationship between salt and hypertension has been argued for a long time. Epidemiological cross-sectional studies demonstrated higher incidence of hypertension in populations with higher dietary salt than in those with lower dietary salt and interventional studies investigated the effects of drastic changes in dietary salt in individuals. However, there is not sufficient evidence proving that individuals with relatively high salt intakes show an accelerated increase in blood pressure compared to those with a relatively low salt intakes over a long period of observation. Thus, the present observational study was designed to investigate whether individual levels of dietary salt affect future increases in blood pressure in the general population.

Design and method: Individual salt intake was estimated by calculating 24-hour urinary salt excretion using a spot urine in normotensive 6,249 participants in our physical check-up program (53.3 ± 11.4 year-old). After baseline examination, they were followed up for the median of 1,089 days with the endpoint being the development of hypertension.

Results: During the follow-up period, hypertension developed in 1,027 participants (73.0 per 1,000 person-years) with the incidence being more frequent in male than female participants. After adjustment for possible risk factors, the hazard ratio of incident hypertension in participants with salt intake higher than the target recommended by the Japanese Ministry of Health, Labour and Welfare (male, <9.0 g/day; female, <7.5 g/day) was 1.25 (95% confidence interval 1.04 to 1.50). In multivariate Cox hazards regression analysis, baseline salt intake and the yearly change in salt intake during the follow-up period (as continuous variables) correlated with the incidence of hypertension. Furthermore, both the yearly increase in salt intake and baseline salt intake showed significant correlations with the yearly increase in systolic blood pressure in multivariate regression analysis after adjustment for possible risk factors.

Conclusions: Both relatively high levels of dietary salt intake at baseline as well as gradual increases in dietary salt during the follow-up period are associated with future increases in blood pressure and the incidence of hypertension in the general population.

5C.02 PREVALENCE OF HYPERTENSION AND OTHER CARDIOVASCULAR RISK FACTORS IN PARTICIPANTS IN THE 2014 HYPERTENSION WORLD DAY CAMPAIGN IN ITALY

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Objective: Aim of our study was to obtain information on prevalence and awareness of hypertension and other cardiovascular risk factors in individuals participating in the 2014 "World Hypertension Day" in Italy.

Design and method: During the 2014 "World Hypertension Day", health care providers from 50 hypertension centers affiliated to the Italian Society of Hypertension, spread all over the country, anonymously interviewed individuals spontaneously participating in this campaign. Information on demography, cardiovascular risk factors prevalence, awareness of hypertension and of its consequences was obtained. The average of two conventional blood pressure (BP) measurements, taken in seated position after a few min rest by a validated oscillometric device (Microlife BP A150), was recorded.

Results: Data were collected from 6356 individuals (53.2% females, 46.8% males) aged 57.8 years. (18–105 years).
43.6% of subjects were aware of being hypertensive, 89.9% being treated. In this cohort active and former smokers were respectively 19.2% and 22%; 28.6% reported hypercholesterolemia and 8.3% diabetes. Mean systolic BP > 139mmHg was found in 34.8% and mean diastolic BP > 89mmHg in 18.3% of the entire cohort and in 47.7% and 23.5% of aware hypertensive individuals, respectively. In 14.5% of participating subjects and in 19.6% of aware hypertensives both systolic/diastolic BP were found above 139/89mmHg respectively. On average, BP was higher in aware hypertensive individuals, in spite of being treated, than in the overall cohort (139.6/81.7 ± 19.7/14.5 vs 133.1/79.7 ± 20.3/15 mmHg, respectively, $p < 0.005$). Awareness of hypertension complications was imperfect, acute myocardial infarction, stroke and renal failure being recognized as consequences of hypertension by 85.1%, 61.6% and 28.6% of individuals, respectively.

Conclusions: Our data, obtained in Italy at the time of the 2014 World Hypertension Day show a yet high hypertension prevalence, accompanied by an unsatisfactory awareness of its complications and by a frequent occurrence of other cardiovascular risk factors in participants in this initiative. Even considering that these individuals may not be fully representative of the general Italian population, our results strongly indicate that more efforts are still needed to improve hypertension control and to increase patients' awareness of the risks associated to this condition.

5C.03 HYPERTENSION IS NOT ASSOCIATED WITH SURVIVAL IN 90 YEARS OLD: THE JERUSALEM LONGITUDINAL STUDY

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Objective: Hypertension is among the most common chronic problems of older people. Among very old people with common co-morbidities, it remains uncertain whether the benefits of long-term treatment seen among younger people, are also observed. Our objective was to assess the relationship of blood pressure (BP) at age 90 with 3-year all-cause mortality.

Design and method: A longitudinal prospective cohort study, of an age-homogenous, representative sample born 1920–1921.
Comprehensive geriatric assessment of numerous health variables was obtained. BP was determined as the average of 6 measurements, from 2 separate home visits. Hypertension (HTN) defined as either treatment with antihypertensive medications, or blood pressure >140 mm Hg systolic, or >90 mm Hg. The study outcome was all-cause 3-year mortality. Mortality data were collected from the National Ministry of Interior.

Results: Sixty (12.1%) were normotensive, 60 (12.1%) untreated hypertensives and 374 (75.7%) treated hypertensives. During 3 years 83 (17.6%) patients died. Kaplan-Meier survival curves and log rank analysis showed no difference in mortality between normotensive, untreated and treated hypertensive subject. Subjects that were treated for Hypertension (HTN) had the lowest survival rate comparing to untreated hypertensives and normotensive (81.3%, 85.7% and 88% respectively). There was no significant difference in survival between the normotensives, untreated hypertensive and treated hypertensives after excluding the subjects who need assistance in activities of daily living, those with lower than median Hand grip strength and those with lower than median Timed up and go (TUG) test although there was a trend towards a shorter survival for the treated hypertensives.

Conclusions: Hypertension was not associated with increased 3-year mortality among a representative cohort of community-dwelling 90-year-olds although there was a trend towards a shorter survival for the treated hypertensives.

5C.04 SCREENING FOR HYPERTENSION IN THE BARBERSHOP: A FRANCO-MOROCCAN FEASIBILITY STUDY (THE "DECOIFFA" STUDY)

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Objective: High Blood Pressure (HBP) is responsible for 7.5 million deaths per year worldwide. About 15 million of French people are hypertensive and 4 millions of them are undiagnosed. More than 7 millions of Moroccans are hypertensive. Today, a high percentage of hypertensive patients remain undiagnosed and mass screening programs in pharmacies or shopping centers are not very efficient. Therefore, there is a need to develop new strategies to identify untreated hypertensive patients.
To evaluate the feasibility and the effectiveness of a HBP screening strategy for unknown or insufficiently treated hypertensive patient with Self-Blood Pressure Measurements (SBPM) in barbershops.

Design and method: Prospective multicenter study of HBP screening in France and Morocco. Willing customers of 23 barbershops in France and 6 in Morocco were included between January and April 2013. Three validated humeral Omron M7 Automatic BP monitors connected to a printer were needed in each barbershop. An information formular was delivered to all customers. Customers were free to give their phone number to be contacted 3 months later for a standardized follow-up questionnaire. Suspected HBP was defined by an average of 3 SMBP > = 135 and/or > 85 mmHg. The primary endpoints of the study were: number of patients with treated or untreated HBP, number of patients referred to their physicians, proportion of permanent HBP diagnosis after screening and the acceptability of this screening strategy.

Results: Table 1:

	Participants	Pourcentage of Women (n)	Average age (years ± SD)	Percentage of patients treated for HBP (n)	Percentage of SMBP ≥ 135/85 mmHg (n)	Percentage of patients treated for HBP and suspected uncontrolled (n)	Percentage of patients suspected for unknow HBP (n)
France	1011	74 (n=753)	50±18	19.0 (n=192)	25.7 (n=370) p<0,0001	57.3 (n=110) p<0,0001	25.7 (n=260) p<0,001
Morocco	299	53 (n=157)	61±11	13.7 (n=41)	71.9 (n=215) p<0,15	82.9 (n=34) p<0,091	70.2 (n=181) p=0,091

The screening identified a very high percentage of untreated hypertensive patients particularly in Morocco (70.2%) and France (25.7%).
In France, 40.2% (n = 41) of customers having an average of SMBP > = 135/85 mmHg have consulted a physician after screening. 75.8% (n = 213) of participants contacted for the follow-up considered the screening test to be innovating and none have found it inappropriate.

Conclusions: HBP screening by SMBP in the barbershop helped to identify unknown or insufficiently treated hypertensive patients in proportions consistent with published data in USA (threshold > = 135/85 mmHg). This method was well accepted. Our results may further inspire HBP screening in unconventional spots in particular in developing countries where direct access to health care may be limited.

5C.05 DIFFERENCES IN PREVALENCE, AWARENESS, TREATMENT AND CONTROL RATES OF HYPERTENSION BETWEEN MALE AND FEMALE

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Objective: To compare differences in prevalence rates, awareness, treatment and control of hypertension between male and female workers of a public university in the Midwest region of Brazil.

Design and method: Cross-sectional study with a representative sample of employers from the Federal University of Goias - Brazil. Data were collected in the workplace with individual questionnaire and measurement of casual blood pressure using semi-automatic devices (OMRON HEM model 711). Individuals using anti-hypertensive drugs and/or with blood pressure (BP) greater than or equal to 140/90mmHg (or 130/80mmHg, in the case of diabetics) were considered hypertensive. The knowledge about the disease was identified among those who claimed to be aware of the diagnosis before the measurements, and the treatment rate was calculated with those who reported using antihypertensive drugs. Controlled blood pressure was considered in individuals with values lower than 140/90mmHg (or 130/80mmHg, in the case of diabetics). The study was approved by the Ethics Committee of the institution.

Results: The study included 1000 individuals with a mean age of 42.3 years (± 12.1); 393 (39.3%) patients were male. The prevalence of hypertension was 30.1% (n = 301), being higher among men (34.6%) than women (27.2%) (p < 0.05), aged over 50 years (p < = 0.001) and among those who have also referred hypertensive parents (p < 0.05). Among the hypertensive men 62.5% knew the diagnosis, 82.4% of those were under treatment, and 60.0% of those had BP under control. Among the hypertensive women 83,6% knew the diagnosis, 90,6% were under treatment and 79,4% were with controlled BP (p < 0,05 for the three variables).

Conclusions: Despite the higher prevalence of hypertension in men, women had a greater knowledge of the diagnosis, higher rates of treatment and control of the disease in a population of workers from a Brazilian public university.

5C.06 HYPERTENSION AND CARDIOVASCULAR RISK FACTORS: A SHOT ON NORTHERN ITALY POPULATION IN REAL LIFE SETTING

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Objective: Hypertension (HT) represents the most important cardiovascular (CV) risk factor and blood pressure (BP) measurements are generally performed in medical settings, while data deriving from real life are generally poor. This work was conducted during public events out of medical setting (i.e. world hypertension day) in order to assess the prevalence of HT and evaluate other CV risk factors.

Design and method: Each participating subject, after signing an informed consent, was asked to fulfil a questionnaire investigating his/her comorbidities, CV risk factors and ongoing therapies. BP measurement was performed according to the ESH/ESC guidelines. A brief counselling was then offered and brochures dealing with HT prevention provided.

Results: Between May 2011 and May 2014, 1540 subjects were evaluated (mean age = 58y, median = 60y, range = 12–102y, M = 696, F = 845, M/F = 0.82). Among them, 890 (58%) declared themselves «normotensive» (mean age = 52y, median = 53y, range = 12–86, M = 408, F = 482) and 650 (42%) «hypertensive» (mean age = 65y, median = 66, range: = 22–102, M = 287, F = 363). BP measurement resulted < 140/90mmHg in 1137 subjects(=74%). Among them, 408 belonged to the «hypertensive» group, thus representing pts reaching the target pressure (=63%). On the contrary, BP > 140/90mmHg was observed in 403 subjects(=26%), 242 of them belonging to the «hypertensive» group (=non target pts) and 161 to those previously declaring «normotensive». CV risk factors were analysed, the most represented being dyslipidaemia (N = 441), smoke(N = 216), Type 2 Diabetes(N = 121), Coronary artery disease(N = 110), cerebrovascular disease(N = 44). All these risk factors were significantly more expressed in «hypertensive» pts. Number of CV risk factors was 0, 1, 2, 3, > 4 respectively for 500, 522, 312, 150, and 55 subjects. Thirty-five % of «hypertensive» pts had no other CV risk factor, but a significantly higher number of CV risk factors emerged respect to «normotensives».

Conclusions: Despite the possible bias, our data provide a picture of the status of pts out of medical setting. Epidemiological data and CV risk factors were analysed, suggesting, as expected, a higher number of CV risk factors in "hypertensive" pts.

5C.07 A METHOD TO ESTIMATE 24-HOUR SODIUM EXCRETION THROUGH SPOT URINE SAMPLES AND ITS APPLICATION VALUE FOR TARGET-ORGAN DAMAGE ASSESSMENT

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Objective: 24-h urine sodium excretion is considered the most reliable method to evaluate the salt intakes. However, this method is cumbersome. So we want to develop formulas to estimate 24-h urinary sodium excretion using spot urinary samples in Chinese hypertensive population and explore the application value of this method in salt intake assessment and target organ damage.

Design and method: 1.We enrolled 510 cases of hospitalized patients with hypertension, 2/3 of them were arranged randomly to formula group to develop a new formula and the remainings were used to test the performance of the formula. All participants were instructed to collect a 24-h urine sample, a second morning voiding urine sample (SMU), and a post-meridiem urine sample in the late afternoon or early evening, prior to the evening meal (PMU). All samples were sent to measure sodium and creatinine concentration.2. We compared the differences of office blood pressure, 24-hour ambulatory blood pressure and left ventricular hypertrophy, vascular stiffness and urine protein among groups of different sodium intake.

Results: 24hour sodium excretion formulas was obtained using SMU and PMU respectively, which have good cosistency. The difference between the estimated and measured values in sodium excretion is 12.66mmol/day (SMU) and 9.41mmol/day (PM), to be equal to 0.7 g (SMU) and 0.6 g (PM) salt intake. Comparing with Kawasaki and Tanaka method, the new formula shows the lower degree of deviation, and higher accuracy and precision. Blood pressure of high urinary sodium group is higher than that in low urinary sodium group (P < 0.05). Left ventricular hypertrophy and urinary albumin/creatinine aggravated with the salt intake increase, this has eliminated the influence of other factors. All of morphologies of the relationship

between ambulatory arterial stiffness index, pulse wave velocity and carotid intima-media thickness with quartiles of sodium intake resembled a J-shaped curve.

Conclusions: In Chinese hypertensive population, the formulas to estimate 24-h urinary sodium using spot urinary samples spot urine are considered useful for estimating the mean level of population salt intake, and have a role in evaluating target organ damage.

5C.08 AGE AND GENDER SPECIFIC CARDIO-METABOLIC RISKS AND THEIR RELATIONS TO LIFE STYLE DISORDER IN THE GENERAL POPULATION: THE WATARI STUDY

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Objective: In developed countries, systolic blood pressure is known to increase with age. Metabolic risks may generally worse with increasing age. But this trend may be modified by environmental factors which are different between gender and generation. The aim of this study was to examine the relationship between age and gender-related difference in cardio-metabolic risks and life style factors in the Japanese general population.

Design and method: We studied 3628 inhabitants of Watari (mean age 63.9 yrs, 42.5% men), Miyagi prefecture, who participated in a health check-up in 2009. Anthropometry, sitting blood pressures, fasting blood samples were examined. Unhealthy dietary behaviors (night meal, late dinner, fast eating, skipping breakfast, smoking, heavy drinking, lack of regular exercise) were evaluated by standard questionnaire. Presence or absence of each behavior was scored 0 or 1 and total score was calculated as healthy life style score (range 0 to 7, higher the better). Gender difference in age-related changes in blood pressures, BMI, lipid and glucose metabolism were examined by two way ANOVA.

Results: Systolic blood pressure was continuously increased from age 30 s to 70 s in both genders. Systolic blood pressure was significantly higher in men than in women in age 30 s (122.0 ± 13.9 vs. 113.3 ± 12.8 mmHg, $p < 0.001$) but the difference decreased with an increase in age. Similar gender interaction was observed for diastolic blood pressure, BMI, triglyceride and high density lipoprotein (all $p < 0.001$) but was not for HbA1c. The healthy life style score was lowest in men age 30 s (5.1 ± 1.5) and it increased with an increase in age. Women demonstrated significantly higher healthy life style score than men in all generations. The gender difference in the score was largest in age 30 s and decreased with an increase in age.

Conclusions: Cardio-metabolic risks are worse in men than in women in young generation but this gender difference diminishes with age. The gender difference in the young may be largely attributable to life style factors. Glucose metabolism may be less affected by life style than blood pressure or lipid.

5C.09 HERITABILITY OF RENAL FUNCTION PARAMETERS AND ELECTROLYTE LEVELS IN THE SWISS POPULATION

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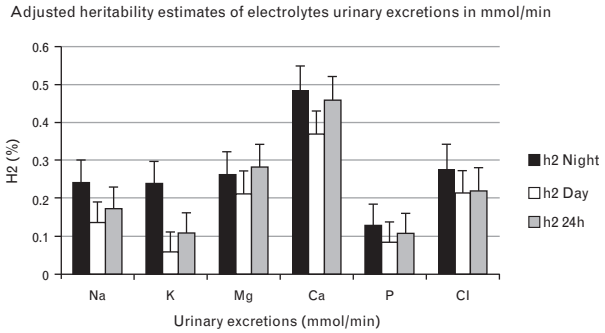
Objective: Electrolytes handling by the kidney is essential for volume and blood pressure (BP) homeostasis but their distribution and heritability are not well described. We estimated the heritability of kidney function as well as of serum and urine concentrations, renal clearances and fractional excretions for sodium, chloride, potassium, calcium, phosphate and magnesium in a Swiss population-based study.

Design and method: Nuclear families were randomly selected from the general population in Switzerland. We estimated glomerular filtration rate (eGFR) using the CKD-EPI and MDRD equations. Urine was collected separately during day and night over 24-hour. We used the ASSOC program (S.A.G.E.) to estimate narrow sense heritability, including as covariates in the model: age, sex, body mass index and study center.

Results: The 1128 participants (537 men and 591 women from 273 families), had mean (sd) age of 47.4(17.5) years, body mass index of 25.0 (4.5) kg/m2 and CKD-EPI of 98.0(18.5) mL/min/1.73 m2. Heritability estimates (SE) were 46.0% (0.06), 48.0% (0.06) and 18.0% (0.06) for CKD-EPI, MDRD and 24-hour creatinine clearance ($P < 0.05$), respectively. Heritability [SE] of serum concentration was highest for calcium (37%[0.06]) and lowest for sodium (13%[0.05]). Heritabilities [SE] of 24-h urine concentrations and excretions, and of fractional excretions were highest for calcium (51%[0.06], 44%[0.06] and 51%[0.06], respectively) and lowest for potassium (11%[0.05], 10%[0.05] and 16%[0.06], respectively). All results were statistically different from zero.



Conclusions: Serum and urine levels, urinary excretions and renal handling of electrolytes, particularly calcium, are heritable in the general adult population. Identifying genetic variants involved in electrolytes homeostasis may provide useful insight into the pathophysiological mechanisms involved in common chronic diseases such as kidney diseases, hypertension and diabetes.

ORAL SESSION

ORAL SESSION 5D
LIFESTYLE CHANGES AND LIPIDS

5D.01 DECREASE IN EXCESS SALT CONSUMPTION FOR HYPERTENSIVE SUBJECTS LIVING IN THE PARIS AREA

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Objective: Since 2005, France has implemented a salt reduction campaign; however, there are no data on salt intake in hypertensive subjects as assessed by 24-hour urinary sodium.

Design and method: We performed a cross-sectional study, involving 1635 hypertensive subjects followed-up in a Hypertension specialist center in Paris. Dietary salt intake was measured by 24-hour urinary sodium excretion for 494 subjects in 2011, for 483 subjects in 2012, for 394 subjects in 2013 and for 264 subjects in 2014. An excessive salt intake was defined as Na24 h > 200 mmol (Salt > 12 g/d), a recommended salt intake was defined as Na24h < 100 mmol (Salt < 6 g/d).

Results: The mean salt intake was 8.4 g/d for the total population. A higher salt intake was noted in men vs. women (9.2 vs.7.7, p < .0001) and in obese vs. lean (9.0 vs.7.6, p < .0001). Twenty-nine percent had a recommended salt intake and 18 % an excessive salt intake. Between 2011 and 2014, salt intake has had a stepwise decrease for women (8.2 to 7.0, p < .001) and no change for men except in 2014 (9.3 then 8.8). On the same period, the percentage of subjects with an excessive salt intake decreased from 20% to 16%.

Conclusions: This study demonstrates that gender and obesity are two major determinants for salt intake in hypertensive subjects living in Paris area. The reason for the stepwise decrease in salt intake which is observed in women is possibly in relationship with the salt reduction campaign implemented in France on the period.

5D.02 WHY DOES WAKAYAMA PREFECTURE HAVE THE HIGHEST RATES OF HYPERTENSION IN JAPAN? CONSIDERATION ON EXERCISE INCORPORATED INTO EVERYDAY LIFE

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Objective: In Japan, there are 47 prefectures with differences in topography, industrial structure, population distribution and hypertension rate as well. The authors' home prefecture of Wakayama has the highest incidence of hypertension in the nation at 25.0%. This shows 7.6 point spread compared with the prefecture with the lowest rate at 17.4%.
The aim of our study is to search for the reasons of high rate of hypertension in Wakayama, and to consider effective prevention of hypertension in Wakayama as well as in Japan.

Design and method: Correlation analysis was performed using hypertension rate for each prefecture versus the variables of: 1. salt intake, 2. vegetable intake, 3. alcohol habits, 4. smoking habits, and 5. walking paces per day (walking), using 5% significance level. To find the social causes that impact walking, correlation analysis was performed with the variables of: 1. number of train stations, 2. vehicle ownership rate, 3. light-vehicle ownership rate, and 4. slope of habitable areas (index of steepness), versus walking, as well as hypertension rate. Lastly, with hypertension rate as the dependent variable, all aforementioned variables, adding the rate of health examination and the number of hospitals, multiple regression analysis was performed.

Results: There was a significant negative correlation between hypertension rate and walking (r = -0.440, p = 0.004). Walking was positively correlated with number of train stations (0.381, 0.008) and negatively with vehicle ownership rate (-0.424, 0.003) as well as light-vehicle ownership rate (-0.616, 0.000). Hypertension rate was most strongly affected by walking and slope. There were no significant correlations for the salt, vegetable, alcohol, smoking, rate of health examination, or number of hospitals. R2 coefficient was 0.442.

Conclusions: It is suggested that high incidence of hypertension in Wakayama may be due to less walking habits. In the prefectures with larger mountainous areas where transportation rely on vehicle rather than train, people walked less. Use of light-vehicle particularly reduced walking. It is suggested that the daily habits shaped by the characteristics of living environments such as topography and transportation infrastructure could affect the habitants' health.

5D.03 HIGH SALT INTAKE IS INDEPENDENTLY ASSOCIATED WITH A HIGHER RISK OF CARDIOVASCULAR EVENTS. A 12 YEARS EVALUATION OF A HYPERTENSIVE COHORT

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Objective: It is still controversial whether high salt intake is associated with cardiovascular events (CE) and particularly how far this relation is independent of blood pressure (BP) rise. Since Portugal exhibits higher salt consumption and higher mortality by stroke than other European countries it may be a propitious location for a study with this aim.

Design and method: We evaluated a population of 1084 adult hypertensive patients with no previous CE ageing 53 + 16, 59% female that has been followed in the last 12 years in a hospital hypertension reference consultation. Besides basic clinic evaluation, 823 patients underwent 24-h ambulatory BP and 608 had one or two valid (by urinary creatinine) 24-h urinary sodium excretion (UNa+) measurements within the first 3 months after admission.

Results: During the follow-up CE occurred in 122 patients (80 strokes, 36 coronary events, 6 others). UNa+ data was determined in 101 of 122 with CE and in 507 of 962 patients without CE. At baseline, comparing to patients without CE, those with CE were (p < 0.01) older (50 + 13 v 59 + 15 yrs), had higher 24 h systolic BP (134 + 16 v 142 + 21), nighttime SBP (123 + 19 v 132 + 21 mm Hg), UNa + (198 + 71 v 260 + 98 mmol/24 h) but no different was found on body mass index and metabolic parameters. Using a cox hazard model, after adjustment for risk factors and office BP, only age (OR = 1.032, 95%CI [1.019–1.046], night-time systolic BP (SBP) (OR = 1.025, 95%CI [1.014–1.036] and UNa + (OR = 1.009, 95%CI [1.006–1.012] significantly (all P < 0.001) predicted any CE. Also UNa + values above the median (190 mmol/24 h) independently predicted CE (P < 0.000, OR = 4.539, 95%CI [2.235–9.218]. No difference on these points was observed between gender.

Conclusions: We conclude that in a cohort of hypertensive patients beyond the influence of nighttime systolic BP the high salt intake independently predicts the occurrence of cardiovascular events.

5D.04 NON PHARMACEUTICAL STRESS MANAGEMENT AND LIFESTYLE CHANGE PROGRAMME (HEAL STRESS STUDY) FOR BLOOD PRESSURE CONTROL AND PSYCHOSOCIAL WELLBEING IN 553 PATIENTS IN ATTICA, GREECE

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Objective: Cardiovascular disease is the principal cause of death worldwide. Although the dose-response relationship between stress and hypertension is well established, there is a paucity of non-pharmaceutical intervention programs. The purpose of this study was to investigate the effectiveness of a stress management and lifestyle change program on blood pressure (BP) control and psychosocial wellbeing.

Design and method: This was a quasi-experimental design with a waitlist control group in Attica, Greece, which was funded from EPANAD 2007–2013 (N = 553, 50% women and mean age 52.4 ± 8.46 years). The study comprised of an 8-week stress management and lifestyle change program including weekly sessions of stress management, dietary counseling, physical exercise and psychoeducation. Pre- and post- intervention BP measurements and psychosocial wellbeing factors were assessed.

Results: Post-intervention there was a statistically significant reduction in systolic BP levels (mean: 126.05 vs 129.37, $p < 0.001$, intervention (IG) and control (CG) group, respectively). A 35.7% of the IG receded BP category vs. 17.5% of the CG ($p < 0.001$). After controlling for gender, age, educational level and BP cutoffs, we found significant improvements in stress, anxiety, self-esteem, spirituality, body weight, hours of sleep and in the subscales of the Healthy Lifestyle and Personal Control Questionnaire. Concerning the sub-categories of chance and powerful others in the health locus of control scale, improvements were recorded for the individuals of tertiary education.

Conclusions: This non-pharmaceutical stress management and lifestyle change program resulted in significant benefits for regulation of BP, as well as for body weight, lifestyle and the psychosocial wellbeing of the participants. Future non-pharmaceutical programs are strongly encouraged both for the clinical and the community settings.

5D.05 VASCULAR EFFECTS OF A REGULAR AEROBIC EXERCISE PROGRAMME IN YOUNG HEALTHY ADULTS

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Objective: The aim of this study was to evaluate the vascular benefits of an aerobic exercise program, particularly over the endothelial function and the central arterial hemodynamics in healthy young individuals.

Design and method: A randomized controled study was conducted involving 60 healthy and young sedentary subjects, randomized into two groups: control group (CG, n = 30) and intervention group (IG, n = 30). The IG completed a plan of aerobic exercise, which consisted of a daily 45 minute brisk walk (weekly - 5 days) for a month. All the individuals were submitted to two clinical evaluations, basal and after one month, in which their weight, height, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), flow-mediated dilation (FMD), Augmentation Index(AIX), aortic pulse wave velocity (PWV) and pulse wave analysis over the carotid artery (PWA) were assessed.

Results: CG and IG were homogeneous from the point of view of fundamental demographic characteristics. After intervention, no significant changes in BMI and brachial SBP in CG were found, however these variables have been improved in the IG. Central systolic blood pressure significantly decreased in the GI (108.13 ± 6.87 to 104.07 ± 5.30mmHg, $p = 0.043$). No significant variations of central PP were found in both groups ($p = 0.196$ for CG and $p = 0.459$ for IG), although the IG exhibited a trend towards a PP reduction after the intervention. The AiX improved significantly after the exercise period in IG ($p = 0.040$), but not in the CG. Aortic PWV did not change significantly over time in both groups. As for the FDM, a significant increase was depicted in the IG after the intervention (7.40 ± 3.91% at baseline and 11.47 ± 3.51% post-intervention, $p = 0.03$), but no significant changes were seen in the CG (8.87 ± 4.63% at baseline and 8.42 ± 5.65% after intervention, $p = 0.536$).

Conclusions: The practice of regular moderate-intensity aerobic exercise, for one month, improves vascular function in young healthy individuals.

5D.06 EFFECTS OF SODIUM AND POTASSIUM SUPPLEMENTATION ON ENDOTHELIAL FUNCTION AND INFLAMMATION IN UNTREATED (PRE)HYPERTENSIVES: A FULLY CONTROLLED DIETARY INTERVENTION STUDY

L. Gijsbers[1,2], J.I. Dower[1,2], C.G. Schalkwijk[1,3], Y.H.A.M. Kusters[1,3], S.J.L. Bakker[1,4], P.C.H. Hollman[1,2], J.M. Geleijnse[1,2]. *[1] Top Institute Food and Nutrition, Wageningen, NETHERLANDS, [2] Wageningen University, Division of Human Nutrition, Wageningen, NETHERLANDS, [3] Maastricht University Medical Centre, Department of Internal Medicine, Maastricht, NETHERLANDS, [4] University Medical Center Groningen, Department of Internal Medicine, Groningen, NETHERLANDS*

Objective: High sodium and low potassium have been associated with detrimental effects on blood pressure. However, the role of these minerals in endothelial dysfunction and low-grade inflammation, which may predispose to cardiovascular disease, has not yet been established. We performed a randomized placebo-controlled crossover study to examine the effects of sodium and potassium supplementation on endothelial function and inflammation in untreated (pre)hypertensive adults.

Design and method: During the study, subjects were on a fully controlled diet that contained on average 2.4 g of sodium and 2.3 g of potassium per day for a 2500 kcal intake. After one-week run-in, subjects were randomized to ingest capsules with supplemental sodium (3 g/d), supplemental potassium (3 g/d), or placebo, for four weeks each, in random order. After each intervention period, brachial artery flow-mediated dilation, and circulating biomarkers of endothelial function (e.g. nitric oxide, endothelin-1, cellular adhesion molecules) and inflammation (e.g. tumor necrosis factor-α, C-reactive protein, interleukins) were measured.

Results: Of 37 randomized subjects, 36 completed the study. Subjects had a mean pre-treatment blood pressure of 145/81 mmHg. Sodium supplementation increased serum endothelin-1 by 0.24 pg/ml (95% CI: 0.03, 0.45), but had no effect on other endothelial or inflammatory biomarkers, or flow-mediated dilation. Potassium supplementation reduced interleukin-8 levels by 0.28 pg/ml (95% CI: 0.03, 0.53), without affecting other circulating biomarkers. Flow-mediated dilation was 1.16% (95% CI: 0.37, 1.96) higher after potassium supplementation than after placebo, with 83% of the subjects showing an improvement (Figure).

Conclusions: Sodium and potassium supplementation had little impact on circulating endothelial and inflammatory biomarkers, and only for potassium an effect on flow-mediated dilation was observed. This study suggests different actions for sodium and potassium in the pathophysiological processes leading to cardiovascular disease.

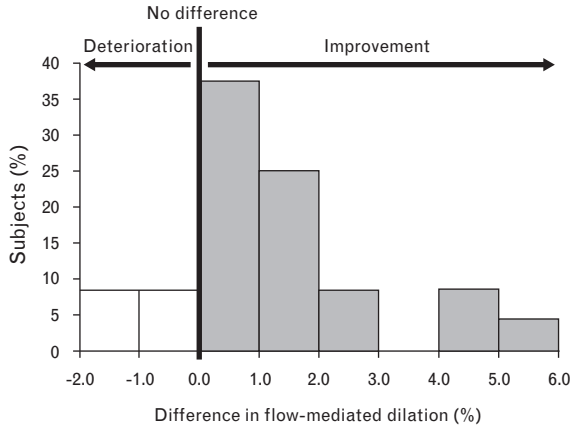

Figure. Effects of four-week potassium supplementation on flow-mediated dilation in untreated (pre) hypertensive adult, compared to placebo

5D.07 THE IMPACT OF FLAVONOL-RICH DARK CHOCOLATE ON BLOOD PRESSURE AND VASCULAR FUNCTION IN HEALTHY SUBJECTS

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Objective: Flavanoids may have a beneficial effect on blood pressure (BP) and endothelial function. There is however, limited data on this effect during a longer period (8 weeks) and no data on the effect on EPC (endothelial progenitor cells) in healthy subjects.

Design and method: Healthy, non-smoking, male and female volunteers aged 35–65 year with no history of diabetes or cardiovascular disease and with normal or mild hypertensive blood pressure (<160/100 mmHg) were included. Subjects could not take any medication affecting blood pressure or endothelial function. The subjects were randomised (double-blind) in two groups: Group 1(n = 25): daily consuming 20 gram of high-flavanol dark chocolate (High-DC). Group 2 (n = 26): daily consuming 20 gram of low-flavanol dark chocolate (Low-DC). At week 0,4,6,7 and 8 blood pressure was assessed in all subjects, and endothelial function (FMD, flow mediated dilation) in a subgroup. A blood sample was taken in each subject at week 0 and 8 for measuring glucose, lipids and EPC.

Results: Baseline characteristics were comparable between both groups. There was a decrease in systolic and diastolic blood pressure over time in both groups, however at 8 weeks there was no statistically significant difference between groups (delta SBP -2.17 + /-8.53 mmHg in gr 1 versus -4.06 + /-8.05 mmHg in gr 2, $p = 0.4$; delta DBP -3.97 + /-7.1 mmHg in gr 1 versus -4.67 + /-5.99 mmHg in gr 2, $p = 0.7$).
FMD was performed in 9 subjects from each group, no significant difference was noted between both groups over time (delta FMD gr 1: -3.50 + /- 6.00 % versus gr 2: + 0.12 + /- 2.51 %, $p = 0.06$). EPC values did not differ between groups at baseline (T0) and at the end of the study (T8) (ISHAGE count (T8-T0): gr1: 3.23 (-68.01 - 41.71) versus gr 2: -9.23 (-57.59 - 17.28), $p = 0.4$). Glucose and lipids were comparable between both groups at baseline and at the end of the study ($p = ns$).

Conclusions: In this study, no beneficial effect was noticed in favour of the consumption of flavanol-rich dark chocolate during 8 weeks on blood pressure or vascular function, in healthy subjects.

ORAL SESSION

ORAL SESSION 6A
BLOOD PRESSURE MEASUREMENT

6A.01 TREATMENT-INDUCED CHANGES IN AMBULATORY ARTERIAL STIFFNESS INDEX: ONE-YEAR PROSPECTIVE STUDY AND META-ANALYSIS

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Objective: The ambulatory arterial stiffness index (AASI) has been introduced as an index of arterial function, predicting cardiovascular events. However, treatment-induced changes in AASI are rather equivocal. This study aimed to: (i) evaluate AASI changes in untreated subjects administered antihypertensive drug treatment for 1 year, and (ii) perform a meta-analysis of studies reporting on treatment-induced change in AASI.

Design and method: Untreated hypertensive individuals were subjected to 1-year antihypertensive treatment based on renin-angiotensin system blocker. Ambulatory blood pressure (ABP) monitoring and arterial stiffness assessment (AASI, pulse wave velocity) were performed at baseline and at the end of the follow up. A systematic review and meta-analysis of relevant studies was also performed.

Results: A total of 104 subjects (mean age 51.4 ± 10.3 years, 62% males, mean follow up: 13.6 ± 2.4 months) were analysed. Despite significant reductions in 24-hour systolic/diastolic ABP, pulse pressure, and pulse wave velocity (mean decline 15.9 ± 12/10.4 ± 7.6 mmHg, 5.4 ± 6.8 mmHg, 0.7 ± 1.9 m/s respectively, all $p < 0.05$), there was no significant change in AASI values (0.01 ± 0.17, p = NS). The treatment-induced change in AASI was correlated with baseline AASI (r = -0.61), baseline 24-hour pulse pressure (-0.26), treatment-induced change in 24-hour pulse pressure (0.26) and systolic/diastolic nocturnal dipping (-0.25/-0.40 respectively). Meta-analysis of 8 trials (n = 990) revealed a marginal decrease in AASI with antihypertensive treatment (pooled change: -0.018, 95% CI: -0.033,-0.003). Additional analysis restricted to studies using only renin-angiotensin system blockers (n = 755, 76% of total) showed similar results (pooled change -0.028, 95% CI -0.048, -0.007).

Conclusions: Although AASI has been shown to independently predict cardiovascular events, its response to antihypertensive treatment is only marginal and clinically uncertain, which may render its use as a therapeutic target in clinical practice questionable.

6A.02 WHITE-COAT HYPERTENSION AS PREDICTOR OF LONG-TERM NORMOTENSION IN SUBJECTS SCREENED FOR STAGE 1 HYPERTENSION

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Objective: For how long subjects with stage 1 hypertension should be followed with lifestyle measures before deciding whether antihypertensive treatment should be started is not well known. The aim of this study was to evaluate whether and to what extent a normal ambulatory (A) blood pressure (BP) can predict long-term normotension.

Design and method: This investigation was conducted in 1114 subjects aged 33 ± 9 years initially screened for stage 1 hypertension, who remained untreated for at least 3 months and had complete follow-up data for at least two years (range 2–20 years). Criteria for starting antihypertensive drug treatment were based on current available guidelines. At baseline, after 3 months, and at study end 24 h ABP monitoring was performed.

Results: After a mean follow-up of 11 ± 6 years, BP fell to within normal values in 214 (19%) participants (Normotensives); the BP decline was -7 ± 11/-5 ± 7 mmHg after 1 year and was -14 ± 11/-8 ± 7 mmHg at follow-up end. White-coat hypertension was present at baseline in 35% of Normotensives and in 19% of the participants who met the criteria for treatment (Hypertensives)($p = 0.000001$ versus Normotensives). After 3 months, the rate of participants with normal ABP was 42% in Normotensives and 22% in Hypertensives ($p < 0.000001$). The follow-up decline of heart rate was 6 ± 10 bpm and 2 ± 11 bpm, respectively, in the two groups ($p = 0.000006$). ABP after 11 years remained virtually unchanged in Normotensives (-1 ± 9/1 ± 8 mmHg) and increased by 4 ± 12/3 ± 9 mmHg in Hypertensives ($p < 0.000001/0.002$). In a multivariable Cox regression, a normal ABP at baseline (Hazard ratio = 0.76, 95%CI = 0.64–0.90) or after 3 months (HR = 0.69, 0.58–0.81) was a significant predictor of future normotension. However, an office BP decline > 10 mmHg after 1 year was an additional potent predictor of future normotension (HR = 0.58, 0.47–0.72). Cardiovascular events occurred in 0.5% of the Normotensives and 5.5% of the Hypertensives ($p = 0.001$).

Conclusions: In low risk young-to-middle-age stage 1 hypertensives a long period of observation should be allowed before deciding whether to start drug treatment. A normal ABP, especially after 3 months, but also the office BP decline after 1 year are strong independent predictors of this favourable outcome.

6A.03 THE RELATIONSHIP BETWEEN INTER-ARM SYSTOLIC BLOOD PRESSURE AND CARDIOVASCULAR RISK FACTORS

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Objective: To analyze the relationship between the inter arm blood pressure difference (IASBPD) and other cardiovascular risk factors. To identify what factors are associated with this difference in a general population.

Design and method: The study subjects were 1426 individuals. The BP was measured simultaneously in both arms by VP1000 vascular profiler (Omron Colin, Japan). The inter-arm BP difference was expressed as the absolute difference (|R - L|). The various risk factors, ba-PWV, carotid IMT and plaque were compared between IASBPD more than 10mmHg group and IASBPD less than 10mmHg group. The relationship between IASBPD more than 10mmHg and various cardiovascular risk factors were analyzed by multivariate logistic analysis.

Results: Left upper limb systolic blood pressure was higher than the right upper limb, while right upper limb diastolic pressure was higher than the left upper limb. The prevalence of hypertension was higher in IASBPD increasing group than normal group (40.5% vs 22.6%, $p < 0.05$). The weight, BMI, systolic and diastolic blood pressure were also higher in IASBPD increasing group($p < 0.05$). The mean IMT and max IMT in any segment carotid artery except for mean IMT of internal carotid artery were thicker in IASBPD increasing group than normal group($p < 0.05$). Ba-PWV was higher, while ABI was lower in IASBPD increasing group(1.04 ± 0.16 vs 1.09 ± 0.16, $p < 0.05$). By multivariate logistic regression analysis, after adjusting for age, sex, BMI, hypertension, diabetes, smoking, SBP, TC, TG, LDL-C,HDL-C,ABI, PWV, mean IMT and plaque, IASBPD more than 10mmHg was positive associated with BMI(OR 1.081 95%CI: 1.030,1.134,p = 0.002), SBP (OR 1.032 95%CI: 1.023,1.041,p < 0.001), and negative associated with ABI(OR 0.051 95%CI: 0.009,0.273,p = 0.001).

Conclusions: The increasing IASBPD was associated with systolic blood pressure, BMI and ABI independently, which may partly explain the mechanism that increasing IASBPD is associated with cardiovascular disease.

6A.04 DEFINING SPURIOUS SYSTOLIC HYPERTENSION IN YOUNG HYPERTENSIVE MEN USING CENTRAL BLOOD PRESSURE REFERENCE VALUES

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Objective: Definition of spurious systolic hypertension in youth has been unclear due to absence reference values for central BP and has been mainly empirically based on difference between brachial and aortic systolic BP. We used the recently published data of the multinational Reference Values for Arterial

Measurements Collaboration (Eur Heart J 2014;35(44):3122–33 to analyze level of central systolic BP in hypertensive men 18–27 years old.

Design and method: The analysis included 124 men (age 21 + 0,14 years, office BP 147 ± 15/88 ± 13 mmHg)) diagnosed with arterial hypertension by the repeated office BP measurements and ambulatory BP monitoring. Among those 73 had isolated systolic hypertension (ISH), 51 - systolo-diastolic hypertension (SDH). For subjects < 20 years normal SBP was considered normal if it was below 50th percentile (<109 mmHg), high normal - between 50th and 75th percentile (109–116 mmHg), mildly elevated - between 75th and 90th percentiles (117–127 mmHg), definitely elevated > 90th percentile (> 127 mm Hg). For subjects 20–27 years old corresponding thresholds were < 110, 110–119, 120–130 and > 130 mmHg.

Results: Normal central SBP was found in 12 (9,7%), and was observed in 7 (9,6%) in those with ISH and in 5 (9,8%) in those with SDH. High normal central BP was observed in 46 (37,1%), and was more prevalent men with ISH (n = 36, 49,3%) than in SDH (n = 10, 19,6%) (p = 0,001). Mildly elevated was revealed in 44 (35,5%) in total population, in 24 (32,9%) with ISH and in 20 (39,1%) with SDH. Central SBP was definitely elevated in 22 (17,7%), in 6 (8,2%) patients with ISH and in 16 (31,4%) with SDH (p = 0,001).

Conclusions: The results obtained suggest that measurement of central SBP reveals definitely elevated values in 37,7% young hypertensive men. The odds ratio to have elevated central SBP is 5,1 in subjects with SDH. The findings confirm potential usefulness of central BP measurement in young men with arterial hypertension

6A.05 THE PROGNOSTIC VALUE OF AMBULATORY ARTERIAL STIFFNESS INDEX AS A PREDICTOR OF CARDIOVASCULAR EVENTS IN RESISTANT HYPERTENSIVE PATIENTS?

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Objective: The prognostic value of ambulatory arterial stiffness index (AASI) is not well established in resistant hypertension as much as in general population. Our aim was to evaluate, on resistant hypertensive patients (RH, the prognostic significance of AASI as an independent predictor of cardiovascular events (CV).

Design and method: Retrospective observational analysis of RH outpatients defined by abnormal 24 h ambulatory blood pressure monitoring (24 h ABPM) under 3 or more anti hypertensive drugs. The follow-up was defined since the first appointment until the 31st December 2014 or until a CV event (acute coronary syndrome, stroke, heart failure or arrhythmia).

Results: Included 217 patients, 119 male and 98 female, mean age 56,4 +/- 14,6 years. During a mean follow-up of 6,0 +/-3,1 years, 53 patients (24,4%) had CV (5,1% acute coronary syndromes, 10,1% strokes and 9,2% acute heart failure and arrhythmias). There were 24 deaths (50% cardiovascular and 50% non-cardiovascular). When analysed those with CV events versus without, those with events showed more frequently reverted dipper (22 % vs 12%) and extreme dipper patterns (10% vs 4,4%) X2 8,242 p < 0.05)) and worse AASI (0.4918 vs 0,4046 p < 0,02). In analysis of Kaplan Meier survival curves free of events those who were above median (cut off 0,41), of AASI had worse prognosis compared to those who were below it (Log Rank 8,347, p= 0.004) for CV event and (Log Rank 9,562, p = 0,002) for global mortality. In a Cox hazard model adjusted for confounding factors ((sex, age, body mass index (BMI) and systolic blood pressure (SBP)) AASI was an independent predictor for CV event (HR 8,34; 95%CI 1,76–39,57; p 0,008) even when analysed in the same model with SBP night fall, 24 h PP, and 24 h SBP (HR 11,20; 95% CI 2,16 -58,15; p 0,004) and also for global mortality (HR 42,64; 95%CI 3,72–488,58; p 0,003).

Conclusions: In this population AASI was the ABPM marker with the strongest predictor value for CV. Perhaps in resistant hypertension AASI (traducing higher arterial stiffness) is a more potent CV predictor than in non resistant essential hypertension.

6A.06 REPRODUCIBILITY OF NOCTURNAL BLOOD PRESSURE IN SLEEP APNEA SYNDROME

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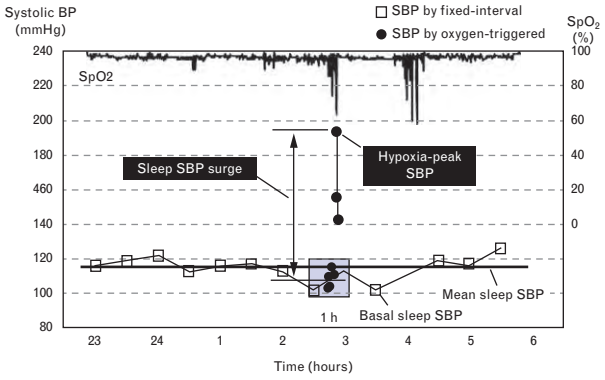
Objective: Obstructive sleep apnea (OSA) causes blood pressure (BP) surge while OSA episode occurs. It could lead to increase of not only nocturnal BP level but also nocturnal BP variability, both of which increase the cardiovascular risk. Therefore, the assessment of BP surge could be valuable for the risk stratification and predicting cardiovascular events. We recently developed a trigger sleep BP monitoring (TNP) method that initiates BP measurement when oxygen desaturation falls below a variable threshold, and demonstrated that it can detect BP surge during apnea episodes. In this study, we evaluated the reproducibility of nocturnal BP parameters measured by TNP.

Design and method: 149 outpatients in whom polysomnography (PSG) was planned for the diagnosis of OSA (mean age 59.5 ± 13.7, 86.6% men) were subjected to TNP with PSG in the hospital for 2 consecutive days. In the same way as our previous study (J Clin Hypertens. 2014;16:459–466), we defined the hypoxia-peak SBP as the maximum SBP measured by an oxygen-triggered function, sleep SBP surge as the difference between hypoxia-peak SBP and the average of the SBPs measured by a fixed-interval function (30 min. intervals) within 30 minutes before and after the hypoxia-peak SBP, mean sleep SBP as the average of the sleep BPs measured only by the fixed-interval function, and minimum (basal) sleep SBP as the lowest SBP among all the sleep BPs measured by both oxygen-triggered and fixed-interval functions. Reproducibility was evaluated using the Repeatability Coefficient (RC), and the Intraclass Correlation Coefficient (ICC) for agreement.

Results: Mean SBP and mean DBP measured by both fixed-interval function and oxygen-triggered function, and hypoxia-peak SBP measured by oxygen-triggered function corresponded well in each day (ICC ranged 0.69 – 0.88). On the other hand, the reproducibility of sleep SBP surge (ICC 0.33) and minimum (basal) sleep SBP (ICC 0.39) was low.

Conclusions: In conclusion, in the TNP parameters, the reproducibility of the hypoxia-peak SBP was good and comparable to mean sleep SBP measured by ordinary fixed interval BP monitoring.



6A.07 AORTIC SYSTOLIC PRESSURE VALUES BUT NOT INDICES DERIVED FROM WAVEFORM FEATURES ARE CONSISTENT BETWEEN BRACHIAL CUFF-BASED DEVICES USED FOR ESTIMATION OF CENTRAL AORTIC PRESSURE

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Objective: For ease of measurement, and the utility of ambulatory central aortic blood pressure measurement, there has been a move toward brachial cuff-based devices for non-invasive computation of central aortic blood pressure quantities based on waveform features. However, waveforms detected by volumetric cuff displacement techniques are inherently more damped than signals obtained by applanation tonometry, potentially impacting on parameters reliant on higher frequency components of the pulse waveform.

Design and method: In 45 subjects (age 46 ± 17 years, 30 male), in-clinic, seated measurements taken in triplicate using three brachial cuff-based devices (BPLab, [Petr Telgin]; Oscar2, [SunTech/AtCor Medical]; SphygmoCor XCEL, [AtCor Medical]) were compared using repeated measures ANOVA and Bland-Altman statistics against radial tonometric assessment of central aortic pressure (SphygmoCor CvMS, [AtCor Medical]). Results are expressed as means ± standard error.

Results: There was good agreement between devices for aortic systolic pressure (aSP) and aortic diastolic pressure (aDP). There was great variability in aortic augmentation index (aAIx), ejection duration (ED) and subendocardial viability ratio (SEVR, Table). Cuff-based device regression slopes against the tonometer-based method varied markedly for aSP (BPLab, 0.76; Oscar2, 0.92; XCEL, 0.77), aAIx (BPLab, 0.32; Oscar2, 0.74; XCEL, 0.88), ED (BPLab, 1.07; Oscar2 does not report; XCEL, 0.83), and SEVR (BPLab, 0.16; Oscar2 does not report; XCEL, 0.81).

	aSP (mmHg)	aDP (mmHg)	aAIx (%)	ED (ms)	SEVR (%)
tonometer	112±2	79±1	13±2	285±3	174±5
BPLab	117±2	79±2	3±2	320±7	134±5
XCEL	113±2	80±1	18±2	296±3	157±4
Oscar2	116±2	79±1	25±2	does not report	
p (ANOVA)	0.19	0.092	0.003	<0.001	<0.001

Conclusions: Parameters relying on the low frequency components of the peripheral waveform have better agreement between cuff-based devices than parameters that rely on higher frequency waveform components. Further research is required for quantitative assessment of filtering methods utilised in cuff-based devices, as well as the cuff-based approach itself for use in measuring AIx, ED and SEVR.

6A.08 HIGH FREQUENCY OF MASKED HYPERTENSION AND ASSOCIATED ARTERIAL STIFFNESS IN AFRICANS

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Objective: While South Africa has one of the highest rates of hypertension globally, data on masked and white coat hypertension in the region is scant. This study sought to determine the frequency of masked and white coat hypertension in low income South African adults and to evaluate cardiovascular risk through measures of arterial stiffness.

Design and method: We included 81 low income adults (50% men, 96% black, 4% coloured) aged 19–63 years, and measured clinic blood pressure four times (twice on each upper arm) with the Omron M10-IT automated device; also 24 hour ambulatory blood pressure with pulse wave analysis (Mobil-O-Graph ABPM), anthropometry and HIV status. We collected sociodemographic, stress and depression data by questionnaires.

Results: When viewing hypertension criteria for both clinic and ambulatory BP, we found that 15% complied to all criteria, classified as sustained hypertensives; 3% had white coat hypertension; and 48% had masked hypertension. The sustained hypertension group had a higher mean body mass index and waist circumference than both the masked hypertension and normotensive groups ($p = 0.004$ and $p = 0.007$). Both the sustained hypertensives and masked hypertensives presented elevated 24-hour, daytime and nighttime pulse wave velocity compared to normotensives (all $p < 0.001$), but we found no differences between the sustained and masked hypertensives for pulse wave velocity and augmentation index. Other traditional cardiovascular risk factors including smoking, alcohol consumption, physical activity levels, occupation, stress or depression were also comparable between sustained and masked hypertensives.

Conclusions: Almost half of African adults measured had masked hypertension and individuals presented comparable estimates for arterial stiffness to Africans with sustained hypertension. Since masked hypertension cannot be detected by clinic blood pressure measurement alone, these results may have far-reaching implications in hypertension detection, treatment and control strategies, and imply underestimations of country-specific hypertension prevalence rates. Further studies are required to determine the most cost effective method to detect undiagnosed hypertension cases in the African region.

6A.09 DIAGNOSIS OF SODIUM SENSITIVITY FROM MEAN ARTERIAL PRESSURE MEASURED AT THE ARM OR AT THE FINGER

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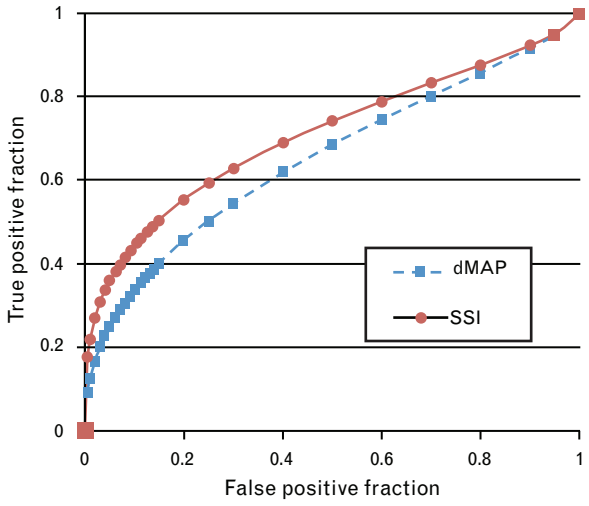
Objective: The severity of sodium sensitivity is quantified or 1) by the difference in mean arterial pressure (MAP) between high- and low-sodium diets (δMAP), or 2) by the sodium-sensitivity index (SSI), i.e. ratio between δMAP and the difference in urinary sodium excretion rates at the end of the two diets. MAP is usually measured with an arm cuff but the use of finger blood pressure monitors is rapidly increasing. Thus, our aim is to evaluate whether finger measures of MAP can be reliably used for assessing sodium sensitivity.

Design and method: We enrolled 68 normotensive volunteers who underwent high- and low-sodium diets of 5 days duration. SSI and δMAP were derived from MAP measures taken both at the arm (gold standard) and at the finger (Portapres model-2). First, volunteers were classified as sodium sensitive (SS) or resistant (SR) if δMAP measured at the arm was or not greater than 3 mmHg, and the receiver operator characteristic (ROC) analysis was performed for the SS/SR classification based on finger δMAP. Then volunteers were classified as SS or SR if SSI from arm MAP was or not greater than 20 mmHg/(mol/day), and ROC analysis was performed for the SS/SR classification based on finger SSI.

Results: Fourteen individuals were classified as SS on the basis of arm δMAP greater than 3 mmHg. Similarly, 14 individuals were also classified as SS on the basis of arm SSI greater than 20 mmHg/(mol/day). Classifications based on finger measures were substantially different. In particular, finger measures of δMAP performed poorly for the SS/SR classification: the area under the ROC curve (AUC) was 0.65 only; the best threshold for classification was finger δMAP = 2 mmHg, corresponding to sensitivity = 57%, specificity = 67%. Slightly better performances were obtained for finger SSI (see figure), with AUC = 0.71. The best threshold for classification was finger SSI = 23 mmHg/(mol/day), corresponding to sensitivity = 61%, specificity = 72%.



Conclusions: The assessment of sodium sensitivity depends strongly on the MAP measurement site, with important discrepancies between brachial and finger measures.

ORAL SESSION

ORAL SESSION 6B
EXPERIMENTAL HYPERTENSION

6B.01 EFFECT OF RENAL DENERVATION ON BLOOD PRESSURE AND MICRORNA 181A IN HYPERTENSIVE SCHLAGER MICE

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Objective: Hypertensive Schlager mice (BPH) are hypertensive due to an exaggerated contribution of the sympathetic nervous system (SNS) and renin angiotensin system (RAS). The latter was associated with reduced expression of the renin regulatory micro RNA-181a. We therefore determined the effect of bilateral renal denervation (Rx) on blood pressure in BPH compared to normotensive BPN.

Design and method: Blood pressure was measured by in 16 week old conscious mice by radiotelemetry and Rx was performed by surgery and 10% phenol application.

Results: After 3 weeks recovery, mean 24 hour blood pressure in BPH was 110 ± 1 mmHg in BPN and 128 ± 2 mmHg in BPH. Blood pressure was 8 ± 2 mmHg lower than sham in Rx BPH mice but Rx had no effect in BPN. Following Rx, blocking the renin angiotensin system with enalapril decreased blood pressure more in BPH mice compared to sham group but had no effect in BPN. Micro RNA-181a levels in the kidney were lower and renin mRNA higher in BPH compared to BPN. The depressor response to the ganglionic blocker pentolinium (SNS contribution) was greater in BPN mice following Rx compared with the sham group but the response was unaffected by Rx in BPH. Rx reduced renal norepinephrine levels in both strains but more so in BPH. Rx normalised both miR-181a (0.72 ± 0.02 BPH vs 0.73 ± 0.03 BPN, NS) and renin mRNA (1.9 ± 0.1 BPH vs 1.61 ± 0.2 BPN, NS) in BPH/2J to levels comparable to the control strain.

Conclusions: We suggest that renal sympathetic activity is essential in maintaining hypertension in BPH mice partly by overexpression of renal renin as a result of inhibiting micro RNA-181a. Importantly we demonstrate for the first time that sympathetic activity directly regulates renin expression through inhibition of micro RNA-181a. These findings may explain the positive effectiveness of Rx in neurogenic hypertension.

6B.02 HYPOTHALAMIC AND MEDULLAR MECHANISMS FOR LONG-TERM AUTONOMIC REGULATION OF ARTERIAL BLOOD PRESSURE

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Objective: Hypertensive patients and experimental models of hypertension showed a marked sympatho-excitation. The mechanisms responsible for this sympathetic activation in arterial hypertension (AHT) are not completely elucidated.
Our working hypothesis is that the increased sympathetic activity observed in AHT is a result from an elevated sympathetic drive from the rostroventrolateral medulla (RVLM) and the paraventricular nucleus of the hypothalamus (PVN). Both areas are included in the autonomic network and have an increased neuronal activity in hypertensive conditions.

Design and method: A decrease in neuronal excitability in PVN and RVLM was promoted to modulate the central sympathetic activity in spontaneously hypertensive rats (SHR) by the over-expression of a potassium-channel induced by a lentivirus. Telemetry blood pressure (BP) values, autonomic output, baro- and chemoreceptor function and molecular signalling in hypertensive target organ were evaluated.

Results: Chronic over-expression of potassium-channels in the PVN and RVLM caused a sustained decrease in systolic (26mmHg, 39mmHg), diastolic (22mmHg, 40mmHg) and mean BP (22mmHg,40mmHg) in conscious unrestrained SHR. This BP decrease were accompanied by a decrease in sympathetic-output as revealed indirectly by a decrease in the low frequencies band of systolic BP (from 0.79 ± 0.13 to 0.42 ± 0.09mmHg2 and from 0.69 ± 0.11 to 0.42 ± 0.10mmHg2,$p < 0.05$) in PVN and RVLM, respectively, at 60 days post-microinjection.
In the PVN the baro- and chemoreceptor function were restored but no changes were observed in the RVLM. Signalling changes occurred in heart, kidney and vessels, mainly through the up-regulation of angiotensinogen and AT-2 genes in the kidney and down-regulation of AT-1 receptors in the heart.

Conclusions: These results give support to PVN and RVLM role as powerful sites to control BP in neurogenic hypertension and we expect, by identifying the role of these central areas, to provide realistic targets for therapeutic interventions.

6B.03 TETRAHYDROBIOPTERIN EFFECTS LEFT VENTRICULAR DIASTOLIC FUNCTION BY UPREGULATING PROTEIN KINASE C ε SIGNALING PATHWAY IN DESOXYCORTICOSTERONE ACETATE-SALT HYPERTENSIVE MICE

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Objective: To identify the influence of tetrahydrobiopterin (BH4) on left ventricular diastolic function and the expression of protein kinase C ε(PKCε) in desoxycorticosterone acetate (DOCA)-salt hypertensive mice.

Design and method: We used the DOCA-salt mouse model, which demonstrates mild hypertension, myocardial oxidative stress, and diastolic dysfunction. Mice were divided into DOCA group(n = 22), DOCA + BH4 group(n = 22), SHAM group(n = 20) and SHAM + BH4 group(n = 20). Arterial pressure, echocardiography and hemodynamic method were used to investigate the DOCA model establishment, cardiac structure and function. Cyclic guanosine monophosphate(cGMP), malonaldehydeby, BH4 and PKC ε were detected by enzyme linked immunosorbent assay(ELASA), western-blot or high-performance liquid chromatography(HPLC) in cardiac tissues of all groups.

Results: Compared to Sham group, systolic blood pressure (SBP) and diastolic blood pressure (DBP) in DOCA group were increased ($P < 0.05$), but between DOCA + BH4 group and DOCA group, there was no significant statistical differences in blood pressure ($P > 0.05$). The ratio of left-ventricular early diastolic filling velocity to early diastolic mitral annular velocity (E/E'), end-diastolic pressure-volume relation (EDPVR) and Tau index were increased in DOCA group when compared with Sham group [(14.27 ± 0.79) vs (10.6 ± 0.52) ms, (38.49 ± 3.91) vs (25.77 ± 5.21), (0.22 ± 0.05) vs (0.15 ± 0.02) mm, all $P < 0.05$]. After BH4 treatment in DOCA mice, EDPVR and Tau index were reduced [(0.17 ± 0.04) vs (0.22 ± 0.05), (12.05 ± 1.35) vs (14.27 ± 0.79), $P < 0.05$]. Superoxide dismutase (SOD) and nitric oxide (NO) in DOCA group were reduced when compared with Sham group. After BH4 treatment in DOCA mice, SOD and NO were increased. Compared to Sham group, the protein level of PKC ε in DOCA group was decreased ($P < 0.05$), while it was increased in DOCA + BH4 group as compared with DOCA group ($P < 0.05$).

Conclusions: BH4 had little effect on BP, but it could improve left ventricular diastolic dysfunction in hypertensive mice, which was related to lowering the levels of oxidative stress, increasing amounts of NO by upregulating PKC ε signaling pathway.

6B.04 COMPLEMENT-INHIBITED PERIVASCULAR ADIPONECTIN EXPRESSION CONTRIBUTES TO VASCULAR INJURY IN HYPERTENSIVE MICE

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Objective: Perivascular adipose tissue (PVAT) is implicated in the regulation of hypertensive vascular injury and our previous study showed that macrophage-derived complement 3 (C3) is involved. However, whether complements regulate PVAT-derived adipokines is still not clear.
We conducted a gene chip analysis of adipokines in the PVAT from deoxycorticosterone acetate (DOCA)-salt hypertensive mice and control SHAM mice. C3 knockout (C3KO) mice or complement 5a (C5a) antagonist (AntiC5a) were used to blockade complement pathway in DOCA-salt hypertensive mice. Flow cytometry, Immunoflurenrescence and Western blot were performed to identify the adipokines expression in the PVAT of DOCA-salt mice.

Design and method: We conducted a gene chip analysis of adipokines in the PVAT from deoxycorticosterone acetate (DOCA)-salt hypertensive mice and control SHAM mice. C3 knockout (C3KO) mice or complement 5a (C5a) antagonist (AntiC5a) were used to blockade complement pathway in DOCA-salt hypertensive mice. Flow cytometry, Immunoflurenrescence and Western blot were performed to identify the adipokines expression in the PVAT of DOCA-salt mice.

Results: DOCA-salt treatment resulted in a decreased expression of adiponectin (APN) in the PVAT, which plays an anti-inflammatory role in cardiovascular disease. C3KO or AntiC5a treatment rescued APN expression in the PVAT of DOCA-salt mice. In vitro, although complement did not directly inhibit APN expression in 3T3-L1 adipocytes, C5a treated macrophage-conditioned medium inhibited APN expression. In addition, C5a-induced Tumor Necrosis Factor α (TNFα) in macrophage contributed to the decrease of APN in adipocytes. TNFα siRNA transfection in C5a-treated macrophages enhanced APN expression in adipocytes. In vivo, APN knockout blocked the protective role of AntiC5a in the DOCA-salt hypertensive mice accompanied with increased macrophage infiltration and inflammatory factor expression in the PVAT of DOCA-salt mice.

Conclusions: These data suggest that the expression of PVAT-derived APN is decreased in hypertensive mice. Complement plays a role in the regulation of APN in the PVAT via macrophage-derived TNFα, which contributes to perivascular inflammation and vascular injury in the DOCA-salt hypertensive mice.

6B.05 SALT-SENSITIVITY OF ANGIOGENESIS INHIBITION-INDUCED BLOOD PRESSURE (BP) RISE: ROLE OF INTERSTITIAL SODIUM ACCUMULATION?

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Objective: Angiogenesis inhibition with the VEGF-inhibitor sunitinib, an established anti-cancer therapy, induces hypertension and proteinuria. Exposed to osmotic stress, the Mononuclear-phagocyte-system cells produces VEGF-C and exert homeostatic regulatory activity by promoting lymphatic Na+ drainage; interference with this process resulted in salt-sensitive hypertension. Therefore, we hypothesized that sunitinib via blockade of the VEGF pathway leads to Na+ accumulation in the skin and salt-sensitive hypertension.

Design and method: In male WKY rats, mean arterial pressure (MAP) was monitored telemetrically during oral treatment with sunitinib (7 mg/kg.day, n = 4–8) or vehicle (n = 4–8) after a normal salt diet (NSD: 0.5–1.0% NaCl and tap water) or a high salt diet (HSD: 8% NaCl and saline water) for 2 weeks. After 8 days of sunitinib or vehicle administration, 24-h urine was collected. After sacrificing, blood was collected for biochemical measurements and skin for Na+ concentration ([Na+]) using dry-ashing.

Results: MAP during NSD was 101 ± 0.9 mmHg. HSD increased MAP by 27 ± 3 mmHg ($P < 0.05$ vs. NSD). Sunitinib increased MAP by 16 ± 1 mmHg during NSD ($P < 0.05$ vs. NSD alone) and by 23 ± 4 mmHg during HSD ($P < 0.05$ vs. HSD alone). Although body weight, serum [Na+] and plasma [cystatin-C] did not change in response to HSD and/or sunitinib, skin [Na+] increased from 89 ± 1 (NSD) to 92 ± 3 (HSD), and 97 ± 3 mmol/L (HSD+sunitinib), respectively ($P < 0.03$ for linear trend). Plasma endothelin-1 (ET-1) increased from 0.4 ± 0.09 (NSD) to 0.8 ± 0.05 pg/mL during HSD, and remained elevated with sunitinib. Skin [Na+] correlated both with MAP ($r = 0.76$, $P < 0.01$) and plasma ET-1 ($r = 0.53$, $P < 0.05$). Compared to NSD, proteinuria and endothelinuria increased during HSD, rising further ($P < 0.05$) with sunitinib.

Conclusions: Angiogenesis inhibition-induced hypertension is salt-sensitive. The parallel increases in BP and skin [Na+], in the face of unaltered serum [Na+] and body weight, support the existence of a Na+-buffering compartment in the skin that may contribute to the salt-dependent volume and BP homeostasis during VEGF inhibition. Our data indicate that ET-1 may play a causal role in this phenomenon.

6B.06 CARDIAC AQP1 NITROSYLATION IN RESPONSE TO OSMOTIC STRESS INDUCED BY WATER RESTRICTION DURING POSTNATAL GROWTH

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Objective: Aquaporin-1 (AQP1) is expressed in the heart and it has been reported to transport nitric oxide (NO), an important regulator of cardiac function. Our aim was to study AQP1 abundance and localization, NO synthase (NOS) activity and AQP1 nitrosylation in response to osmotic stress induced by water restriction during postnatal growth.

Design and method: Male Sprague-Dawley rats aged 25 and 50 days (n = 10) were divided in: R: water restriction 3 days; C: water ad libitum 3 days. NOS activity (14C-Arginine), AQP1 protein levels (Western Blot) and localization (immunohistochemistry) and AQP1 nitrosylation (colocalization of immunofluorescence signals of AQP1 and nitrosylated cysteine by confocal microscopy) were determined in cardiac tissue. We also evaluated the effects of NO donor sodium nitroprusside (SNP) on osmotic water permeability of cardiac membrane vesicles expressing AQP1 by stopped-flow spectrometry.

Results: Water restriction induced a dehydration state in both age groups. Cardiac AQP1 was localized in the endocardium and endothelium in both age groups in control animals. Water restriction did not change AQP1 abundance or localization in the 25-day-old R group; however, in the 50-day-old group, AQP1 protein levels were increased and immunohistochemistry showed its localization on cardiomyocyte plasma membrane after water restriction. Cardiac NOS activity was increased in the youngest R group but it did not change in the 50-day-old R group. AQP1 nitrosylation was increased in R25 group, whereas there are no significant differences in colocalization of fluorescent signals between C or R animals aged 50 days. On the other hand, cardiac membrane vesicles expressing AQP1 presented a high water permeability coefficient (Pf: 326+/-17 μm/s, n = 6) indicated water transport by aquaporins and pretreatment with SNP decreased water permeability (Pf: 102+/-4 μm/s, n = 5).

Conclusions: Cardiac NO system and AQP1 abundance and localization during osmotic stress in vivo depend on postnatal age. Increased activity of cardiac NO system in the youngest group may induce AQP1 nitrosylation, decreasing osmotic water permeability of cardiac membranes and having a negative impact on cardiac water balance. In the 50-day-old group, changes in AQP1 abundance and localization may contribute to maintaining cardiac water homeostasis during hypovolemic state.

6B.07 HYPERTENSIVE PATIENTS EXHIBIT GUT MICROBIAL DYSBIOSIS AND AN INCREASE IN TH17 CELLS

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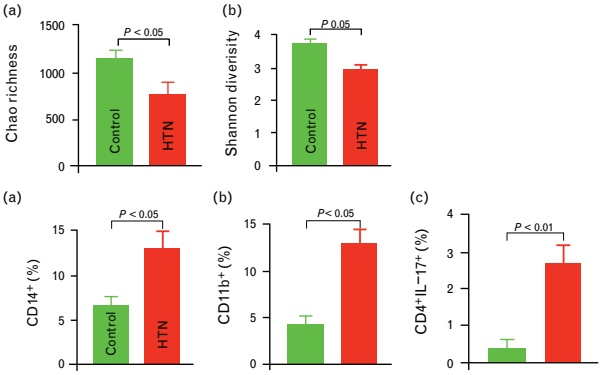
Objective: Hypertension (HTN) is a most prevalent risk factor associated with diabetes, obesity, metabolic syndrome and cardiovascular disease, all of which have been recently associated with gut microbial dysbiosis. However, a relationship between gut microbiota and HTN has not been studied. Thus, the objective of our study was to investigate if gut dysbiosis is present in hypertensive patients.

Design and method: We conducted a pilot study using fecal and blood samples obtained from hypertensive (n = 7, systolic BP > 125 mmHg) and normotensive (n = 13, systolic BP < 125 mmHg) patients. Samples were analyzed for Chao richness, Shannon diversity and Pielou evenness using 16 s rRNA sequencing to determine microbiome composition. FACS analysis was used to examine changes in the inflammatory cells levels in these patients.

Results: We observed marked decreases in microbial richness and diversity in the HTN patients (Figure 1). In addition, this group also showed a trend towards a decrease in evenness in species from certain genus such as bacteriodetes. Furthermore, increases in myeloid inflammatory cells (94% increase in CD14+ cells, 200% increase in CD11b+ cells) and Th17 cells (700% increase in CD4+ IL17+ cells) were observed in HTN patients compared to normotensives (Figure 2). An increase

in the Th17 cells is extremely relevant finding since levels of these cells are regulated by gut-intrinsic mechanisms that generate pro-inflammatory cytokines such as TGF-β1, TNF-α, IL-1β and IL-6.

Conclusions: Taken together, these observations suggest that gut microbial dysbiosis plays a key role in HTN and the establishment of a systemic proinflammatory status through regulation of Th17 cell levels. Thus, restoring the gut microbial balance could be a novel therapeutic strategy for the treatment of HTN.



6B.08 EFFECTS OF TREATMENT WITH ENALAPRIL OR LOSARTAN ASSOCIATED WITH AEROBIC PHYSICAL TRAINING ON CARDIOVASCULAR AUTONOMIC CONTROL IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR)

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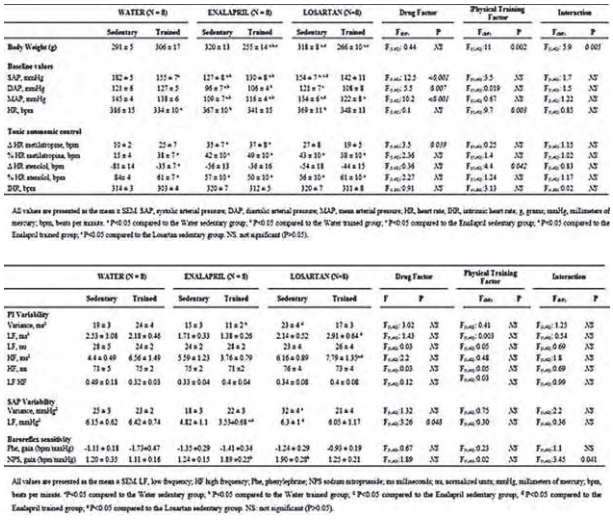
Objective: To investigate the effects of treatment with enalapril or losartan associated with swimming training program on cardiovascular autonomic control in spontaneously hypertensive rats (SHR).

Design and method: Eighteen-week-old SHR (N = 48) were divided into six groups: control sedentary group (water) (CS), control trained group (CT), enalapril sedentary group (10 mg/kg) (ES), enalapril trained group (ET), losartan sedentary group (05 mg/kg) (LS) and losartan trained group (LT).
The animals received daily doses of drugs diluted in drinking water, for ten weeks. The 10-week swimming training program was 5 times/week, 1 hour/day.
Polyethylene cannulae (PE 10) were inserted into the left femoral vein and artery of the animals in the end of the treatments, and, in this way, were analyzed using different approaches: 1) pharmacological evaluation of autonomic tonus with methylatropine and atenolol; 2) analysis of heart rate (HRV) and systolic arterial pressure variability (SAPV); 3) baroreflex sensitivity (BRS) with the use of phenylephrine and sodium nitroprusside.
Ethics Committee on Animal Experimentation, FMRP/USP, N.092/2012.

Results: The ES and ET had lower systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressure than CS and CT. The LS had lower SAP than CS. The LT had lower DAP than CS. The CT had lower SAP than CS.
The CT had lower baseline heart rate (HR) than all sedentary groups.
All groups had a sympathetic predominance in determining the HR. ES, ET, LS and LT, showed attenuation of this predominance. There was no difference in intrinsic pacemaker HR between groups.
The ET, in HRV, presented lower variance when compared to CT and LS. The LT presented, in absolute units, higher low-frequency oscillations (LF = 0.25–0.75 Hz) than ET, and higher high-frequency oscillations (HF = 0.75–2.5 Hz) than CS and ET.
The LS, in SAPV, showed higher values of variance than ES. The ET showed lower LF values than CS, CT and LS.
The ET and LS, when compared to CT, had higher tachycardic responses after sodium nitroprusside administration.



	WATER (N = 8)		ENALAPRIL (N = 8)		LOSARTAN (N=8)		Drug Factor		Physical Training Factor		Interaction	
	Sedentary	Trained	Sedentary	Trained	Sedentary	Trained	F$_{ser.}$	P	F$_{ser.}$	P	F$_{ser.}$	P
Body Weight (g)	291 ± 5	306 ± 17	320 ± 13	225 ± 14***	318 ± 8***	266 ± 10***	F$_{(5,42)}$ 0.44	NS	F$_{(5,42)}$ 11	0.002	F$_{(5,42)}$ 5.9	0.005
Baseline values												
SAP, mmHg	102 ± 5	115 ± 7*	127 ± 8***	130 ± 8***	134 ± 7***#	142 ± 11	F$_{(5,42)}$ 12.5	<0.001	F$_{(5,42)}$ 3.5	NS	F$_{(5,42)}$ 1.7	NS
DAP, mmHg	121 ± 6	127 ± 5	96 ± 7*#	106 ± 4#	121 ± 7+	106 ± 8	F$_{(5,42)}$ 5.5	0.05*	F$_{(5,42)}$ 0.019	NS	F$_{(5,42)}$ 1.5	NS
MAP, mmHg	145 ± 4	138 ± 6	109 ± 7*#	116 ± 4*#	134 ± 8+#	122 ± 8+	F$_{(5,42)}$ 10.2	<0.001	F$_{(5,42)}$ 0.67	NS	F$_{(5,42)}$ 1.22	NS
HR, bpm	366 ± 15	334 ± 10+	367 ± 10+	341 ± 15	369 ± 11+	348 ± 13	F$_{(5,42)}$ 0.1	NS	F$_{(5,42)}$ 9.7	0.003	F$_{(5,42)}$ 0.85	NS
Tonic autonomic control												
Δ HR metilatropine, bpm	10 ± 2	25 ± 7	35 ± 7+	37 ± 8+	27 ± 8	39 ± 5	F$_{(5,42)}$ 3.5	0.039	F$_{(5,42)}$ 0.25	NS	F$_{(5,42)}$ 1.15	NS
% HR metilatropine, bpm	15 ± 4	38 ± 7+	42 ± 10+	49 ± 10+	43 ± 10+	58 ± 10+	F$_{(5,42)}$ 2.36	NS	F$_{(5,42)}$ 1.4	NS	F$_{(5,42)}$ 1.02	NS
Δ HR atenolol, bpm	-81 ± 14	-35 ± 7+	-56 ± 13	-36 ± 16	-54 ± 18	-44 ± 15	F$_{(5,42)}$ 0.36	NS	F$_{(5,42)}$ 4.4	0.042	F$_{(5,42)}$ 0.83	NS
% HR atenolol, bpm	-84± 4	-61 ± 7+	-57 ± 10+	-50 ± 10+	-56 ± 10+	-61 ± 10+	F$_{(5,42)}$ 2.27	NS	F$_{(5,42)}$ 1.24	NS	F$_{(5,42)}$ 1.17	NS
IHR, bpm	314 ± 3	303 ± 4	320 ± 7	312 ± 5	320 ± 7	311 ± 8	F$_{(5,42)}$ 0.91	NS	F$_{(5,42)}$ 3.13	NS	F$_{(5,42)}$ 0.02	NS

All values are presented as the mean ± SEM. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate, IHR, intrinsic heart rate, g, grams; mmHg, millimeters of mercury; bpm, beats per minute. *P<0.05 compared to the Water sedentary group; #P<0.05 compared to the Water trained group; +P<0.05 compared to the Enalapril sedentary group; ‡P<0.05 compared to the Enalapril trained group; ‡P<0.05 compared to the Losartan sedentary group. NS: not significant (P>0.05).

	WATER (N = 8)		ENALAPRIL (N = 8)		LOSARTAN (N=8)		Drug Factor		Physical Training Factor		Interaction	
	Sedentary	Trained	Sedentary	Trained	Sedentary	Trained	F	P	F$_{ser.}$	P	F$_{ser.}$	P
FI Variability												
Variance, ms^2	19 ± 3	24 ± 4	15 ± 3	11 ± 2*	23 ± 4#	17 ± 3	F$_{(5,42)}$ 3.02	NS	F$_{(5,42)}$ 0.41	NS	F$_{(5,42)}$ 1.25	NS
LF, ms^2	2.23 ± 1.08	2.18 ± 0.48	1.71 ± 0.33	1.38 ± 0.26	2.14 ± 0.52	2.91 ± 0.64#	F$_{(5,42)}$ 1.43	NS	F$_{(5,42)}$ 0.003	NS	F$_{(5,42)}$ 0.54	NS
LF, nu	28 ± 5	24 ± 2	24 ± 2	28 ± 2	23 ± 4	26 ± 4	F$_{(5,42)}$ 0.03	NS	F$_{(5,42)}$ 0.05	NS	F$_{(5,42)}$ 0.69	NS
HF, ms^2	4.6 ± 0.49	6.56 ± 1.49	5.59 ± 1.23	3.76 ± 0.79	6.16 ± 0.89	7.79 ± 1.35*#	F$_{(5,42)}$ 2.2	NS	F$_{(5,42)}$ 0.48	NS	F$_{(5,42)}$ 1.8	NS
HF, nu	71 ± 5	75 ± 2	75 ± 2	71 ± 2	76 ± 4	73 ± 4	F$_{(5,42)}$ 0.03	NS	F$_{(5,42)}$ 0.05	NS	F$_{(5,42)}$ 0.69	NS
LF/HF	0.49 ± 0.18	0.32 ± 0.03	0.33 ± 0.04	0.4 ± 0.04	0.34 ± 0.08	0.4 ± 0.08	F$_{(5,42)}$ 0.12	NS	F$_{(5,42)}$ 0.03	NS	F$_{(5,42)}$ 0.99	NS
SAP Variability												
Variance, mmHg^2	25 ± 5	23 ± 2	18 ± 3	22 ± 3	32 ± 4+	21 ± 4	F$_{(5,42)}$ 3.32	NS	F$_{(5,42)}$ 0.75	NS	F$_{(5,42)}$ 2.2	NS
LF, mmHg^2	6.15 ± 0.62	6.42 ± 0.74	4.82 ± 1.1	3.53±0.68*#	6.3 ± 1+	6.05 ± 1.17	F$_{(5,42)}$ 3.26	0.048	F$_{(5,42)}$ 0.30	NS	F$_{(5,42)}$ 0.36	NS
Baroreflex sensitivity												
Phe, gain (bpm/mmHg)	-1.11 ± 0.18	-1.73±0.47	-1.35 ± 0.29	-1.41 ± 0.34	-1.24 ± 0.29	-0.93 ± 0.19	F$_{(5,42)}$ 0.67	NS	F$_{(5,42)}$ 0.23	NS	F$_{(5,42)}$ 1.1	NS
NPS, gain (bpm/mmHg)	1.20 ± 0.35	1.11 ± 0.16	1.24 ± 0.15	1.89 ± 0.22#	1.90 ± 0.28#	1.25 ± 0.21	F$_{(5,42)}$ 1.89	NS	F$_{(5,42)}$ 0.02	NS	F$_{(5,42)}$ 3.45	0.041

All values are presented as the mean ± SEM. LF, low frequency; HF high frequency; Phe, phenylephrine; NPS sodium nitroprusside; ms milliseconds; nu, normalized units; mmHg, millimeters of mercury; bpm, beats per minute. *P<0.05 compared to the Water sedentary group; #P<0.05 compared to the Water trained group; +P<0.05 compared to the Enalapril sedentary group; ‡P<0.05 compared to the Enalapril trained group; ‡P<0.05 compared to the Losartan sedentary group. NS: not significant (P>0.05).

Conclusions: Enalapril treatment showed a positive effect on arterial pressure and SAPV. Pharmacological treatments associated with aerobic physical training, did not have synergistic effects in the studied parameters.

6B.09 EFFECT OF CANNABINOID RECEPTOR ACTIVATION ON ABERRANT MITOCHONDRIAL BIOENERGETICS IN HYPERTROPHIED CARDIAC MYOCYTES

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Objective: We recently reported that activation of endocannabinoid receptors attenuates cardiac myocyte hypertrophy. Mitochondrial dysfunction has emerged as a critical determinant of aberrant myocyte energy production in cardiac hypertrophy. Thus, we determined endocannabinoid influence on mitochondrial function in the hypertrophied cardiac myocyte.

Design and method: The experimental paradigm of hypertrophy in this study was neonatal rat cardiac myocytes treated with endothelin-1 (ET1; 0.1 μM). Ligand activation of cannabinoid receptors was achieved using CB13 (1 μM), a peripherally-restricted dual agonist of cannabinoid receptor subtypes CB1 and CB2. Changes in mitochondrial membrane potential (δψm) were assessed by fluorescence microscopy using the potential sensitive dye, JC-1. Biochemical modulators of mitochondrial function (i.e. peroxisome proliferator-activated receptor-γ coactivator 1α [PGC-1α - a driver of mitochondrial biogenesis], carnitine palmitoyl transferase 1β [CPT-1β - facilitator of fatty acid uptake], and AMP-activated protein kinase [AMPK – energy sensor]) were assessed by real-time PCR and western blotting. The Seahorse Bioscience XF24 Analyzer was used to measure fatty acid oxidation-related bioenergetics parameters.

Results: ET1 caused mitochondrial aberrations which included membrane depolarization (δψm 80 ± 5% vs. control; $p < 0.05$), reduced PGC-1α (59 ± 7% vs. control; $p < 0.01$) and CPT-1β (81 ± 5% vs. control; $p < 0.05$) expression, as well as depressed palmitate-dependent respiration (basal/maximal/reserved respiration respectively: 81 ± 5%, 78 ± 4%, 74 ± 5% vs. control; $p < 0.05$), coupling efficiency (83 ± 6% vs. control; $p < 0.05$), and respiratory control ratio (79 ± 5% vs. control; $p < 0.01$). CB13 treatment restored all mitochondrial parameters to normal. Incidentally, CB13 activated AMPK via phosphorylation at Thr172 (354 ± 58% vs. control; $p < 0.01$), and the ability of CB13 to improve mitochondrial membrane potential and PGC-1α was abolished by compound C (a chemical inhibitor of AMPK) or shRNA knockdown of AMPK. These data suggest that AMPK contributes to the mitochondrial protective effects of CB13.

Conclusions: The cardioprotective actions of liganded cannabinoid receptors extend to the mitochondrial level. Therefore, a cannabinoid-based treatment for cardiac disease remains a potential therapeutic strategy that warrants further study.

ORAL SESSION

ORAL SESSION 6C

GENETICS, GENOMICS, PROTEOMICS, METABOLOMICS

6C.01 CULLIN-3 MUTATIONS LEADING TO SKIPPING OF EXON 9 ARE RESPONSIBLE FOR SEVERE CASES OF FAMILIAL HYPERKALAEMIC HYPERTENSION

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Objective: Familial hyperkalaemic hypertension (FHHt) also known as Gordon syndrome is a rare form of hypertension.

Design and method: In 2001, WNK1 and WNK4, have been identified as responsible for this syndrome, regulating the ion transport in the kidney. In 2012, an American laboratory as well as ours, have identified two other genes, KLHL3 and CUL3 as responsible for the disease. These two unexpected genes are part of an E3-ubiquitin-ligase complex involved in the degradation of target proteins after ubiquitination, among them the WNK1 and WNK4 kinases.

Results: We have identified 22 different mutations in KLHL3 in 27 index or familial cases. 19 are autosomal dominant, four recessive inheritance and four de novo mutations. There is a wide phenotypic variability, recessive cases have an earlier age at diagnosis, but blood pressure levels and similar serum K+ and Cl- levels.
We have also identified seven missense mutations in the CUL3 gene in nine cases. All these mutations are located at the splice sites of exon 9, resulting in a loss in phase of 57 amino acids. Five cases have the mutations at a de novo state and two exhibit autosomal dominant proved. These patients are characterized by an earlier age of diagnosis and a severe phenotype. Patients with a CUL3 mutation have a stronger phenotype compared to other patients affected by other genes responsible for FHHt (WNK1, WNK4, KLHL3), suggesting other damages, vascular particularly. For some patients, a growth delay was observed, a possible consequence of the high metabolic acidosis and/or an effect of the mutation CUL3-delta-exon9 on the half-life of proteins involved in the development.
Analysis by Bioluminescence Resonance Energy Transfer shows a direct interaction between KLHL3-CUL3-delta-exon9 stronger compared to the KLHL3-CUL3-wt. The CUL3-delta-exon9 mutation also causes an increase in the CUL3 neddylation, suggesting an increased ability to degrade its partners to the proteasome.

Conclusions: In conclusion, there is a large phenotypic heterogeneity of FHHt, largely explained by genetic heterogeneity. CUL3-delta-exon9 mutations cause a severe disease in these patients, opening the way for additional research on the E3-ubiquitin-ligase complex CRL.

6C.02 EXOME SEQUENCING IN SEVEN FAMILIES AND GENE-BASED ASSOCIATION STUDIES SUPPORT GENETIC HETEROGENEITY AND SUGGEST POSSIBLE CANDIDATES FOR FIBROMUSCULAR DYSPLASIA

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Objective: Fibromuscular dysplasia (FMD) is a group of nonatherosclerotic and noninflammatory vascular disease leading to stenosis, aneurysm and dissection of medium-sized arteries, mainly renal arteries and carotids. FMD occurs predominantly in females with a prevalence of $\sim$ 4/1000 for clinical forms that cause hypertension, renal ischemia or stroke. The pathogenesis of FMD is unknown and a genetic origin is suspected given its demonstrated familial aggregation. Our study objective is to identify genetic variants involved in FMD aetiology.

Design and method: We performed whole exome sequencing (WES) in 16 FMD cases from 7 families (5 sibpairs and 2 sibtrios). Coding variants in 3,971 genes confidently called (read depth > 20X) were prioritized on their frequency (allele frequency < 0.01) and in silico predicted functionality.

Results: No gene harbored variants that were shared among all affected members of at least 3 out of 7 families. Rare coding variants from 16 known causative genes of vascular and connective tissue syndromes (e.g. FBN1, TGFB2 and COL3A1) were excluded as causative in these families. Genes with at least 4 rare coding variants identified in the 16 patients were followed-up using genotyping data by exome chip (Illumina HumanExome-12v1_A Beadchip) from 249 FMD unrelated cases and 689 controls. Gene-based association of rare variants using SKAT-O showed nominal significant ($P < 0.05$) association with multifocal FMD ($N = 164$) for OBSCN encoding a sarcomeric protein ($P = 0.003$), DYNC2H1 encoding a cytoplasmic dynein ($P = 0.02$) and RNF213 previously associated with Moyamoya disease ($P = 0.01$).

Conclusions: Our study reports data from the first WES investigation conducted for familial forms of FMD. It supports strong genetic heterogeneity for FMD and excludes the implication of several known vascular diseases causative genes in familial FMD etiology. We provide some evidence of association with multifocal FMD for OBSCN, DYNC2H1 and RNF213, though these findings need to be confirmed in independent cohorts. More powerful WES and association studies (e.g GWAS) will better decipher the genetic basis of FMD.

6C.03 A CASE OF SEVERE HYPERALDOSTERONISM CAUSED BY A DE NOVO KCNJ5 MUTATION

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Objective: Familial hyperaldosteronism type III (FH-III) is a rare autosomal dominant and clinically heterogeneous condition, that can display mild as well as severe phenotypes. Point mutations in the KCNJ5 gene, affecting the ion selectivity of the inward rectifier K+ channel 4 (Kir3.4), represent the molecular basis of FH-III. So far, five germline mu- tations in the KCNJ5 gene have been identified and functionally characterized in patients with FH-III. Objective of the present study was to characterized the effect of a de novo KCNJ5 germline substitution in vitro.

Design and method: We describe the case of a girl affected by severe hyperaldosteronism. KCNJ5 gene was PCR amplified from peripheral blood and sequenced. Electrophysiological and gene expression studies were performed to establish the functional effects of the new mutation on the membrane potential and adrenal cell CYP11B2 (aldosterone synthase) expression.

Results: The index case is a Caucasian girl born to nonconsanguineous parents. She came to medical attention at the age of two years because of polydipsia, polyuria and failure to thrive. The patient, affected by hypertension and hypokalemia, was diagnosed with primary aldosteronism on the basis of extremely high aldosterone levels and suppressed plasma renin activity. At the age of 19 she was on four antihypertensive medications and potassium supplements; transthoracic echocardiography revealed mildly dilated aortic root and ascending aorta without left ventricular hypertrophy. The patient consented to bilateral adrenalectomy which was performed laparoscopically. KCNJ5 sequencing in the index case and her parents revealed a de novo p.Glu145Gln germline mutation. The substitution resulted in Na+-dependent depolarization of adrenal cells and increased intracellular calcium concentration, which activated the transcription of NR4A2 and, in turn, CYP11B2. Pharmacological studies revealed that the mutant channel was insensitive to tertiapin-Q and calcium-channel blocker verapamil.

Conclusions: Herein we report on the identification of a novel KCNJ5 germline mutation responsible for severe hyperaldosteronism that presented in infancy with symptoms of diabetes insipidus. The findings of this study further elucidate the etiology of FH-III and expand our knowledge of this rare condition.

6C.04 INTEGRATED SNP ANALYSIS AND METABOLOMIC PROFILES OF METABOLIC SYNDROME

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Objective: Metabolic syndrome (MS) has become a health and financial burden worldwide. Susceptibility of genetically determined metabotype of MS has not yet been investigated. We aimed to identify a distinctive metabolic profile of blood serum which might correlates to the early detection of the development of MS associated to genetic polymorphism.

Design and method: We applied high resolution NMR spectroscopy to profile blood serum from patients without MS (n = 945) or with (n = 291). Principal component analysis (PCA) and projection to latent structures for discriminant analysis (PLS-DA) were applied to NMR spectral datasets. Results were cross-validated using the Venetian Blinds approach. Additionally, five SNPs previously associated with MS were genotyped with SNPlex and tested for associations between the metabolic profiles and the genetic variants. Statistical analysis was performed using in-house MATLAB scripts and the PLS Toolbox statistical multivariate analysis library.

Results: Our analysis provided a PLS-DA Metabolic Syndrome discrimination model based on NMR metabolic profile (AUC = 0.86) with 84% of sensitivity and 72% specificity. The model identified 11 metabolites differentially regulated in patients with MS. Among others, fatty acids, glucose, alanine, hydroxyisovalerate, acetone, trimethylamine, 2-phenylpropionate, isobutyrate and valine, significantly contributed to the model. The combined analysis of metabolomics and SNP data revealed an association between the metabolic profile of MS and genes polymorphism involved in the adiposity regulation and fatty acids metabolism: rs2272903_TT (TFAP2B), rs3803_TT (GATA2), rs174589_CC (FADS2) and rs174577_AA (FADS2). In addition, individuals with the rs2272903-TT genotype seem to develop MS earlier than general population.

Conclusions: Our study provides new insights on the metabolic alterations associated with a MS high-risk genotype. These results could help in future development of risk assessment and predictive models for subclinical cardiovascular disease.

6C.05 STK39 AND WNK1 ARE POTENTIAL HYPERTENSION SUSCEPTIBILITY GENES IN THE BELHYPGEN COHORT

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Objective: The serine threonine kinase WNK1 activates the thiazide-sensitive Na+/Cl- co-transporter in the distal tubule, at least partly through phosphorylation of another serine threonine kinase named SPAK, encoded by the STK39 gene. We looked for a possible association of WNK1 and STK39 genes with blood pressure (BP) and hypertension in Belgium.

Design and method: 779 Caucasian hypertensive patients (HYP) recruited in six academic centres from Belgium and 906 normotensive (NT) controls were genotyped for rs3754777 (STK39) and rs1468326 (WNK1) using the Snapshot® methodology.

Results: Hypertensive patients were aged 56.9 years, had a mean BMI of 28.3 kg/m2 and systolic BP of 147.9 mmHg on an average of 1.9 drugs. Controls (mean systolic BP: 117 mmHg) were younger (mean age: 36.6 years) and leaner (mean BMI: 23.4 kg/m2). The rare TT genotype at the STK39 locus was overrepresented in HYP vs. NT (7.3 vs. 3.0%, p = 0.0002). In the whole study population, with adjustments applied for sex, age, BMI and the number of antihypertensive drugs, the odds ratio (OR) of having hypertension associated with the TT genotype was 5.9 (CI, 2.2–15.6); the corresponding effect size on a continuous scale was a 10 mmHg higher systolic BP in TT carriers (140.1 vs. 130.4 mmHg in wild type subjects, p = 0.002). Similarly, the AA genotype at the WNK1 locus was twice as frequent in HYP vs. NT (5.5 vs. 2.3%, p < 0.0001), and associated with an increased multivariable-adjusted OR of hypertension (4.1; 1.5–11.7) and a higher systolic BP (139.8 in AA vs. 130.1 mmHg in wild-type, p = 0.003). In the whole cohort, a dose-dependent increase in systolic BP was observed according to the number of at-risk genotypes (0: 129.8 mmHg; 1: 133.0 mmHg; 2: 149.3 mmHg, p = 0.02). Subjects harbouring the risk alleles at the heterozygous state did not differ from wild type for the studied parameters, consistent with a recessive effect at both loci.

Conclusions: Our multicentre Belgian case-control study identifies STK39 and WNK1 as potential hypertension susceptibility genes. Replication in different clinical settings and study of other candidate loci belonging to the same metabolic pathway is warranted.

6C.06 GENES INVOLVED IN BLOOD PRESSURE RESPONSE TO ACUTE AND CHRONIC SALT MODIFICATIONS: IDENTIFICATION OF A NEW PATHWAY

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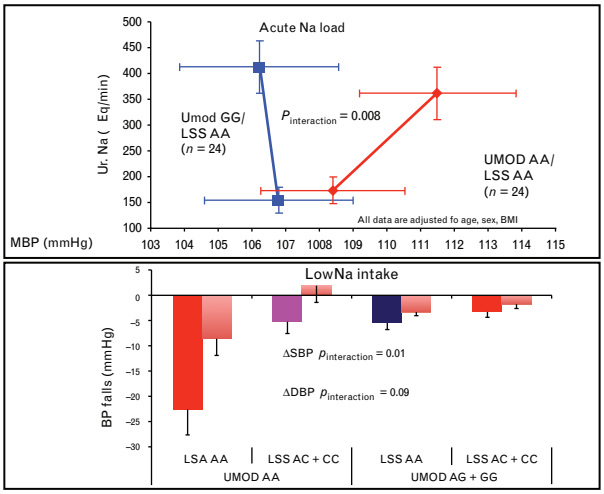
Objective: A moderate reduction in salt intake reduces BP in most but not all individuals. Identification of genetic loci combination is a difficult task. Recently, the uromodulin (UMOD) gene has been associated with renal damage and hypertension.

Design and method: Present study evaluated the role Endogenous Ouabain (EO), polymorphisms in a candidate gene related to its synthesis, Lanosterol Synthase (LSS), and in UMOD in variability of response to acute and chronic body Na variations. Acute Na load protocol in 608 naïve hypertensive patients (NHP) was carried out. 183 NHP followed a low Na intake diet for 15 days. UMOD and LSS gene polymorphisms have been tested.

Results: Acute protocol: NHP carrying UMOD GG/LSS AA display a pressure-natriuresis curve with negative slope (Salt Resistant), while those with UMOD AA/LSS AA showed a right shift of pressure-natriuresis curve (Salt Sensitive, upper panel). Low Na intake: In a dietary compliant group with the reduction of UNa excretion, a direct (β=0.213) relationship (p = 0.026) between the change in EO and BP was found. When LSS and UMOD gene variants were analyzed together, a significant interaction was detected: those patients homozygous for the A alleles of both gene variants displayed a 5-fold greater decline in SBP than patients carrying other allele combinations (lower panel).



Conclusions: We identify a genetic interaction that characterized a subgroup of patients. In this pathway UMOD may affect renal tubular Na excretions, whereas LSS affects vasoconstrictor activity modulating circulating EO levels. This new pathway is relevant for blood pressure response during both acute and chronic salt modification.

6C.07 INCREASE THE PREDICTIVE CAPACITY OF CORONARY RISK WITH A GENETIC SCORE

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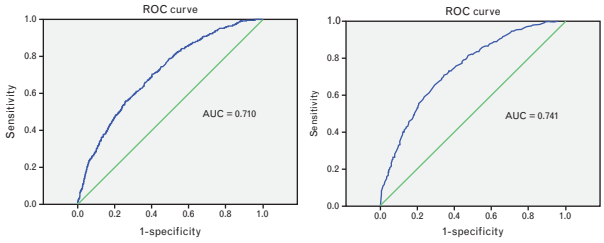
Objective: Genes associated with coronary artery disease (CAD) and traditional cardiovascular risk factors (TCRF) present a limited individual predictive value. It is expected that the inclusion in global scores may increase the predictive ability. In genetic terms, there are no validated risk scores to predict the occurrence of cardiovascular disease or its complications.

Objective: Evaluate the ability of a multifactorial genetic risk score (GRS) be able to add predictive power, for the development of CAD, to the model developed only with TCRF.

Design and method: A case-control study was performed with 1321 consecutive coronary patients (mean age 53.4 ± 8.1 years, 78.8% male) and 1148 controls selected to be similar to cases in terms of gender and age. Traditional risk factors (hypertension, diabetes, dyslipidemia, smoking, obesity, sedentary lifestyle, family history) were evaluated according to the International criteria. The genetic variants were analyzed with specific primers and the GRS was determined in the entire population, based on 29 genetic polymorphisms previously associated with atherosclerotic disease in general and, in particular, with CAD. A multiplicative model was then used based on risk multiplication (odds ratio - OR) of each genotype of the 29 studied genes. Subsequently, a multivariate analysis was done with the TCRF only or the TCRF with the GRS and a ROC curve was constructed for both situations.

Results: After multivariate analysis, the GRS was found to be an independent predictor for CAD (OR = 2.1; CI: 1.7–2.5; p < 0.0001). The AUC increased from 0.71 to 0.74 after the inclusion of GRS to the TCRF in the multivariate analysis (Figure).



Conclusions: In our population, the multiplicative GRS was an independent predictor for CAD. When analyzed together with traditional risk factors, it adds little predictive value. Its usefulness, in clinical practice, may be directed to the intermediate risk group, in which a possible risk reclassification can have different therapeutic measures.

ORAL SESSION

ORAL SESSION 6D
ENDOTHELIUM

6D.01 OBESTATIN INDUCES NITRIC OXIDE-DEPENDENT VASODILATION AND INHIBITS ENDOTHELIN-1 ACTIVITY IN HUMAN OBESITY

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Objective: Obese patients have vascular dysfunction related to impaired nitric oxide (NO)-dependent vasodilation and enhanced endothelin (ET)-1 activity. Obestatin is a gastrointestinal peptide with favorable metabolic actions linked to obesity and type 2 diabetes; it has also been shown to exert cardiovascular benefits in experimental models by producing vascular relaxation via specific activation of endothelium-dependent NO signaling. In the present study we tested the hypothesis that obestatin might also have advantageous impacts on the NO pathway and the ET-1 system in patients with central obesity.

Design and method: To this purpose, forearm blood flow responses to intra-arterial infusion of graded doses of exogenous obestatin (0.2; 0.4; 0.8; 1,6; 3.2 nmol/min, each dose for 5 min) were assessed in lean subjects (n = 5) and in patients with central obesity (n = 14), during the concurrent infusion of saline and after NO inhibition by L-NMMA (4 micromol/min for 15 min). In another group of obese patients (n = 10), vascular responses to selective blockade of ETA receptors (BQ-123, 10 nmol/min for 60 min) were measured in the absence and the presence of obestatin (0.8 nmol/min).

Results: In lean subjects, before NO synthase inhibition obestatin resulted in a progressive increase in forearm flow (60% at the highest dose; $P < 0.001$ vs. baseline); obestatin-induced vasodilation, however, was completely abolished by L-NMMA ($P < 0.001$ vs. saline). Similarly, in obese patients obestatin induced a significant vasodilation (45%; $P < 0.001$ vs. baseline), which was blunted by L-NMMA (16%; $P < 0.01$ vs. saline). Before obestatin, in obese patients ETA receptor blockade resulted in a marked vasodilation (39% flow increase at 60 min; $P < 0.001$ vs. baseline), which was totally abrogated in the presence of obestatin ($P < 0.001$ vs. absence).

Conclusions: In conclusion, obestatin produces vasorelaxation in healthy humans via specific activation of endothelium-dependent NO signaling. This beneficial effect of obestatin is preserved in obese arteries, where it is associated with inhibition of ET-1 signaling. These actions of obestatin, therefore, may be important in the normal regulation of vascular function and are clearly relevant to obesity, a condition characterized by increased prevalence of hypertension and cardiovascular complications.

6D.02 GHRELIN RESTORES NITRIC OXIDE AVAILABILITY IN THE FOREARM MICROCIRCULATION OF ESSENTIAL HYPERTENSIVE PATIENTS

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Objective: Essential hypertensive patients (EH) are characterized by endothelial dysfunction caused by a reduced nitric oxide (NO) availability due to reactive oxygen species excess and low-grade inflammatory condition. Ghrelin is a recently identified growth hormone-releasing peptide, with recognized cardiovascular actions. Possible effects on endothelial dysfunction have been never investigated in EH. In this study we evaluated whether exogenous ghrelin can improve endothelial dysfunction in the forearm microcirculation of untreated mild-moderate EH.

Design and method: In 9 EH (51.8 ± 8.1 yrs) and 9 normotensive subjects (NS, 50.5 ± 3.5 yrs), we studied the forearm blood flow (FBF, strain-gauge plethysmography) response to intrabrachial acetylcholine (ACh, 0.15–15 mg/100 ml/min) with and without NO synthase blockade by L-NMMA (100 μg/100 ml/min), or the antioxidant vitamin (Vit) C (8 mg/100 ml/min). The protocol was repeated under exogenous ghrelin intra-arterial infusion (200 ng/min, 30' pre-infusion).

Results: In NS, the maximal vasodilation (VD) to ACh ($480 \pm 20\%$) was inhibited by L-NMMA (292 ± 22, $-39 \pm 7\%$; $P < 0.001$) and unchanged by Vit C ($482 \pm 34\%$). Ghrelin failed to modify these vascular responses. In EH, VD to ACh was blunted vs NS ($337 \pm 45\%$; $P < 0.001$) and resistant to L-NMMA (313 ± 32, $-7 \pm 3\%$). Vit C increased the response to ACh ($509 \pm 57\%$; $P < 0.01$ vs ACh alone) and restored the inhibiting effect of L-NMMA (332 ± 42, $-34 \pm 8\%$; $P < 0.001$). Ghrelin, while not modifying the basal FBF, it increased ($P < 0.001$) the VD to ACh (448 ± 55) and restored the inhibitory effect of L-NMMA on ACh (355 ± 43, $-20 \pm 6\%$; $P < 0.001$). Vit C only slightly improved VD to ACh under ghrelin infusion ($486 \pm 45\%$). In EH ghrelin significantly ($P < 0.05$) decreased plasma venous malodialdehyde (from 6.9 ± 1.5 to 5.2 ± 1.0 μmol/L), lipoperoxides (from 9.1 ± 1.9 to 6.6 ± 2.3 μmol/L) and IL-6 (from 11.1 ± 0.6 to 9.3 ± 1.0 pg/mL) and increased plasma antioxidant capacity (from 407 ± 109 to 630 ± 97 mmol/L). Response to sodium nitroprusside was similar between EH and NS and not affected by ghrelin.

Conclusions: Exogenous ghrelin is able to increase endothelial dysfunction by restoring NO availability in the forearm microcirculation of EH, an effect probably determined by antioxidant and/or anti-inflammatory activities.

6D.03 FLOW-MEDIATED DILATATION (FMD) AND ENDOTHELIUM-INDEPENDENT DILATATION (EID) IN PATIENTS WITH MULTIFOCAL FIBROMUSCULAR DYSPLASIA: A CROSS-SECTIONAL STUDY

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Objective: Fibromuscular dysplasia (FD) is a rare idiopathic, segmental, non-atherosclerotic non-inflammatory vascular disease. We previously showed that FD is a general arterial disease with focal exacerbation of the trait. However, whether endothelial dysfunction may be involved in the pathophysiology of FD is unclear.

Design and method: In a cross sectional study, we compared the endothelial function between 50 patients with multifocal FD of renal/carotid arteries confirmed by CT-angiography, 50 essential hypertensive (EH) patients matched for age, sex, ethnicity and BP and 50 healthy subjects (HS) matched for age, sex and ethnicity. Exclusion criteria were: tobacco consumption, hypercholesterolemia, diabetes, aspirin or statin treatment. Brachial artery (BA) FMD after release of hand ischemia and glyceryl trinitrate (GTN)-induced EID was measured using a high-resolution radiofrequency–based echotracking system blind to the diagnosis.

Results: FD, EH and HS were well matched (52yrs, 85% women, 80% caucasian). SBP was higher in FD (125 ± 15mmHg) and EH (121 ± 12mmHg) than EH (113 ± 10mmHg) despite antihypertensive treatments. BA external diameter was significantly lower in FD than in both HS and EH before, during and after hand ischemia and after GTN. BA intima media thickness (IMT), internal diameter did not differ between the 3 groups. FMD (%) or EID (%) did not significantly differ between the 3 groups. BA flow velocity did not significantly differ in any experimental condition.

	FD	EH	HS
Age, yrs	52±9	52±9	52±9
Women, n (%)	43 (86%)	43 (86%)	42 (84%)
Caucasian, n (%)	38 (76%)	38 (76%)	42 (84%)
Office SBP, mmHg	125±15***	121±12***	113±10
Antihypertensive drugs, n (range)	2 (1-4)	2(1-4)	0
BA structure			
External diameter, mm	3.91±0.72°	4.19±0.69	4.00±0.64
Internal diameter, mm	3.34 ± 0.64	3.56 ± 0.66	3.47 ± 0.57
IMT, µm	319±79	330±85	303±97
FMD			
Basal BA diameter, mm	3.86±0.70*°	4.17±0.63	4.02±0.65
BA diameter (hand ischemia), mm	3.91±0.71°°	4.22±0.64	4.04±0.61
BA diameter (hand hyperhemia), mm	3.98±0.73*°	4.29±0.63	4.16±0.62
Change in BA diameter, %	2.39 [0.31; 5.41]	2.85 [-0.23; 6.15]	2.67 [0.20; 5.73]
Basal BA flow velocity, cm/s	7.70±5.99	7.39±5.98	7.66±8.53
BA flow velocity (ischemia), cm/s	3.71±5.25	2.68±5.01	0.98±2.54
BA flow velocity (hyperhemia), cm/s	73±29	69±27	78±38
EID			
Basal BA diameter, mm	3.92±0.69°°	4.22±0.67	4.02±0.67
Post-GTN BA diameter, mm	4.43±0.69**°°	4.82±0.61	4.74±0.71
Change in BA diameter, %	13.8 [7.9; 19.0]	15.3 [10.2; 18.9]	18.4 [12.9; 21.1]
Post-GTN BA flow velocity, cm/s	7.27±8.12	5.55±6.84	4.76±10.29

Data are mean±SD or median[IQR]. * P<0.05, ** P<0.01, *** P<0.001 vs. HS ; ° P<0.05, °° P<0.01 vs. EH

Conclusions: In conclusion, despite showing similar acute vasodilatory responses to flow and GTN, FD patients differed from EH and HS in terms of arterial morphology with smaller BA diameter associated with similar IMT. This paradoxical remodeling may suggest a chronic defect in the endothelium-dependent pathways involved in arterial remodeling in FD patients.

6D.04 EFFECTS OF INCREASED POTASSIUM AND SODIUM ON ENDOTHELIAL AND VASCULAR FUNCTION

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Objective: Increased potassium intake has been related to improved endothelial function and a high sodium intake is known to impair endothelial function. The effect of increasing potassium in the presence of high sodium in the postprandial state is not known. The aim was to determine the effect of increased potassium and increased sodium on post prandial endothelial function (as assessed by flow mediated dilatation (FMD)) and arterial compliance as assessed by pulse wave velocity (PWV) and augmentation index (AIx).

Design and method: Thirty nine healthy, normotensive volunteers (age 37 ± 15 and BMI 23.0 ± 2.8) received a meal with 3.1mmol potassium and 65mmol sodium (LKHN), a meal with 38mmol potassium and 65mmol sodium (HKHN) and a control meal (LKLN) with 5.5mmol sodium and 3.1mmol potassium on three separate occasions in a randomized order. FMD, PWV, AIx and BP were measured while participants were fasting and at 30, 60, 90 and 120 minutes after the meal. Repeated-measures ANOVA was used to assess the effects of the meal type on the dependent variables over time.

Results: The addition of potassium (HKHN meal) significantly attenuated the post meal decrease in FMD when compared to the high sodium meal ($p < 0.05$ meal by time) (Figure 1). FMD was significantly lower following the LKHN meal when compared to the HKHN meal at 30 minutes ($p < 0.05$). AIx decreased after all meals ($p < 0.05$). There were no significant differences in AIx, PWV or BP between treatments over time.

Conclusions: The addition of potassium to a high sodium meal attenuates the post meal reduction in endothelial function as assessed by FMD. There were no between meal differences on PWV and AIx.

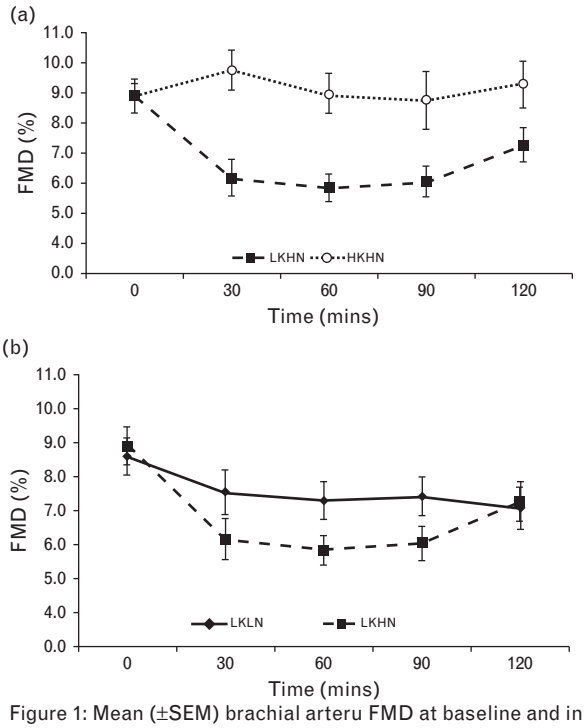

Figure 1: Mean (±SEM) brachial arteru FMD at baseline and in response to consumption of test meais containing 3 mmot of potassium and 65 mmol of sodium (LKHN) versus 38 mmol of potsssium and 65 mmol of sodium (LKHN). n = 39 (18 men and 21 women). Repeated-measures ANOVA: p<0.01 for meal effect; p=0.07 for time; p=o.02 for meal x time interaction. (b) Mean (±SEM) brachial artery FMD at baseline and in response to consumption of tes meals containing 3 mmol of potassium and 6 mmol of sodium (LKLM) versus 3 mmol of potassium and 65 mmol of sodium (LKHN). n = 39 (18 men and 21 women). Repeated-measures ANOVA: p=0.05 for meal effect; p=0.07 for time; p=0.07 for meal x time interaction

6D.05 ENDOTHELIAL DYSFUNCTION IN ANIMAL MODELS OF GLUCOSE INTOLERANCE AND DIABETES IS ACCOMPANIED BY DIFFERENT EXPRESSION OF KEY ENZYMES OF EPOXYEICOSATRIENOIC ACIDS PATHWAY

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Objective: Epoxyeicosatrienoic acids (EETs) are a group of auto/paracrine mediators derived from arachidonic acid with vasculoprotective and vasodilatory properties. Hydroxyeicosatetraenoic acids (HETEs) act predominantly as physiological antagonists of EETs. Our objective was to compare expression of CYP enzymes involved in production and degradation of EETs and HETEs in two animal models with different levels of glucose metabolism impairment - glucose intolerance model (GI) and diabetic model (DIA).

Design and method: 12–13 weeks old male Wistar rats (n = 6–7 per group) were treated by streptozotocin for 3 consecutive days, at dose of either 25 mg/kg/day i.p. postprandially (GI) or 30 mg/kg/day i.p. after overnight fasting (DIA). Control groups (C) received vehicle. After 10 weeks we measured preprandial glycaemia and performed oral glucose tolerance test. We evaluated endothelial function in isolated aortas by acetylcholine and sodium nitroprusside and used RT-qPCR to analyze the expression of enzymes producing EETs (Cyp2j4, Cyp2c23), HETEs (Cyp4a2 and Cyp4a3) and soluble epoxide hydrolase (Ephx2) degrading EETs.

Results: Preprandial glycaemia was markedly increased in the DIA model (C: 6.0 ± 0.2 vs. DIA: 29.57 ± 0.4 mmol/l, $p < 0.001$), animals in the GI model had normal preprandial glycaemia, but impaired glucose tolerance (glucose AUC: C: 1835 ± 55 vs. GI: 3079 ± 415 mmol/l x 270 min, $p < 0.01$). Both models exhibited similar degree of endothelial dysfunction (acetylcholine pD2: C: 6.70 ± 0.16 vs. GI: 6.27 ± 0.08, $p < 0.01$; C: 6.85 ± 0.09 vs. DIA: 6.30 ± 0.08, $p < 0.01$). Ephx2 was significantly upregulated in the GI model (+153% vs. C, $p < 0.05$) although it remained unaltered in DIA model. DIA model furthermore exhibited increased expression of Cyp2j4 (+216% vs. C, $p < 0.01$) and Cyp4a3 (+135% vs. C, $p < 0.05$). We did not observe any changes in the expression of Cyp2c23 and Cyp4a2 in both models.

Conclusions: Despite differences in glucose metabolism impairment, the glucose intolerance model and the diabetic model displayed a similar degree of endothelial dysfunction. In the glucose intolerance model, one of contributing factors could be increased degradation of EETs by elevated expression of Ephx2. Findings in the diabetic model suggest a different mechanism, pointing to a shift in the balance between the EETs and HETEs production caused by changes in Cyp2j4 and Cyp4a3 expression.

6D.06 VITAMIN D DEFICIENCY AND ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS PATIENTS

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Objective: Vitamin D deficiency is commonly associated with rheumatoid arthritis (RA), with an inverse correlation between Disease Activity Score (DAS28) and Health Assessment Questionnaire (HAQ). Vitamin D is known to have a systemic anti-inflammatory action. We aimed to evaluate the effects of vitamin D supplementation on biomarkers of inflammation and endothelial activation [high sensitivity C-reactive protein (hs-CRP) and endothelin-1 (ET-1)], flow mediated dilation (FMD) in patients with RA.

Design and method: We studied 29 subjects (20 females and 9 males, aged 40 to 80) with RA and coexistent hypovitaminosis D, in treatment with tumor necrosis factor (TNF)-α inhibitors. Patients were divided in two groups: 15 subjects treated with oral cholecalciferol (10.000 UI-25drops/week, for 12 weeks), 14 subjects not treated with vitamin D supplementation.

Results: We found no differences in anthropometric and metabolic parameters between the two groups. In the subjects treated with cholecalciferol a decrease in PTH was observed ($p = 0,03$), associated with no changes of serum calcium and phosphorus. Among patients treated with cholecalciferol hs-CRP ($p = 0.03$), DAS28 ($p = 0.01$), ET-1 levels ($p = 0.04$) decreased after treatment, and FMD increased ($p = 0,02$) after treatment. No differences in hs-CRP, DAS28, ET-1 levels and FMD were observed after 12 weeks among subjects that did not receive cholecalciferol therapy.

Conclusions: Vitamin D supplementation exerts beneficial effects in terms of inflammation biomarker levels and disease activity. Furthermore vitamin D supplementation positively modulates endothelial function, decreasing serum ET-1 and improving FMD. In conclusion, our study shows that vitamin D supplementation improves symptoms and inflammation in RA patients and could reduce cardiovascular risk in patients with RA.

6D.07 AMLODIPINE ALONE COMPARED TO AMLODIPINE + ACETYLSALICYLIC ACID ON INFLAMMATION AND ENDOTHELIAL DAMAGE MARKERS IN HYPERTENSIVE PATIENTS

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Objective: To evaluate the effects of amlodipine alone, compared to amlodipine + acetylsalicylic acid (ASA), on some inflammatory and endothelial damage markers in patients affected by essential hypertension.

Design and method: We enrolled 213 hypertensive patients with mild to moderate hypertension. Patients were randomised to amlodipine 5 mg, or amlodipine 5 mg + ASA for three months; then, if adequate blood pressure control was not reached, amlodipine was up-titrated to 10 mg/day for further 3 months and compared to amlodipine 10 mg + ASA 100 mg.
We evaluate, at baseline, after 3 and 6 months: high sensitivity C-reactive protein (Hs-CRP), adiponectin (ADN), tumor necrosis factor-alfa (TNF-alfa), interleukin-1beta (IL-1beta), myeloperoxidase (MPO), soluble CD40 ligand (sCDL40).

Results: After 3 months of therapy, no variations of the above cited markers were recorded with amlodipine alone. Patients treated with amlodipine 5 mg + ASA 100 mg, instead, showed a reduction of Hs-CRP, TNF-alfa, MPO, and sCDL40, and an increase of ADN, both compared to baseline ($p < 0.05$ for all) and to amlodipine alone ($p < 0.05$ for all). Regarding IL-1beta, it decreased with amlodipine 5 mg + ASA 100 mg compared to baseline ($p < 0.05$ for all), but no differences were recorded compared to amlodipine alone. One hundred and seven patients continued the study, and were up-titrated to amlodipine 10 mg + ASA 100 mg or to amlodipine 10 mg alone. We observed a decrease of Hs-CRP, TNF-alfa, MPO, and sCDL40 and an increase of ADN in both groups compared to baseline ($p < 0.05$ for amlodipine alone, and $p < 0.01$ for amlodipine + ASA). Values recorded with amlodipine 10 mg + ASA were better than the ones recorded with amlodipine 10 mg alone ($p < 0.05$ for all). Regarding IL-1beta, it decreased compared to baseline only with amlodipine 10 mg + ASA. No significant serious adverse events were reported.

Conclusions: The addition of ASA to anti-hypertensive therapy gave a better improvement of inflammatory parameters compared to amlodipine alone, suggesting a role of ASA in reducing inflammation and endothelial damage independently from the blood pressure reduction.

ORAL SESSION

LATE-BREAKERS SESSION 2

LB02.01 CHANGES IN BLOOD PRESSURE IN PATIENTS WITH HYPERTENSION RECEIVING USUAL CARE IN RANDOMISED CONTROLLED TRIALS. FINDINGS FROM A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: On reviewing the evidence for allied health professional led interventions in the management of hypertension, we observed that blood pressure (BP) also falls within the usual care arms of included studies. Therefore we have undertaken further analysis to quantify the change in blood pressure in control arms of BP intervention studies included in the review.

Design and method: We used data from our Cochrane review (A115) that included 58 randomised controlled trials in 6897 patients identified in searches up to October 2013. This review included any nurse, pharmacist, or allied health professional-led intervention designed to improve control of BP, compared to usual management of hypertension.
We used the primary outcome of change in systolic and diastolic BP from baseline to final follow up reported in usual care control arms of included trials. Changes in BP were expressed as weighted mean differences pooled using generic inverse variance taking account of within patient correlation.

Results: Mean systolic BP fell by −3.9mmHg (95% CI: −5.5 to −2.4) and diastolic BP fell by −2.7mmHg (−3.4 to −1.9) during usual care. Heterogeneity between studies was marked (systolic I2 = 97% and diastolic I2 = 94%). Usual care consisted of routine care only (45 trials) or enhancement with educational support for health professionals or patients (13 trials). Type of usual care did not account for observed heterogeneity, however restricting analyses to 24 high quality studies indicated a trend towards greater BP reductions with enhanced usual care compared to routine care only: diastolic −4.6mmHg (−6.5 to −2.7) for enhanced vs. −1.9mmHg (−3.1 to −0.7; p = 0.02) for routine care and systolic −6.9mmHg (−11.5 to −2.2) for enhanced vs. −4.2mmHg (−6.9 to −1.6; p = 0.33) for routine care.

Conclusions: Statistically and clinically significant reductions in BP were seen in the control arms of BP intervention studies in this review, with greater reductions when usual care is enhanced within studies. Further work to establish whether this finding can be generalised to other BP intervention studies is required. This trend should be considered when interpreting BP intervention studies and in designing future interventions.

LB02.02 EFFECT OF ARTERIOVENOUS ANASTOMOSIS ON BLOOD PRESSURE REDUCTION IN PATIENTS WITH ISOLATED SYSTOLIC HYPERTENSION COMPARED TO COMBINED HYPERTENSION

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Objective: Several interventional therapeutic options for blood pressure (BP) lowering in patients with treatment-resistant hypertension (TRH) were introduced, such as renal denervation (RDN) and creation of an arteriovenous (AV) anastomosis using the ROX coupler. It was shown that BP response after RDN is greater in patients with combined hypertension (CH) compared to patients with isolated systolic hypertension (ISH). We analyzed now the effect of ROX coupler implantation in the subgroups with CH and ISH.

Design and method: The randomized, controlled, ROX CONTROL HTN study included patients with true TRH (office systolic BP >=140mmHg, and average daytime ambulatory BP >=135/85mmHg, despite treatment with at least 3 antihypertensive drugs including a diuretic). In our post-hoc analysis we have stratified the patients of the ROX coupler group (n = 42) according CH (n = 31) versus ISH (n = 11).

Results: Baseline systolic office (177 ± 18 versus 169 ± 17 mmHg, p = 0.163) and ambulatory BP (159 ± 16 versus 154 ± 11 mmHg, p = 0.463) did not differ between CH and ISH. Creation of an AV anastomosis resulted in a significant reduction in systolic office (CH: −28 ± 22 versus ISH: −22 ± 31 mmHg, p = 0.572) as well as ambulatory BP (CH: −14 ± 20 versus ISH: −13 ± 15 mmHg, p = 0.672), but without significant differences between the two subgroups. The non-responder rate (systolic office BP reduction < 10 mmHg) after 6 months was not different between the subgroups (CH: 18 % versus ISH: 23 %, p = 0.844).

Conclusions: Thus, our data suggest that creation of an AV anastomosis using the ROX coupler reduces systolic office and ambulatory BP, without any significant difference between CH and ISH. In contrast to RDN, creation of an AV anastomosis reduced BP to similar extent in both subtypes of TRH.

LB02.03 EVALUATION OF DAY-BY-DAY BLOOD PRESSURE VARIABILITY IN CLINIC (DO WE STILL NEED STANDARD DEVIATION?)

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Objective: Blood pressure (BP) variability correlates with cardio-vascular disease as BP level itself. There is not known easy way to evaluate the BP variability in clinic.
To evaluate the usefulness of maximum-minimum difference (MMD) of BP in a month compared to standard deviation (SD), as an index of BP variability.

Design and method: Study-1: Twelve patients (age 65.9 ± 12.1 y/o) were enrolled. Measurements of home systolic (S) BP were required in the morning. The 12 months consecutive data and at least 3 times measurements a month were required for including. (Mean 29.0 ± 4.5 times/month in the morning). We checked the correlation between MMD and SD. Study-2: Six hemodialized patients monitored with i-TECHO system (J of Hypertens 2007: 25: 2353–2358) for longer than one year were analyzed. As in study-1, we analyzed the correlation between SD and MMD of SBP. Measurements: 17.4 ± 11.9 times per month. Study-3: The data from our previous study (FUJIYAM study Clin. Exp Hypertens 2014: 36:508–16) were extracted. 1524 patient-month morning BP data were calculated as in study-1. Picking up data measuring more than 24 times a month, 517 patient-month BP data were analyzed. We compared the ratio to 25 times measured data of SD and MMD, in the setting 5, 10, 15, 20 times measured data.

Results: Study-1: SBP, MMD was correlated very well to SD (p < 0.0001, R=0.923). Equation of SBPSD = 1.275+ 0.208xMMD. Study-2: R = 0.884 (P < 0.0001) SBPSD = 2.17+ 0.22xMMD. Study-3: R = 0.842(P < 0.0001), if we used all data measurements > 2 times. If data were extracted (measurements>24 times), correlation was 0.927 (P < 0.0001). The equation of SBPSD = 1.520+ 0.201xMMD. The ratios of SD to 25 times were as follows; 0.956 in 5 times, 0.956 in 10, 0.979 in 15, 0.991 in 20 times. The ratios of MMD to 25 times were as follows; 0.558 in 5, 0.761 in 10, 0.874 in 15, 0.944 in 20.

Conclusions: We can assume SD easily by measuring MMD as an index of day-by-day BP variability of a month. The equation formulas were very similar though the patients' groups were different. But we have to be careful how many times patients measure in a month.

LB02.04 GASTRIN AND D1 DOPAMINE RECEPTOR INTERACT TO INDUCE NATRIURESIS AND DIURESIS

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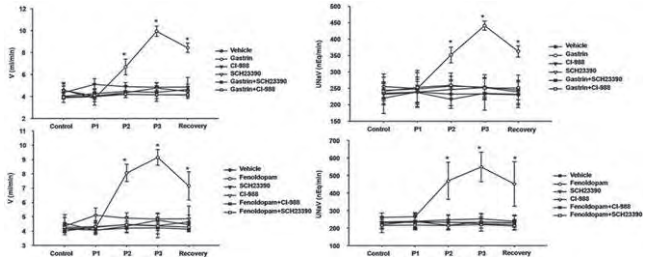
Objective: Oral NaCl intake produces stronger natriuresis and diuresis than venous infusion of the same amount NaCl, indicating the potential existence of renal-gastric axis. Gastrin, from gastrointestinal tract, is dominant one due to its natriuretic effects and taken-up by the renal proximal tubule (RPT) cells. We hypothesize that gastrin interacts with dopamine receptors in kidney, resμlting in synergistically increased sodiμm excretion. The impaired interaction might be involved in the pathogenesis of essential hypertension (EH).



Design and method: Wistar-Kyoto (WKY) rats, spontaneously hypertensive rats (SHR) and RPT cells were stimμlated or blocked through D1-like dopamine and gastrin receptors to observe Na +-K +-ATPase activity and natriuresis.

Results: Gastrin infusing WKY rats via renal artery induced natriuresis and diuresis, which was blocked in the presence of CI-988, a gastrin receptor blocker. Similarly, effect hereinbefore of Fenoldopam, a D1-like receptor agonist, was blocked by D1-like receptor antagonist, SCH23390, indicating gastrin and fenoldopam exert natriuretic and diuretic effect through individual receptors. Lower dosages of gastrin or Fenoldopam failed to induce natriuresis and diuresis alone, while putting together induced the effects. The above-mentioned effects were lost in SHRs. Natriuresis and diuresis was partially blocked by SCH23390 or CI-988, indicating the interaction between gastrin and D1-like receptor. Stimulation of either receptor increased the expression of the other and inhibited Na+-K+-ATPase activity, while the inhibitory effect of Na+-K+-ATPase activity was partially blocked throμgh its corresponding receptors due to respective existence of SCH23390 and CI-988.

Conclusions: It indicated the synergistic effect between gastrin and D1-like receptor would increase the sodium excretion in WKY rats; the impaired interaction might be involved in the pathogenesis of hypertension.

LB02.05 CONTROLLING AND LOWERING BLOOD PRESSURE WITH THE MOBIUSHD DEVICE: FIRST-IN-MAN RESULTS (CALM-FIM STUDY)

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Objective: This is a multi-center (6 centers) non-randomized, first-in-man assessment of a nitinol self-expanding rectangular cuboid implant (MobiusHD) designed to increase carotid sinus arterial wall strain without impacting pulsatility or laminar flow. The geometric changes of the carotid sinus enhance baroreceptor sensitivity thus decreasing sympathetic activity and lowering BP. Patients with stage 2 resistant hypertension (3 or more antihypertensives, of which one is a diuretic, and office SBP 160 mmHg or higher), without obstructive carotid disease received a unilateral carotid sinus MobiusHD implant. Incidence of serious adverse events and unanticipated adverse device effects were collected along with changes in blood pressure (BP) measured during 1-year follow-up.

Design and method: This is a multi-center (6 centers) non-randomized, first-in-man assessment of a nitinol self-expanding rectangular cuboid implant (MobiusHD) designed to increase carotid sinus arterial wall strain without impacting pulsatility or laminar flow. The geometric changes of the carotid sinus enhance baroreceptor sensitivity thus decreasing sympathetic activity and lowering BP. Patients with stage 2 resistant hypertension (3 or more antihypertensives, of which one is a diuretic, and office SBP 160 mmHg or higher), without obstructive carotid disease received a unilateral carotid sinus MobiusHD implant. Incidence of serious adverse events and unanticipated adverse device effects were collected along with changes in blood pressure (BP) measured during 1-year follow-up.

Results: So far 15 patients, mean age 55 (39–76) years, of the anticipated 40 patients received a MobiusHD implant. Mean pretreatment office BP was 181/102 (±18/11) mmHg with a median of 4.5 prescribed antihypertensives (daily defined dose (DDD): 6.6) and 6 patients had failed on renal denervation. During follow-up 3 patients had serious adverse events related to procedure or device: hypotension (n = 2) and closure device failure requiring repair (n = 1). During follow-up eleven (11) patients showed significant BP lowering (i.e. more than 10/5 mmHg decrease in office BP) and 8 required reduction in antihypertensives.

Changes in DDD and BP after MobiusHD implant

	Pre-implant	Δ Day 7	Δ Day 30	Δ Day 90	Δ Day 180	Δ Day 365
Patients (n)	15	15	15	10	9	4
DDD (n)	6.6	6.4	5.7	6.1	6.5	6.9
Office BP (mmHg)	181/102	-27/-15	-21/-9	-12/-3	-19/-9	-32/-19
24-hr BP (mmHg)	155/94	-	-	-2/-1	-10/-6	-

Conclusions: So far, implanting the MobiusHD device in patients with stage 2 resistant hypertension seems to be safe and shows promising results in BP lowering.

LB02.06 CLINICAL IMPLICATIONS OF THE DIASTOLIC BLOOD PRESSURE 'J CURVE' IN TREATED HYPERTENSIVE PATIENTS

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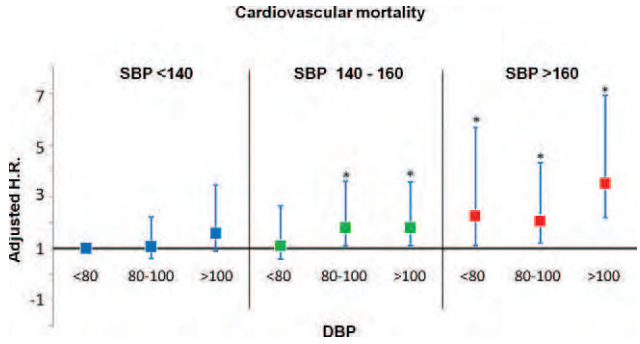
Objective: Recent studies have shown that low diastolic blood pressure is associated with increased cardiovascular outcomes especially in those with pre-existing cardiovascular disease (DBP 'J' Curve). Whether this has practical implications in real life hypertension practice is unknown.

Design and method: We analysed the achieved blood pressure of 6,072 patients between years 2 and 5 following initial presentation to the Glasgow Blood Pressure Clinic. Patients were classified into nine groups based on the area under the curve(AUC) of at least 3 blood pressure(BP) readings during this period. Multivariable adjusted 30 years survival analysis was performed using Cox proportional hazards model.

Results: The age of first visit was 53±13 years, BMI 27.6 ± 5.2, baseline BP 169 ± 29/100 ± 18 mmHg, 52% were females, 60% drank more than 6 units of alcohol/week, 44% were ever smokers, 26% had prevalent CVD and 26% had eGFR<60. Of 6,072 individuals, 418(7%) achieved AUC-BP =<140/80; 365(12%) had isolated systolic hypertension(ISH) (>140/<80mmHg) of whom 98 had severe ISH (SBP>160/ DBP<80). There were only 199(0.7%) subjects with AUC-DBP<70 mmHg. 30 year survival data was available for 5,451 individuals with 1,662 all-cause deaths and 65,430 person-years of follow-up. Figure 1 presents the adjusted hazard ratios for cardiovascular mortality showing significant excess risk associated with DBP<80 only in subjects with SBP>160.



Conclusions: In treated hypertensive patients, the DBP 'J 'curve is not apparent with achieved BP 2 - 5 years from presentation. This may be explained partly by the low likelihood of achieving DBP<70 2-5 years after commencing treatment.

LB02.07 EFFECT OF ACUTE DA2 DOPAMINERGIC RECEPTOR BLOCKADE ON PERFORMANCE OF ADRENAL VEIN SAMPLING FOR SUBTYPING OF PRIMARY ALDOSTERONISM

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Objective: As dopamine tonically inhibits aldosterone release via DA2 receptors, we hypothesized that acute DA2 blockade during adrenal vein sampling (AVS) might improve the assessment of lateralization of aldosterone excess in the subtyping of primary aldosteronism.

Design and method: we prospectively investigated the acute effect of metoclopramide on the lateralization index [LI, defined as the ratio of aldosterone over cortisol plasma concentration (PAC:PCC) in the dominant over the PAC:PCC in the contralateral side] and on the relative aldosterone secretion index in adrenal vein blood [RI, defined as the ratio of plasma aldosterone concentration (PAC) in the adrenal vein over PAC in inferior vena cava (IVC), normalized by the ipsilateral Selectivity Index]. To this end we compared baseline and post-metoclopramide LI and RI values in 92 consecutive patients undergoing AVS from 2008 to 2014. As gold standard we used the diagnosis of aldosterone-producing adenoma (APA), based on pathology and follow-up data according to the four corners criteria.

Results: Metoclopramide increased aldosterone in the IVC and in adrenal vein blood of both sides ($p < 0.0001$ for all). Even though post-metoclopramide LI provided an accurate identification of APA (AUC = 0.880, $p = 0.0001$ vs identity line; Youden Index >2.7, sensitivity 81%, specificity 83%), it showed no incremental diagnostic gain over baseline LI ($p = 0.75$ for ROC curves comparison). Metoclopramide also increased the RI ($p < 0.001$) both from the dominant and the non-dominant side [3.13 (2.53–4.33) to 8.76 (5.31–12.21); 0.91 (0.68–1.36) to 2.19 (1.61–3.23), respectively]. However, metoclopramide raised the RI on the APA side to values > 1.00 in all the 39 unequivocally diagnosed APA patients. Therefore, a post metoclopramide cut-off for the RI < 1.00 offered 100% specificity in excluding an APA on that side.

Conclusions: acute DA2 antagonism exerts a prominent secretagogue effect on aldosterone, but due to a proportionally similar effect on the RI of both sides it did not increase the LI. However, it can increase the specificity of the RI for excluding an APA. This finding might be of particular diagnostic value for AVS studies that are not bilaterally selective.

LB02.08 PREDICTORS OF RECURRENCE OF PHEOCHROMOCYTOMAS/PARAGANGLIOMAS: PRELIMINARY DATA FROM A RETROSPECTIVE MULTICENTER STUDY IN PIEDMONT

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Objective: Pheochromocytomas and paragangliomas (PPGLs) are rare neoplasms often releasing cathecolamines, mainly originating from adrenals but occasionally observed in sympathetic and parasympathetic ganglia, with a genetic base up to 25% of the cases. After radical surgery of these tumors, disease recurrence was believed to be under 10% but recent studies reported a higher rate even after many years. Apart from familiar forms, little evidence exist about predictors of disease relapse, so we aimed to research predictors of recurrence with a retrospective analysis on patients referred to our Centers from 2000.

Design and method: We collected data of patients with diagnosis of PPGL that underwent radical surgery. 76 subjects were recorded (Men/women: 42/34, Age: 45.9 ± 16.2 years) for a mean follow up of 64.9 ± 66.5 months. Genetic test for mutation of known susceptibility genes was performed in 37 cases, resulting positive in 23.

Results: 20/76 (26.3%) patients had disease recurrence. These patients were younger (30.7 ± 14.8 vs 51.4 ± 12.9 years; $p = 0.000$), had higher rate of positive familiarity and genetic mutations (53.3% vs 13.0%; $p = 0.002$ and 75% vs 14.3%; $p = 0.000$, respectively), lower rate of abnormal metanephrines levels (27.3% vs 64.4%, $p = 0.003$), larger tumors (72.4 ± 37.6 vs 45.3 ± 20.2 mm; $p = 0.000$) and lower biochemical normalization rate (66.6% vs 96.3%, $p = 0.004$). We also analysed data on follow-up with Kaplan Meier curves, searching for variables associated with cumulative incidence of recurrence by Log Rank test: age at diagnosis < 45 years ($p = 0.003$), neoplasm dimension > 40 mm ($p = 0.009$), positive familiarity ($p = 0.007$) or genetic test ($p = 0.000$) and lack of biochemical normalization after surgery ($p = 0.004$) were associated to disease recurrence.

Conclusions: Recurrence in PPGLs develops more frequently in young subjects, in patients with mutations in susceptibility genes, larger tumors, normal levels of metanephrines and incomplete normalization of biochemical markers after radical surgery. Patients with these characteristics should be monitored with strictly follow-up.

LB02.09 DETECTING RISK OF POSTURAL HYPOTENSION IN THE ELDERLY (DROP-HE): THE INCHIANTI STUDY

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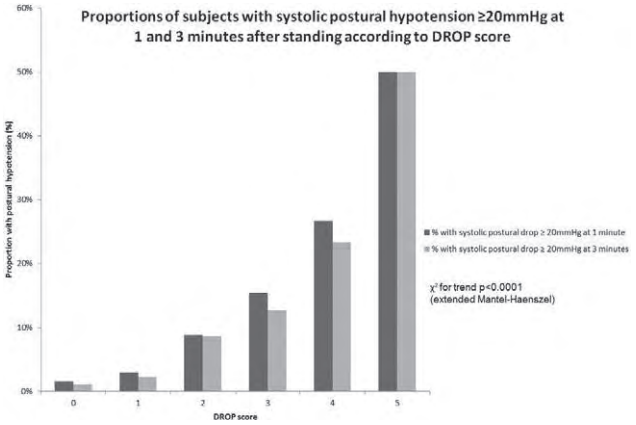
Objective: Postural hypotension (PH) is a risk factor for falls, and associated with excess mortality. Recommendations on testing for PH vary: NICE (2011) advises checking in the presence of falls or symptoms whilst ESH/ESC (2013) advises checking in elderly and diabetics. It is recommended that blood pressure (BP) is measured both 1 and 3 minutes after standing; this is seldom done in clinical practice. We studied the InChianti dataset to identify associations of PH that could inform clinical practice.

Design and method: The InCHIANTI study is a population-based study established to understand causes of walking difficulties in older persons. Subjects were randomly selected from population registries in the Chianti area of Italy in 1998; they underwent extensive baseline interviews and examinations, and are being followed up triennially. BP at recruitment was measured supine and after one and three minutes standing with a mercury sphygmomanometer. Systolic PH was defined as a >=20mmHg fall in supine BP on standing. Survival with or without PH was analysed and Cox proportional hazard ratios (HRs) calculated. Univariable cross

sectional associations for PH were analysed using $\chi 2$ tests. Potentially significant associations ($P<0.1$) were included in multivariable linear regression models. Significant multivariable associations were used to derive a simple prediction score (DROP score).

Results: At recruitment 101/1352 (7.5%) and 89/1352 (6.6%) participants had PH after 1 and 3 minutes standing respectively. PH was associated with increased all-cause mortality over 10 years (HR 2.0 (95%CI 1.5 to 2.7) for both 1 and 3 minutes). On multivariable regression PH was associated with age >=65 years, any fall in the previous year, and previous diagnoses of hypertension, stroke or angina. A simple scoring system of 0 to 5 according to the presence of each of these variables suggested numbers needed to screen of 11 for a score of 2 and 8 for a score of 3 (figure).

Conclusions: The likelihood of PH can be predicted from existing medical history. Presence of diabetes is not a predictor of PH in this cohort. Further work is underway to refine and validate the DROP score.



ORAL SESSION

ORAL SESSION 7A
OBESITY AND METABOLIC SYNDROME

7A.01 INCREASED RISK OF MORTALITY IN OBESE PATIENTS WITH HIGH NOCTURNAL BLOOD PRESSURE VARIABILITY. RESULTS FROM THE ABP-INTERNATIONAL STUDY

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Objective: The association between obesity and all-cause mortality is controversial and may differ according to subjects' characteristics. Blood pressure variability (BPV) may be increased in obese individuals and thus impair prognosis. The purpose of this study was to evaluate whether the relationship between obesity and mortality is influenced by short-term ambulatory BPV.

Design and method: The analysis was performed in 8724 participants (54% men) aged 51 ± 15 years enrolled in 8 prospective studies in Australia, Italy, Japan, and U.S.A. The predictive power of obesity (BMI >=30 kg/m2) for mortality was evaluated from multivariable Cox models in the subjects stratified by high or low nocturnal BPV (above or below the median).

Results: Obese participants (N = 1286) had higher age-and-sex adjusted systolic and diastolic BPV than the non-obese participants (p = 0.002/<0.001). Obese subjects with high systolic or diastolic BPV had higher nocturnal heart rate (p = 0.01/<0.001) than obese subjects with low BPV and were more frequently diabetic (p<0.001) and heavy alcohol drinkers (p < 0.001). During a median follow-up of 6.4 years there were 361 deaths, 4.7% in the obese and 4.0% in the non-obese individuals (P = NS). However, the risk of mortality among the obese subjects greatly differed according to BPV level. In Cox models including age, sex, mean ambulatory BP, smoking, alcohol use, diabetes, cholesterol, creatinine, and nocturnal heart rate, the obese group with high systolic BPV had a doubled risk of mortality compared to the non-obese group (HR,2.0, 95%CI,1.4–2.9, p < 0.001), whereas the risk was not increased in the obese group with low BPV (P = 0.81). Similar results were found for diastolic BPV, with a HR of 1.7 (1.2–2.5, p = 0.002) in the high BPV group and no association at all with mortality (p = 0.87) in the low BPV group. Inclusion of night-time BP dipping in the regressions did not change the strength of the associations.

Conclusions: These data show that high nocturnal BPV greatly increases the risk of mortality related to obesity. High BPV is accompanied by increased heart rate and may reflect the influence of transient BP elevations related to sleep apnea and/or baroreflex dysfunction.

7A.02 CARDIOMYOPATHY IN OBESE AND DIABETIC MALE DB/DB MICE IS INHIBITED BY OXYTOCIN TREATMENT

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Objective: Obesity and diabetes enhance the risk of developing cardiovascular diseases and heart failure. The heart/cardiac oxytocin (OT) system was discovered by our group and shown to regulate cardiovascular cell survival pathways and cardioprotection. OT is also involved in the regulation of cardiac energy metabolism and cardiac OT receptor is downregulated in diabetes. Our hypothesis is that OT prevents development of diabetic cardiomyopathy.
We evaluated whether chronic treatment with OT could prevent the metabolic and cardiac abnormalities associated with diabetes and obesity using the db/db mice.

Design and method: Four-week-old C57BL/KsJ-db/db obese diabetic mice (db/db) and their lean control littermates (db/+) were treated with OT (125 ng/kg/h) or saline during 12 weeks (n = 10/group). Serial blood and tomography analysis were performed. Cardiac function was determined by echocardiography, and biochemical and histological heart and fat analysis were also performed.

Results: Compared to db/+ mice, the saline-treated db/db mice developed obesity, hyperglycemia and hyperinsulinemia. These mice also exhibited a deficient cardiac OT/natriuretic system and developed systolic and diastolic dysfunction resulting from cardiomyocytes hypertrophy, fibrosis and apoptosis. These abnormalities were associated with increased ROS production, inflammation and suppressed AMP-kinase signaling pathway. The db/db mice displayed reduced serum levels of adiponectin and adipsin and elevated resistin. OT treatment increased circulating OT levels, significantly reduced serum resistin, body fat accumulation (19%: p < 0.001), fasting blood glucose levels by (23%; p < 0.001), and improved glucose tolerance and insulin sensitivity. OT also normalized cardiac OT receptors, ANP and BNP expressions and prevented systolic and diastolic dysfunction as well as cardiomyocytes hypertrophy, fibrosis and apoptosis. Furthermore, OT reduced cardiac oxidative stress and inflammation, and normalized the AMP-activated protein kinase signaling pathway. The complete normalization of cardiac structure and function by OT treatment in db/db mice contrasted with only partial improvement of hyperglycemia and hyperinsulinemia.

Conclusions: The results indicate that chronic treatment with OT partially improves glucose and fat metabolism, reverses abnormal cardiac structural remodeling, preventing cardiac dysfunction in db/db mice. These observations clearly suggest a potential role for OT in replacement therapy for the prevention of cardiovascular complications of diabetes and obesity.

7A.03 TRANSGENERATIONAL INHERITANCE OF GENOME-WIDE DNA METHYLATION PROFILES IN PULMONARY VASCULAR ENDOTHELIAL DYSFUNCTION FOLLOWING EXTRAUTERINE GROWTH RESTRICTION

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Objective: Early postnatal life is considered as a critical time window for determination of long-term metabolic states and organ functions. Extrauterine growth restriction (EUGR) causes the development of adult onset chronic diseases, including pulmonary hypertension (PH). However, the mechanisms involved and the possibilities of transgenerational transmission on pulmonary vascular consequences in later life are still unclear. Epigenetic information can be inherited and represents a plausible transgenerational carrier of environmental information. Our study was designed to test whether epigenetics dysregulation mediates the cellular memory of this early postnatal event.

Design and method: To test this hypothesis, the EUGR pups were established by undernutritional until weaning. We isolated pulmonary vascular endothelial cells (PVEC) by magnetic-activated cell sorting (MACS) from EUGR and control rats. MeDIP-chip (Methyl-DNA immune precipitation chip), genome-scale mapping studies to search for differentially methylated loci. A postnatal insult, nutritional restriction-induced EUGR caused development of an increased PH at 9-week of age in male rats (First-generation of EUGR, F1-EUGR male). We intercrossed female adult control and F1-EUGR-male rats to obtain the second-generation (F2) offspring in two groups: C male-C female, EUGR-male -C-female.

Results: We found that significantly decreased pulmonary artery pressure in F2 female offspring in EUGR-male-C-female group (F2-EUGR-female), compared with controls to some degrees. we carried out genome-wide DNA methylation profiles screen for genes in rats between F1-EUGR-male and F2-EUGR-female. The EUGR and control group comparisons revealed consistently and distinctively methylated loci, with 74.8% F1-EUGR-male group and 84.5% F2-EUGR-female group changes in hyper-methylation loci enriched for highly significant group differences. Gene ontology (GO) analysis on no consistent differentially methylated genes (approximately 37%) between F1-EUGR-male and F2-EUGR-female groups showed that are lipid metabolic process, calcium signaling, methylation and PH-associated genes. We validated candidate dysregulated loci with quantitative assays of cytosine methylation and gene expressions.

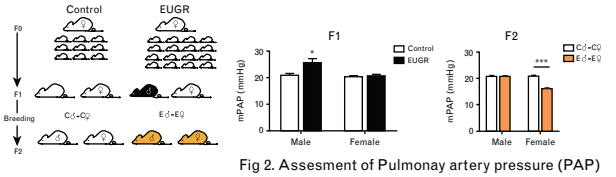

Fig 2. Assesment of Pulmonay artery pressure (PAP)

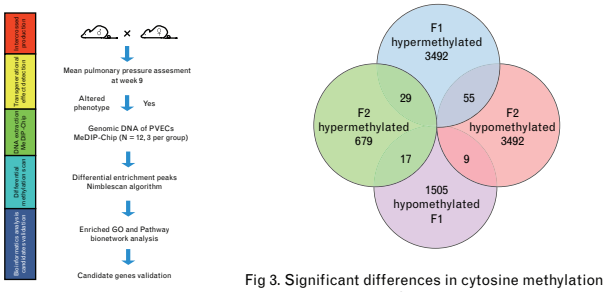

Fig 3. Significant differences in cytosine methylation between EUGR and control rats.

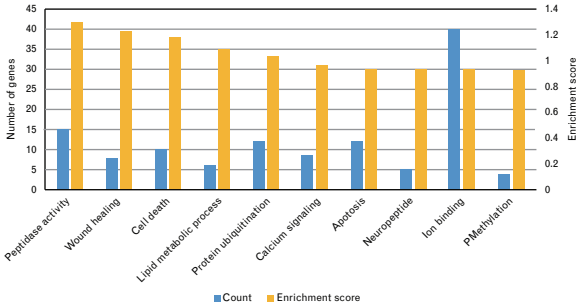

Fig 4. Gene ontology (GO) analysis on no consistent differentially methylated gene between F1-EUGR ♂and F2-EUGR♀ groups

Conclusions: These results, in conjunction with recent human epidemiological data, demonstrate that DNA methylation is a strong mechanism for propagating the cellular memory of early postnatal events, causing changes in expression of genes and transgenerational transmission on pulmonary vascular consequences in later life.

7A.04 DYSFUNCTIONAL ADIPOSE STEM CELL IS LINKED TO OBESITY, ELEVATED INFLAMMATORY CYTOKINES AND RESISTANT HYPERTENSION

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Objective: Obesity is the most important risk factor for hypertension (HTN) and they are strongly associated with chronic inflammation. Treatment resistant hypertension (TRH) subjects, accounting for ~20% of HTN, have high levels of inflammatory cytokines. This coupled with the fact that the role of adipose stem cells (ASCs) in obesity associated TRH has not been investigated, led us to hypothesize that ASCs from obese-HTN patients expressing heightened inflammatory cytokines contribute to pathogenesis of TRH. Thus, we aim to determine the relationship between ASCs, inflammation, obesity, and TRH.

Design and method: 611 Subjects from the Women's Ischemia Syndrome Evaluation (WISE) study were grouped to normotensive [N, n=99, systolic BP (SBP) 120 ± 12mmHg], controlled HTN (CH, n = 247, SBP 123 ± 11mmHg), and TRH (n = 48, SBP 158 ± 21mmHg). Sera from these subjects were analyzed for high sensitive C-reactive protein (CRP), IL6, serum amyloid A (SAA) and TNF-α level. Human ASCs (hASCs, CD90+/CD11b-/HLA-DR-) were cultured from subcutaneous adipose tissues of overweight-normotensive (ON, n = 6) or obese-hypertensive subjects (OH, n = 6). Rat ASCs (rASCs, CD44+/CD90+/CD34-/CD45-) were isolated from inguinal adipose tissue of normotensive,WKY rats and spontaneously hypertensive rats (SHR).

Results: BP positively correlated with the levels of inflammatory cytokines for the WISE analysis. TRH showed two-fold higher CRP (median 0.7), 1.8-fold more IL-6 (median 4.0) and 50% elevated SAA (median 0.8) than N and CH. Additionally, body mass index (BMI) was significantly associated with levels of CRP($r = 0.25$, $p = 0.0001$), IL6($r = 0.14$, $p = 0.0003$), and SAA($r = 0.12$, $p = 0.0004$). hASCs from OH subjects have higher TNF-α, ROS and proliferative capacities than ON subjects. Likewise, rASCs from SHR demonstrated notably higher levels of inflammatory cytokine (TNF-α and IL-1β), ROS and proliferation than WKYrats.

Conclusions: Although the magnitude of correlation differed, there was significant positive correlation among BMI, BP, and levels of inflammatory cytokines. Obese subjects are more likely to have TRH than those with lower BMI. Hyperproliferative ASCs could contribute to elevated inflammation status. These findings imply that ASCs and inflammation plays a critical role in the BP control. Thus, BMI and inflammation status of serum and stem cells may be useful predictors for TRH.

7A.05 VISCERAL FAT LEVEL DETERMINED USING THE BIOELECTRICAL IMPEDANCE AS A METHOD TO ASSESS OBSTRUCTIVE SLEEP APNEA RISK

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Objective: To determine of visceral fat level (VFL) can be used as the obstructive sleep apnea syndrome (OSAS) severity predictor. To compare the diagnostic value of visceral fat determination and other anthropometric data and indexes.

Design and method: The study involved 62 patients (26 women and 36 men) mean aged 52.78 ± 10.69 years with the II-III stage of arterial hypertension, 1–3 degrees. The first group included 22 patients with mild OSAS (apnea-hypopnea index (AHI) < 15), the second – 40 patient with moderate and severe OSA (AHI = 15 and AHI > 15). The cardiopulmonary monitoring was performed to confirm the diagnosis and to clarify the severity of OSA. The screening system ApneaLink (ResMed, Germany) was used. A non-stretchable measuring tape was used to measure waist and hip circumferences (WC and HC). The smallest abdominal circumference between the lowest rib and the iliac crest was used as WC. Waist to hip ratio (WHR) was calculated by dividing WC by the HC at the level of greater trochanters. Body mass index (BMI) is person's body mass divided by the square of his height being given in units of kg/m2.VFL was measured using Omron BF 508 (Netherlands) and the method of bioelectrical impedance.

Results: In group 1 WC was significantly lower than in group 2 (107.52 ± 16.75 and 120.90 ± 16.7, ♂-0.004). Similar results were obtained for HC (113.23 ± 17.53 and 122.76 ± 16.79, $p = 0.016$), WHR (0.95 ± 0.09 and 0.98 ± 0.07, $p = 0.048$) and BMI (35.57 ± 7.59 and 39.62 ± 8.66, $p = 0.033$), respectively. VFL depended on AHI directly ($r = 0.39$, $p = 0.014$). VFL in group 2 was higher than in group 1 (13.91 ± 4.15 and 17.04 ± 5.14, $p = 0.04$). Besides, VFL linked with WC and WHR directly in both groups ($p < 0.05$). Thus, both the elevation of WC, HC, BMI, WHR or VFL leads to the OSAS severity increasing.

Conclusions: The detection of VFL using bioelectrical impedance can be used to determine OSAS risk as well as other known anthropometric data and indexes.

7A.06 MATERNAL OBESITY AND THE DEVELOPMENTAL PROGRAMMING OF HYPERTENSION: ALTERED LEPTIN SIGNALLING PATHWAY IN THE CENTRAL NERVOUS SYSTEM

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Objective: The prevalence of obesity in women among child baring age is increasing and this has been parallel to the increase in obesity in general population around the world. We investigated the trans-generational 'programming' of leptin signalling in the central nervous system (CNS) to increase blood pressure (BP), heart rate (HR) and renal sympathetic nerve activity (RSNA) following a high fat diet (HFD)feeding in mothers.

Design and method: Female New Zealand White rabbits were fed a high fat (13%) diet (mHFD) or a control diet (mCD) prior mating and during pregnancy. Kittens from mCD rabbits were subdivided and fed HFD for 10days (mCD10dHFD) at 15 weeks of age. All rabbits received an intracerebroventricular (ICV) catheter into the lateral ventricle and a recording electrode on the left renal nerve. Experiments were conducted in conscious rabbits and BP, HR and RSNA was measured. Rabbits received an increasing doses of ICV Melanocortin receptor antagonist (SHU9119),alpha-Melanocortin stimulating hormone (alpha-MSH) and a single dose of Leptin antagonist.

Results: ICV SHU9119 reduced BP (-5.8 ± 0.7mmHg and -4.1 ± 0.9mmHg) and RSNA (-2.4 ± 0.3 nu and -0.7 ± 0.3 nu) in mHFD and mCD10dHFD rabbits ($P < 0.001$). Leptin antagonist reduced BP and RSNA only in mHFD rabbits (-2.1 ± 0.5mmHg and -2.7nu, respectively). alpha-MSH injection increased BP, HR and RSNA in both mHFD and mNFD10dHFD rabbits ($P < 0.05$). Total % fat was increased (50%) in all rabbits that had HFD.

Conclusions: Obesity during pregnancy 'programs' leptin signalling pathway in the CNS of the offspring during development. Leptin via activation of melanocirtin pathway plays a key role in the CNS contributing to the pressor and tachycardic effects as well as renal sympathetic nerve activity in the pathophysiology of obesity.

7A.07 LIMITED CONTRIBUTION OF OBESITY TO VARIATIONS IN OFFICE, AMBULATORY AND AORTIC BLOOD PRESSURES IN A BLACK AFRICAN COMMUNITY WITH PREVALENT OBESITY AND HYPERTENSION

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Objective: Obesity causes an increased blood pressure (BP). This effect may be diminished in communities of African descent. However, the impact of obesity on ambulatory or aortic BP, which are enhanced in groups of African ancestry, has not been assessed. We aimed to determine the extent to which obesity is related to variations in office, ambulatory and aortic BP in a community sample of African ancestry with a high prevalence of obesity.

Design and method: In 1167 randomly selected participants of black South African ancestry >16 years of age (42.5% obese and 45.1% with abdominal obesity), we determined the impact of adiposity indexes on age-related increases in office, ambulatory (n = 767) and aortic (n = 1141) BP. Aortic BP was determined using radial applanation tonometry and SphygmoCor software.

Results: Age was strongly related to all BP values and indexes of metabolic abnormalities ($p < 0.0001$). Independent of age, adiposity indexes were associated with insulin resistance, HDL cholesterol, glucose and triglyceride concentrations ($p < 0.0001$ for all). However, across the adult lifespan neither office, 24-hour, day, night, nor aortic BP were increased in participants with an increased waist circumference (WC), or body mass index (BMI)(> = 30 kg/m2) as compared to participants with a normal WC or BMI. Independent of age, WC accounted for only 0 to 1.02% of the variation in office, 24-hour or aortic BP and translated into only a 0.38 to 1.40 mm Hg increase in office or 24-hour systolic or diastolic BP for every 15.9 to 16.6 cm (1 SD) increase in WC. Neither WC (Odds ratio = 1.12, CI = 0.78 to 1.61, $p = 0.54$) nor BMI (Odds ratio = 1.11, CI = 0.78 to 1.58. $p = 0.55$) were associated with hypertension (38.5%) diagnosed according to 24-hour BP thresholds or the presence of treatment. Independent of age, adiposity indexes were not positively associated with factors that account for age-related increases in BP (aortic pulse wave velocity, and aortic forward and backward wave pressures).

Conclusions: Although obesity and hypertension are prevalent in black African communities and obesity independently associates with metabolic abnormalities, obesity plays little role in the pathogenesis of hypertension in these communities.

7A.08 EXPERIMENTAL STUDY TO EVALUATE THE EFFECT OF A PEPSIN EGG WHITE HYDROLYSATE ON CARDIOMETABOLIC COMPLICATIONS IN DIET INDUCED OBESE RATS

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Objective: In this work we evaluated the effect of the administration of a pepsin egg white hydrolysate (HEW) on some cardiometabolic complications developed in diet induced obese rats.

Design and method: 20 male 8-week-old Wistar were divided into two groups that were given until the 20th week of life the following solid and drinking fluids: high fat diet + dextrose 25% in water (O), high fat diet + (dextrose 25% + 1 g/kg/day of HEW) in water (O-HEW). Body weight and solid and liquid intakes were weekly measured. Last week, the presence of allodynia (a sign of peripheral neuropathy) was assessed using a series of calibrated Von Frey hairs. At the end of the study, direct blood pressure was measured, and after different organs and blood samples were collected to determine the effect of the hydrolysate on lipid metabolism, oxidative stress and glycemia

Results: The consumption of HEW attenuated the body weight gain, decreased the abdominal perimeter and the size of epididymal adipose tissue in O-HEW group. Moreover, the plasma malondialdehyde levels were reduced after administration of HEW in obese animals. The hyperglycemia and allodynia developed in these animals were also improved after intake of HEW. The results also showed that the consumption of HEW restored the autonomic imbalance observed in diet induced obesity.

Conclusions: In conclusion, HEW, consumed directly or added to other foods, may affect simultaneously several functions in the organism, and may offer a therapeutic approach to control the different complications linked to obesity condition.

7A.09 METABOLIC SYNDROME IS ASSOCIATED WITH LEFT VENTRICULAR DILATATION IN PRIMARY HYPERTENSION

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Objective: Metabolic syndrome (MS) has been shown to predict cardiovascular events in patients with hypertension. Recently, a new four-group left ventricular (LV) hypertrophy classification based on both LV dilatation and concentricity was proposed. This classification has been shown to provide a more accurate prediction of cardiovascular events, suggesting that the presence of LV dilatation may add prognostic information. We investigated the relationship between MS and the new classification of LV geometry in patients with primary hypertension.

Design and method: A total of 372 untreated hypertensive patients were studied. Four different patterns of LV hypertrophy (eccentric non-dilated, eccentric dilated, concentric non-dilated, and concentric dilated hypertrophy) were identified by echocardiography. A modified National Cholesterol Education Program definition for MS was used, with body mass index replacing waist circumference.

Results: The overall prevalence of MS and LV hypertrophy was 29% and 61% respectively. Patients with metabolic syndrome showed higher prevalence of LVH ($P = 0.0281$) and dilated LV geometries, namely eccentric dilated and concentric dilated hypertrophy ($P = 0.0075$). Moreover, patients with MS showed higher LV end diastolic volume ($P = 0.0005$) and prevalence of increased LV end diastolic volume ($P = 0.0068$). The prevalence of LV chamber dilatation increased progressively with the number of components of metabolic syndrome ($P = 0.0191$). Logistic regression analysis showed that the presence of MS entails a three time higher risk of having LV chamber dilatation even after adjusting for several potential confounding factors.

Conclusions: MS is associated with LV dilatation in hypertension. These findings may, in part, explain the unfavorable prognosis observed in patients with MS.

7A.10 METABOLIC SYNDROME PREDICTS INDEPENDENTLY FROM ITS COMPONENTS ADVERSE EVENTS IN ESSENTIAL HYPERTENSIVE SUBJECTS

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Objective: Metabolic syndrome (MS) is associated with increased risk for atherosclerotic cardiovascular disease, whereas its prognostic role in hypertension remains controversial. The aim of the present study was to assess the relevant impact of each component of MS on the risk for the incidence of adverse events in a cohort of essential hypertensives.

Design and method: We followed up for a median period of 40 months (IQR 28–60 months) 2176 essential hypertensives free of cardiovascular disease (mean age 57.6 years, 1010 males, office blood pressure (BP) = 143.4/89.2 mmHg). All subjects had at least one annual visit and at baseline underwent complete echocardiographic study for estimation of left ventricular mass index and blood sampling for assessment of metabolic profile and glomerular filtration rate. MS was defined according to the updated NCEP III criteria. Endpoint of interest was the incidence of stroke, coronary artery disease (CAD) and their composite.

Results: MS was present at baseline in 819 hypertensives (37.6%) and DM in 305 (14%). The incidence of the composite end-point was 3.1% (20 patients with stroke, 50 with CAD, 2 with both) over the whole follow-up period. Patients with DM were more likely to experience the composite event in comparison to reference category (5.9% versus 1.9%, log rank $p < 0.001$) or MS (5.9% versus 3.7%, log rank $p = 0.018$). Patients with MS were more likely to experience the event of interest in comparison to reference category (3.7% versus 1.9%, log rank $p = 0.024$). When Cox regression models were implemented, MS predicted the composite end-point (HR = 1.94, 95% CIs 1.42–2.67, $p < 0.001$). MS remained a significant independent predictor after multivariable adjustment for age, gender, left ventricular hypertrophy, glomerular filtration rate and hypertension pattern. When individual components of MS were consecutively inserted into the final multivariable model instead of MS per se, none of them predicted independently the endpoint. Increased triglycerides were associated with increased incidence of composite endpoint but when adjustment for additional confounders was performed this association rendered not significant.

Conclusions: Metabolic syndrome predicts independently from its components adverse events in essential hypertensive subjects.

ORAL SESSION

ORAL SESSION 7B
THERAPEUTIC ASPECTS

7B.01 FINAL ANALYSIS ON ADHERENCE TO ANTIHYPERTENSIVE MEDICATION IN TREATMENT RESISTANT HYPERTENSION (TRH) UNDERGOING RENAL DENERVATION (RDN)

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Objective: Adherence to medication has been repeatedly proposed to represent a major cause of TRH and may affect the BP response to antihypertensive interventions. We assessed adherence rates in patients with TRH at baseline at 6 months after RDN and the potential impact BP response.

Design and method: 80 patients with TRH have been included in two prospective observational follow-up studies (clinicaltrials.gov, NCT01442883 and NCT01687725) that focus on potential antihypertensive and nephroprotective effects of renal denervation (RDN). After ethical approval on 23.08.2013 we retrospectively approached each patient to give us informed consent for analyzing urine samples that had been collected at baseline and 6 months after renal denervation for toxicological urine analysis (by liquid chromatography-mass spectrometry analysis (LC-MS)) of antihypertensive compounds or metabolites. In addition to office BP, 24-h ambulatory BP (ABP) (Spacelab) and central hemodynamics (Sphygmocor) were assed as well.

Results: Informed consent was obtained in 79 patients (mean age 60.4 ± 10 years (ABP: 155 ± 14/88 ± 13 mmHg). All meds were detected at baseline in N = 44 or 56 % [6 month after RDN: in N = 52 or 66%] 1 med was missing in N = 22 or 28% [N = 17 or 22%], > = 2 meds in N = 13 or 16% [N = 10 or 13%] of whom N = 3 did not take any meds at all (p = 0.049) and central systolic pressure (p = 0.012) was higher in non-adherent patients (p = 0.049). A shift analysis revealed that adherence remained the same in 47 subjects (in 35 Ss all meds, in 6 Ss 1 med missing and in 6 Ss > = 2 meds missing), whereas in 21 Ss adherence increased and in 11 Ss decreased after RDN. Adherence did not significantly change (Mc Nemar-Bowker Test, p = 0.362). The decrease in 24-h ABP was not different in those taking all medication at 6 months visit (-7 ± 13 mmHg) compared to those with an increased (-10 ± 13 mmHg) and decreased adherence (-7 ± 14 mmHg) (all p > 0.20).

Conclusions: In our tertiary referral center in Northern Bavaria, Germany, non-adherence to medication in patients with TRH was relatively low. Adherence pattern did not change significantly and had no impact on the overall reported BP changes after RDN.

7B.02 THE ASSOCIATION BETWEEN NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND BLOOD PRESSURE CONTROL IN HYPERTENSIVE PATIENTS AND THE RELATION TO GENDER

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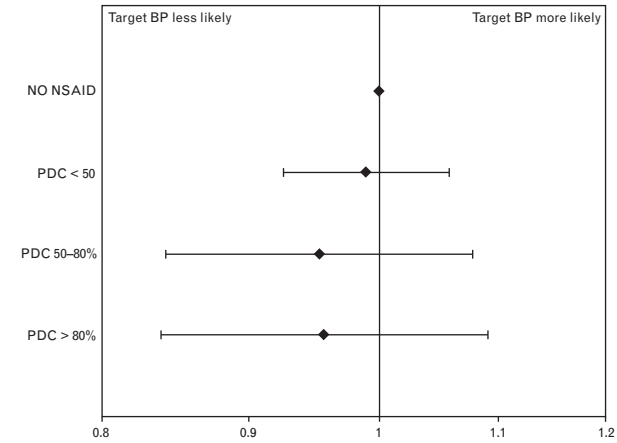
Objective: Approximately 25% of hypertensive patients >65 years are treated for arthrosis, which is the most common cause of long term use of non-steroidal anti-inflammatory drugs (NSAID). NSAID inhibits prostaglandin synthesis and interacts with the renin angiotensin system. The objective of this study was to investigate if concomitant use of NSAID in hypertensive patients is associated with a lower possibility to reach target blood pressure <140/90 mm Hg, and to elucidate if there are gender differences regarding this matter.



Design and method: This cross-sectional cohort study includes 40825 patients with hypertension from the Swedish primary Care Cardiovascular Database (SPCCD) in 2007–2008. Patient characteristics, antihypertensive drug class, dispensations of NSAIDs, comorbidities and blood pressure measurements were analyzed. The proportion of days covered (PDC) with prescription was calculated in order to analyze the NSAID use and the PDC was grouped <50%, 50–80% and >80% of days covered with prescription during 180 days prior to the last blood pressure measurement.

Results: In all 6700 patients had at least one prescription of NSAID. Patients with NSAID were younger (67.9 ± 11.2 vs 69.4 ± 11.9 years, p < 0.0001), and more often female (63.2 vs 56.3%, p < 0.0001) with a diagnosis of musculoskeletal disease (20.8 vs 12.8%, p < 0.0001 and with no cardiovascular comorbidity (26.5 vs 32.1%, p < 0.0001). There was no difference in SBP between patients with and without NSAID (142 ± 16, 142 ± 17 mmHg respectively, ns). Patients with NSAID had a higher DBP (80 ± 10, 79 ± 10 mmHg, respectively p < 0.001). In a logistic regression model adjusted for age, smoking, cardiovascular comorbidity, antihypertensive drug class, education, and country of birth there was no difference in the proportion achieving target blood pressure in patients with and without concomitant use of NSAID irrespective of the PDC for NSAID users (figure 1). The results were similar in both genders.

Conclusions: Concomitant use of NSAID in hypertensive patients does not seem to be associated with a higher blood pressure level. The use of NSAIDs is not associated with a reduced ability of achieving target blood pressure. Thus, hypertensive patients do not à priori need to be discouraged to use NSAID.

7B.03 SAFETY OF BETA-AGONISTS WITH DIFFERENT DURATION OF ACTION IN PATIENTS WITH ARTERIAL HYPERTENSION AND BRONCHO-OBSTRUCTIVE DISEASES

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Objective: To evaluate the safety of beta-agonists (BA) with different duration of action (short-acting (SABA), long-acting (LABA), ultra-long-acting (ULABA) in patients with arterial hypertension (AH) and chronic obstructive pulmonary disease (COPD) or bronchial asthma.

Design and method: 40 patients with AH and COPD (gr.1) and AH and asthma (gr.2) were enrolled and examined initially. At the next three month patients were treated with 3 types of BA: at the 1st month – with salbutamol (SABA), at 2nd month –with formoterol (LABA), at 3rd month –with indacaterol (ULABA). Initially, after one week and at the end of each month blood pressure (BP) and heart rate (HR) on the visit, serum potassium in blood, electrocardiogram, were evaluate. After one week and at the end of three month of treatment with BA all patients underwent Holter monitoring and ambulatory blood pressure 24-monitoring (ABPM). Results are presented as Mean ± sd.

Results: Patients were 64 ± 7,7years (22-male,18-female), with BMI 29,8 ± 5,3 kg/m2; BP in gr.1 was 128,4 ± 14,3/81,1 ± 19,7 and 135 ± 13/83 ± 9,9 mmHg in gr.2, p = NS, initially. Baseline, 1-month, 2-month, 3-month BP and HR levels on the visit were similar among all patients (p = NS). At the end of the third month of treatment with BA different duration of action in gr.1 daily average Systolic BP (SBP) was lowered than initially (129 ± 10,2 vs 124 ± 10,5, p < 0,05). On the contrary in gr.2 daily average SBP became increased than initially (122 ± 14,1 vs 127 ± 16, p < 0,05).Treatment with BA caused significant serum potassium change in blood in both group: in gr.1 initially was 4,5 ± 0,5 mmol/l, after SABA use - 4,2 ± 0,4(p < 0,05), LABA- 4,1 ± 0,4(p = NS), ULABA-4,2 ± 0,4(p < 0,05); in gr.2 initially was 4,4 ± 0,4 mmol/l, after use SABA-4,1 ± 0,3(p < 0,05), LABA- 4,3 ± 0,3(p = NS), ULABA-4,15 ± 0,6(p < 0,05). In gr.2. three patients had hypokalemia.

Conclusions: Treatment with BA in patients with AH and bronchoobstructive diseases significantly decreased levels of serum potassium in the blood in both group and led to reduction of daily average SBP and in contrast treatment of patients with AH and asthma resulted in increasing of daily average SBP. Our results suggested the need for a different treatment of patients with AH and COPD or asthma.

7B.04 EFFECT OF SERTRALINE IN PAROXYSMAL HYPERTENSION

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Objective: Paroxysmal hypertension or pseudopheochromocytoma is a quite common problem in clinical practice. Anxiety or panic disorder may be one of the major causes. Optimal treatment for this condition is not established.

Design and method: Between April 2008 and October 2014 we prospectively enrolled 70 patients referred to our department for symptomatic paroxysmal hypertension. Patients received sertraline (a selective serotonin reuptake inhibitor, 50 mg once daily) as an add-on to their current medication. Effect of this treatment was assessed on next clinical visit at least 3 months later.

Results: Of the 70 enrolled patients, 58 (83%) had also sustained arterial hypertension. Mean office baseline blood pressure (BP) was 146.7/84.3 mmHg and patients used mean 3.0 antihypertensive drugs. 19 patients (27%) were not using sertraline on next clinical visit (6 did not start using sertraline, 10 withdrew because of side effects, 3 were lost to follow-up). Of the remaining 51 patients who were using sertraline on next clinical visit, 46 (90%) reported good effect of this treatment. Symptoms of paroxysmal hypertension fully subsided in 31 (61%) and were partially reduced in 15 (29%). Mean office BP in patients using sertraline decreased by 13.8/8.5 mmHg (P < 0.001 for both).

Conclusions: Sertraline effectively takes away or reduces symptoms of paroxysmal hypertension in majority of patients who use and tolerate this treatment.

7B.05 DIFFERENTIAL EFFECTS NEBIVOLOL AND VALSARTAN ALONE AND IN COMBINATION ON 24-HOUR AMBULATORY RATE-PRESSURE PRODUCT, STROKE LOAD, AND BLOOD PRESSURE-HEART RATE VARIABILITY

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Objective: Beta-blockers are antihypertensive drugs indicated for treatment of cardiomyopathies but little is known about their effects on cardiac workload in the ambulatory setting. We compared the effects of the beta-blocker nebivolol (N), the angiotensin receptor blocker valsartan (V) and combined V/N on 24-hour ambulatory central rate-pressure product (ACRPP, an index of myocardial oxygen consumption rate), stroke load (SL) and blood pressure-heart rate variability (SD and coefficient of variation).

Design and method: Subjects with hypertension (SBP>140 or DBP>90, n = 26 including 21 blacks) were studied in a 3-way, double-blind, randomized crossover study. After 4 weeks of each drug (V 320, N 40, or V/N 320/40 mg daily), ambulatory pulse wave analysis (IEM MobilOGraph) was performed every 20 min for 24-hour with primary (ACRPP) and secondary endpoints analyzed by sequential paired t-analysis. SL = ACRPP/heart rate.

Results: The table displays the main results. All 3 treatments resulted in similar brachial and central BP values. Addition of N to V resulted in lower ACRPP: 24-hour and daytime by 11 and 14% (p < 0.001 each) and nighttime by 4% (p < 0.02). This effect was driven largely by the heart-rate slowing effects of N (by 15–18%, p < 0.001 each). SL, however, was lower with V than either N or V/N (about 10%, p < 0.001 each). Variability (standard deviation and coefficient of variation) of ACRPP and heart rate were lower with N and V/N than V. Separate analysis of blacks revealed values very similar to those of the entire treatment group.

Conclusions: We conclude that 24-hour ambulatory hemodynamic monitoring is feasible in clinical trials. The rate-slowing effects of nebivolol (both N and V/N) cause lower ambulatory cardiac oxygen consumption compared to V alone but at the same time, N and V/N cause an increase in stroke load. Absolute and relative heart rate variability is higher with V than N or V/N. These results are driven primarily by the effects in blacks.

Valsartan (V)	Valsartan + Nebivolol (V+N)	Nebivolol (N)	*P* (V vs. V+N)	*P* (V vs. N)	*P* (N vs. V+N)
Central rate-pressure product (ACRPP, units)					
2762 (479)	2371 (405)	2446 (397)	**0.000**	**0.002**	0.235
Stroke load (units)					
35 (4.6)	39 (3.7)	39 (3.9)	**0.001**	**0.000**	0.588
Central systolic blood pressure (mm Hg)					
132 (15)	134 (15)	136 (14)	0.622	0.248	0.487
Brachial systolic blood pressure (mm Hg)					
143 (16)	145 (16)	147 (15)	0.601	0.224	0.578
Brachial diastolic blood pressure (mm Hg)					
88 (12)	87 (13)	89 (12)	0.623	0.56	0.302
Heart rate (beats/min)					
78 (14)	63 (10)	64 (8)	**0.000**	**0.000**	0.677

7B.06 ROUTINE URINARY DETECTION OF ANTIHYPERTENSIVE DRUGS FOR ESTIMATION OF ADHERENCE TO TREATMENT: A CROSS SECTIONAL STUDY

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Objective: Adherence to antihypertensive treatment (AHT) is usually assessed by scales such as Morisky Medication Adherence Scale questionnaire (MMAS-4) but objective urinary drug levels quantification by liquid chromatography mass spectrometry (LCMS-MS) is now available. Our aim was to compare adherence assessed by LCMS-MS or MMAS-4, in patients with resistant hypertension (RH), compared to patients with well controlled hypertension (CH).

Design and method: RH cohort consisted in 82 patients with daytime ABPM > 135/85 mmHg after 4 weeks treatment with a standardised triple AHT participating to a clinical trial. The CH cohort consisted in 91 patients followed in a routine care practice with controlled office BP (<140/90 mmHg) by a median of 2 (range 1–4) AHT. Urinary levels of 14 AHT or their metabolites were evaluated by LC/MS-MS. MMAS-4 was only available in CH. Patients were aware (RH) or not (CH) of the measurement. Non-adherence was defined as a urinary level of at least one AHT below the limit of quantification.

Results: LCMS-MS results: in the RH cohort, 63 patients (77%) were adherent, 11 (13%) were partly non-adherent and 8 (10%) were fully non-adherent. In the CH cohort, 86 (93%) were adherent, 5 (6%) were partly non-adherent, and 1 (1%) was fully non-adherent. Office SBP in the CH cohort was significantly higher in non-adherent (partially or fully) than in fully adherent patients (median: 140 vs. 130 mmHg, respectively; p = 0.01). Office DBP did not differ. According to LCMS-MS, the full adherence rate was significantly higher in CH compared to RH cohort (p = 0.002). According to MMAS-4 available in 88 CH patients, 76 (86%) were fully adherent, and 12 (14%) were medium or low adherent and no significant difference in office SBP/DBP was observed between the two subgroups. There was low or no agreement between LCMS-MS and MMAS-4, with 15/88 non concordant tests.

Conclusions: In conclusion, measurement of urinary AHT by LCMS-MS gives relevant information on adherence to treatment in patients attending an outpatient clinic. This information is not overlapping with questionnaire tests. It confirms the role of objective non-adherence to treatment in resistance to treatment.

7B.07 CIGARETTE SMOKING REDUCES BLOOD PRESSURE RESPONSE TO ANTIHYPERTENSIVE TREATMENT IN NEWLY DIAGNOSED HYPERTENSIVE PATIENTS

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Objective: Smoking and hypertension are important risk factors in the development of cardiovascular disease (CVD). Control rates of hypertension are quite poor with only <50% of patients achieving target blood pressure (BP) after antihypertensive monotherapy. Smokers may have a blunted response to antihypertensive drugs but this has not been properly investigated. Therefore we studied the interaction between smoking status and BP response in never-treated hypertensive patients.

Design and method: We studied 305 untreated hypertensive subjects (mean age 51 ± 1, mean $\pm$ SEM, F = 124) classified according to their smoking status; non-smoker (n = 134), smoker (n = 64) and ex- smoker (n = 104). Haemodynamic measurements including systolic and diastolic BP and heart rate (HR) were measured before and 1 month after monotherapy with commonly used antihypertensive agents;Data were analyzed using with JMP version 7.1 (SAS) for Windows. Results were expressed as mean $\pm$ SEM, with $p < 0.05$ considered significant.

Results: There was a significant relationship between smoking status and fall in BP; smokers and ex- smokers showed lower reduction than non- smokers for systolic BP (4 ± 1.7 vs. 13.6 ± 1 vs. 17.6 ± 1) and diastolic BP (6.5 ± 1.0 vs. 8.7 ± 0.8 vs. 10 ± 0.7, $p < 0.01$) respectively. In a stepwise regression analysis, baseline systolic BP, smoking status and female gender were the only significant predictors of fall in systolic BP ($R2 = 0.19$, $p < 0.0001$) with smokers exhibiting 2 mm Hg less fall than smokers and ex-smokers. For reduction in diastolic BP, baseline diastolic BP and smoking status were the only significant predictors $R2 = 0.19$, $p < 0.0001$) with smokers showing 2 mmHg less reduction in diastolic BP compared with non-smokers.

Conclusions: Smoking is not only an important cardiovascular risk factor in hypertensive patients but also reduces the response to anti-hypertensive treatment, independent of age, gender and body mass index. Therefore, smoking cessation can achieve not only reduced cardiovascular risk but may also improve BP control in hypertensive patients.

7B.08 HIGH BLOOD PRESSURE AND ITS VARIATION AND THE USE OF BETA BLOCKING AGENTS AND STATINS DECREASE QUALITY OF LIFE IN DRUG-TREATED HYPERTENSIVE PATIENTS

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Objective: To clarify explanatory factors to quality of life in Finnish drug-treated hypertensive patients.

Design and method: SF-36 questionnaire was filled out by 174 hypertensive patients (66 females, 108 males, aged 64.5(8.5)years). All used at least one antihypertensive agent. 24 hour ambulatory blood pressure(ABPM) and pulse wave-velocity(PWV) were performed and laboratory tests taken.

Results: 24-hour ambulatory SBP was 132.1(12.6)mmHg and DBP 76.6(7.2) mmHg and LDL-cholesterol 2.6(0.7) mmol/l. Carotid-femoral-PWV was 11.3(3.7)m/s.
The mean(SD) of the eight SF-36 questionnaire scores was 74.1(18.4) (maximum 100). All scores correlated significantly($p < 0.001$)to each other. The use of beta-blockers correlated negatively to most of the quality of life parameters and the use of statins negatively to role-physical, general health and vitality.
According to the regression model physical functioning was explained by lower ABPM nighttime pulse pressure(PP), daytime DBP standard deviation(SD) and home measured evening PP(model explained 83.6 % of the variation). Role-physical by not using either acetosalicylic acid or clopidogrel (25.5%). Bodily pain rate by lower ABPM daytime mean arterial pressure SD and higher SBP SD and 24 hour heart rate SD, lower age and not using diuretics(64.2%). General health by lower GHbA1c, not using beta-blockers and lower ABPM nighttime PP SD(22.6%). High vitality by lower carotid radial PWV and ABPM daytime DBP SD(41.3%). Social functioning by lower carotid radial PWV and not using ASA or clopidogrel (65.2%). High role-emotional by not using beta blockers or ASA or clopidogrel (54.4%). Mental health by lower carotid radial PWV(56.4%), Reported health transition by higher ABPM nighttime PP SD and the use of ASA or clopidogrel (14.6%). The mean of all the eight SF-36 questionnaire scores by lower home measured evening SBP and not using ASA or clopidogrel (61.2%).

Conclusions: The SF-36 scores of the Finnish drug-treated hypertensive patients did not differ markedly from the same age American healthy population and hypertensive patients used in validation of questionnaire. High BP and its variation seemed to decrease quality of life. Also control of other cardiovascular risk factors seemed to be important. The use of beta- blocking agents and statins seemed to decrease quality of life.

7B.09 BLOOD PRESSURE LOWERING EFFICACY OF AMLODIPINE AND NIFEDIPINE-GITS IN AMBULATORY HYPERTENSION

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Objective: We investigated whether the long-half time dihydropyridine calcium-channel blocker amlodipine was more efficacious than the gastrointestinal therapeutic system (GITS) formulation of nifedipine in lowering morning blood pressure in ambulatory hypertension.

Design and method: The study was designed as a multicentre, randomized, parallel-group comparison trial in patients with stages 1 and 2 clinic (mean of 6 readings on 2 occasions off antihypertensive medication, systolic blood pressure 140–179 mm Hg and/or diastolic blood pressure 90–109 mm Hg) and ambulatory hypertension (24-hour mean blood pressure of at least 130 mm Hg systolic or 80 mm Hg diastolic). Eligible patients were randomly assigned to 8-week treatment with amlodipine 5 mg/day or with nifedipine GITS 30 mg/day, which could be up-titrated, respectively, to 10 mg/day or 60 mg/day at 4 weeks of follow-up. The primary efficacy variable was the change from baseline to the end of 8-week treatment in morning systolic blood pressure (4:00 to 8:00) of the first 24-hour ambulatory monitoring.

Results: In the intention-to-treat analysis, blood pressure at 4 and 8 weeks of follow-up was similarly reduced in the amlodipine (n = 257) and nifedipine GITS (n = 248) groups for clinic measurement and 24-hour, daytime, night-time, and morning ambulatory measurements ($P> = 0.07$). However, amlodipine, compared with nifedipine GITS, was 2–3 mm Hg more efficacious in lowering ambulatory blood pressure within 4 hours of drug ingestion and after a dose of medication was missed ($P< = 0.05$). The results of the per-protocol analysis were confirmatory.

Conclusions: Both amlodipine and nifedipine GITS are efficacious in reducing clinic and ambulatory blood pressure. However, when a dose of medication is delayed or missed, amlodipine, but not nifedipine GITS, remains efficacious in lowering blood pressure.

7B.10 THIAZIDE DIURETICS AND FRACTURE-RISK AMONG HYPERTENSIVE PATIENTS. RESULTS FROM THE SWEDISH PRIMARY CARE CARDIOVASCULAR DATABASE (SPCCD)

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Objective: To investigate whether treatment with thiazide diuretics reduces the risk of osteoporotic fractures in hypertensive patients in primary health care. Further we aimed to examine the impact of duration of thiazide use, the consequences of discontinuation of use and effect-modifications by gender.

Design and method: This retrospective cohort study includes 60 893 individuals, diagnosed with hypertension during 2001–2008 included in the Swedish Primary Care Cardiovascular Database. All patients were followed from a fixed baseline (1 Jan 2006, or the date the patient received their first diagnosis of hypertension if that date came later) until they had an incident osteoporotic fracture, died, or reached the end of the study at 31 Dec 2012, whichever came first. Patients exposed to thiazide diuretics (dispensed drugs recorded through the Prescribed Drug Register) were compared with hypertensive patients never exposed to thiazides.

Results: During follow up 2421 osteoporotic fractures occurred. Current use of thiazide diuretics was found to be associated with significantly reduced risk of osteoporotic fractures (adjusted hazard ratios 0.88; 95% CI 0.81–0.97) independent of blood pressure level. In addition, risk appeared to decline with longer duration of use. In contrast, discontinuation of dispensed prescriptions of thiazides was associated with increased risk of osteoporotic fractures (HR 1.17; 95% CI 1.04–1.31).However, a trend towards attenuation of the increased risk with longer duration past treatment period was seen. When analyzing men and women separately similar results were seen, for both genders, although only statistically significant for men.

Conclusions: In this large retrospective cohort study of hypertensive men and women from Sweden, we could identity a protective effect on osteoporotic fractures among current users of thiazide diuretic drugs independent of blood pressure level. However, the risk of fracture was found to be increased in patients shortly after discontinuation of treatment compared to patients never prescribed thiazide diuretic drugs. The reason for an augmented outcome on osteoporotic fractures among patients with former thiazide diuretic therapy needs to be further elucidated.

ORAL SESSION

ORAL SESSION 7C
LARGE ARTERIES

7C.01 ARTERIAL STIFFNESS IN ISOLATED OFFICE SYSTOLIC HYPERTENSION

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Objective: The aim of this study was to study arterial stiffness in patients indentified as isolated systolic hypertensives.

Design and method: 1056 consecutive subjects (48.6% male) aged 47.26 ± 23.4 years were included in the study. 64.7% of the subjects were never treated before for hypertension. A physician measured office BP three times in each subject using a mercury sphygmomanometer. Pulse wave velocity (PWV) was measured after 15 min of rest in the supine position. Patients were classified as having either normal or elevated systolic and diastolic BP, office isolated systolic (>140mmHg systolic and < 90 mmHg diastolic BP) and diastolic hypertensive (<140mmHg systolic and >90 mmHg diastolic BP) subjects.

Results: Carotid-femoral (c-f) PWV was 8.045 ± 4.591 m/sec in patients with both normal office systolic and diastolic BP (n = 438), 11.481 ± 6.356 m/sec in patients with isolated office systolic hypertension (n = 202), 7.421 ± 5.108 m/sec in patients with isolated office diastolic hypertension (n = 60), and 9.192 ± 6.113 m/sec in patients with both elevated office systolic and diastolic BP. The difference between isolated office hypertensive subjects and those with both normal systolic and diastolic BP was 3.446 ± 0.471 (SE) m/sec (P < 0.001). The difference between subjects with both elevated systolic and diastolic blood pressure and those with both normal BP was 1.147 ± 0.389 (SE) m/sec (P < 0.05). In univariate analysis of variance age (B = 0.076, P < 0.001) and isolated office systolic hypertension (B = 1.622, P < 0.001) were independent determinants of c-fPWV. c-fPWV was found 8.688 ± 0.266 (SE) in patients with both normal office systolic and diastolic BP and 10.575 ± 0.386 (SE) m/sec in patients with isolated office systolic hypertension after adjustment for age, gender, and BMI. The difference in c-fPWV between patients with isolated office systolic hypertension and subjects with normal office systolic and diastolic BP was 1.887 ± 0.489 (SE) after adjustment for age, gender, and BMI. This difference was significant at the 0.001 level after Bonferroni's adjustment for multiple comparisons.

Conclusions: Arterial stiffness was found increased in patients with office isolated systolic hypertension suggesting a role for increased office systolic BP in the pathophysiology of large arteries arteriosclerosis independent of age, gender and obesity or a role of stiffer arteries in the pathogenesis of isolated systolic hypertension.

7C.02 TRAINING AND ENVIRONMENTAL ENRICHMENT TO COUNTERACT COGNITIVE DECLINE: TRAIN THE BRAIN. EFFECTS ON CAROTID STRUCTURE AND FUNCTION

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Objective: Physical activity is beneficial to vascular health; on the other hand, vascular damage is associated with cognitive impairment. Both physical activity and a cognitively stimulating environment are known to delay the onset of dementia. The Train The Brain study evaluates the effectiveness of a comprehensive program of physical training and mental activity in delaying cognitive decline in elderly people with mild cognitive impairment, at the same time investigating the relationship between physical, vascular, neurological, and cognitive fitness

Design and method: Elders age 65–89 were recruited with the help of family physicians and territorial services. All participants underwent a neurological and cardiologic evaluation. In the vascular study, carotid pressure was measured with the SphygmoCor system (AtCor, Australia); longitudinal ultrasound scans of the common carotid were performed and 10-second video clips were recorded to be analyzed offline through the Cardiovascular Suite software (Quipu srl, Italy), with the computation of diameter, intima-media thickness, wall cross-sectional area, distensibility coefficient, compliance, stiffness, and elastic modulus. Subjects classified as mild cognitive impairment at the neurological examination were randomized either to standard care, or a 7-month program of physical training and environmental stimulation (lectures, games, music, social activities) three hours a week. The evaluation was then repeated.

Results: Data were obtained for 57 patients who underwent training (T) and 30 controls (C). The only significant difference at baseline was in the distensibility coefficient (p = 0.045).

	Training		Control		P time x
	Baseline	Post	Baseline	Post	treatment
Diameter, mm	8.03±0.77	7.84±0.85*	7.95±0.95	8.15±0.86*	0.007
IMT, mm	0.77±0.15	0.75±0.11	0.76±0.18	0.82±0.17	0.049
Wall cross-sectional area, mm^2	17.1±3.5	16.1±3.4	16.7±5.2	18.3±5.0	0.010
Distensibility, Pa^{-1}	18.8±5.7	20.2±6.6	23.7±11.4	18.3±6.1*	0.001
Compliance, mm^2kPa^{-1}	0.89±0.28	0.91±0.31	1.07±0.48	0.88±0.27	0.032
Stiffness, m/s	7.67±1.13	7.42±1.06	7.10±1.51	7.75±1.32	0.009
Elastic modulus, kPa	544±250	493±156	445±176	530±212	0.027
Mean arterial pressure, mmHg	95.8±9.5	91.3±10.2*	94.9±9.4	90.6±10.5	0.935
Carotid pulse pressure, mmHg	56.9±14.1	54.0±11.3	59.9±18.5	57.6±13.9	0.844

(* = p<0.05 vs baseline)

Vessel diameter increased in C and decreased in T; distensibility decreased in C; all carotid parameters were influenced by the combination of time and treatment, in a diverging trend, at a statistically significant level, while there was no effect on pressure. Introducing arterial pressures as covariates did not affect the findings.

Conclusions: There was a significant difference in behavior in time of the two groups as for vessel enlargement, wall thickening and arterial stiffening. The proposed program of physical training and environmental enrichening seems to oppose the typical harmful effects of aging on the wall of the common carotid in elderly people with mild cognitive impairment.

7C.03 RESERVOIR PRESSURE ANALYSIS APPLIED AT FIVE LOCATIONS IN THE HUMAN AORTA

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Objective: Despite clear associations with adverse cardiovascular outcomes, the mechanisms driving aortic pressure propagation remain incompletely defined. The reservoir-wave approach has been proposed as a representative model of central aortic pressure generation however its application at differing aortic locations has not been investigated.

Design and method: We analysed invasively acquired aortic pressure waveforms from 40 patients undergoing clinically indicated catheterisation. Waveforms were acquired at the level of the ascending aorta, transverse aortic arch, diaphragm, renal arteries and aortic bifurcation using a solid-state transducer. Reservoir-wave analysis was performed according to previously described techniques to determine reservoir and excess pressures and systolic and diastolic rate constants (ks and kd). ks is inversely related to the product of aortic characteristic impedance and total arterial compliance while kd is inversely related to the product of systemic arterial resistance and arterial compliance and is the reciprocal of the diastolic time constant. Repeated measures 1-way-ANOVA with Dunnett's test for multiple comparisons was used to compare parameters at the 5 aortic sites.

Results: Systolic blood pressure increased predictably from the ascending aorta to the bifurcation, whilst diastolic blood pressure remained constant. ks

(corresponding to characteristic impedance) increased while kd decreased with distal progression. The excess pressure integral increased with distal progression ($P < 0.001$) whereas the reservoir pressure integral decreased and maximal reservoir pressure did not vary. The timing of peak reservoir pressure (relative to the initial systolic upstroke) decreased progressively from the aortic root ($P < 0.001$) whilst the timing of maximal excess pressure did not change.

Summary of Reservoir Pressure Parameters by Aortic Location

Aortic Position	Systolic Blood Pressure (mmHg) Mean (SD)	Diastolic Blood Pressure (mmHg) Mean (SD)	Reservoir Pressure Integral (mmHg.s) Mean (SD)	Maximum Reservoir Pressure (mmHg) Mean(SD)	Excess pressure Integral (mmHg.s) Mean (SD)	Peak Reservoir Pressure time (ms) Mean(SD)	k_s Mean (SD)	k_d Mean (SD)
Ascending Aorta	131.6 (27.4)	65.5(11.5)	20 (6.2)	49.2 (14.5)	5.9 (2.8)	59 (6.1)	15.5 (4.7)	2.6 (0.9)
Aortic Arch	130.8 (25.4)	65.4(10.9)	19.6 (6.3)	47.8 (13.7)	6.0 (2.8)	57 (5.7)*	13.9 (3.8)*	2.6 (0.8)
Diaphragm	140.4 (20.3)*	69.9 (8.8)#	19.7 (5.7)	48.9 (11.6)	7.0 (2.8)*	56 (5.6)*	12.1 (2.3)*	2.8 (0.7)
Renal arteries	138.7 (23.2)*	67.2 (9.7)	18.5 (5.7)*	46.9 (12.2)	7.6 (2.7)*	54 (5.4)*	10.4 (1.5)*	2.9 (0.7)*
Bifurcation	141.3 (24.8)*	67 (9.6)	18.3 (5.7)#	46.9 (12.3)	8.2 (2.8)*	54 (6.2)*	9.7 (1.4)*	3.0 (0.7)*

k_s = Systolic Rate constant
k_d = Diastolic Rate constant
# P < 0.01 * P < 0.001

Conclusions: The increase in maximum excess pressure (probably wave related) between the ascending aorta and bifurcation and the constant time to peak excess pressure suggests that wave transmission is relatively more important in determining distal conduit arterial pressures. The decrease in ks with distal progression is consistent with gradually rising impedance whilst the increase in kd is suggestive of progressively decreasingly compliance. These findings support previous data suggesting a relatively minor role for wave reflection in determining the amplitude of the aortic pressure waveform.

7C.04 DIAGNOSTIC VALUE OF PRESSURE WAVEFORM BASED ANALYSIS FOR IMPAIRED SYSTOLIC FUNCTION

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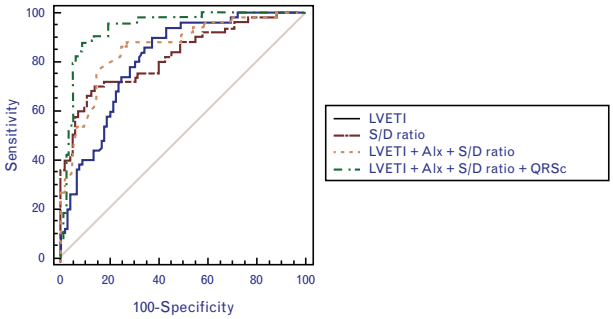
Objective: We recently developed and validated a technique to separate the forward and backward components of the arterial pulse, based on pressure waves alone. While we found the results useful in the workup of heart failure with preserved ejection fraction, little is known about the diagnostic yield in patients with impaired systolic function.

Design and method: Based on non-invasive radial waveforms from tonometry and a Windkessel model derived flow signal, we quantified the forward and backward waves in the aorta of 61 patients with severly reduced systolic function (rEF) and 122 controls with normal ejection fraction, matched for age, gender, and brachial blood pressures. Forward waves were quantified, using wave intensity analysis, resulting in systolic S-wave (increasing pressure and flow) and systolic D-wave (decreasing pressure and flow). Backward waves were quantified, using pulse wave analysis, resulting in Augmentation Index (AIx) and Pressure Augmentation (AP). Ejection duration was indexed to heart rate (LVETI). In addition, QRS duration from 12 lead ECGs was measured and normalized for heart rate, using the formula QRSc = QRS / sqrt(RR-interval).

Results: For the same levels of brachial blood pressures, rEF was associated with shorter LVETI, lower S / D ratio, and lower AIx and AP. Based on ROC curve analysis, AUCs for the detection of rEF for LVETI, AIx, AP, and S/D ratio were 0.81, 0.73, 0.7, and 0.83, respectively ($p < 0.0001$ for all). Combining LVETI with AIx and S/D R increased AUC to 0.86 (CI 0.80–0.91). Adding QRSc significantly ($p = 0.003$) increased AUC to 0.94 (CI 0.89–0.97) and lead to a correct classification of 89.5% of the patients, see figure.



Conclusions: Characteristics of the pressure waveform, which potentially can be derived from oscillometric cuffs with automated algorithms, may help in the diagnosis of patients with impaired systolic function. Adding simple ECG characteristics significantly improves the prediction model. Ultimately, oscillometric blood pressure cuff-derived measures may indicate the need for further investigations, e.g. echocardiography.

7C.05 PREDICTORS OF INCREASED ARTERIAL STIFFNESS IN HYPERTENSIVE PATIENTS

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Objective: To evaluate arterial stiffness in hypertensive patients and to identify predictors of increased arterial stiffness.

Design and method: 798 hypertensives identifyed in SEPHAR II survey (mean age 51.46 ± 5.82 years; 48.1% females) were evaluated by a study questionnaire, blood pressure and antropometric measurements and laboratory work-up. Studied parameters definitions were: increased arterial stiffness: PWVao > 10m/s, visceral obesity: waist circumference >102 cm in men and > 88 cm in women, diabetes mellitus assessed by current ADA criteria, lipid dissorders by NCEP ATPIII recomendations and increased BP variability: mean SBP' standard deviation (s.d.) values above the 75th percentile. Subclinical organ damage definitions were: left ventricular hypertrophy (LVH) on ECG assessed by Cornell product,urinary albumin to creatinine ratio (UACR) of 30 – 300 mg/g) and eGFRCKD-EPI < 60–90 ml/min/1.73m2. Cardiovascular risk was assessed by SCORE system. Binary logistic regression using stepwise LR method (coliniarity analysis and adjustmens for major confunders) was used to validate predictors of increased arterial stiffness.

Results: Mean values of studied parameters were: BP-$149.96 \pm 20.94/89.18 \pm 11.54$, SBP's.d -7.73 ± 8.6mmHg (24.9% of subjects with increased SBP variability), PP-60.99 ± 17.95mmHg, HR-73.75 ± 10.89bpm. Mean PWVao-10.19 ± 2.22m/s, 27.2% of the study sample having PWVao >10m/s. Regression analysis validated as predictors of increased PWVao: age group [OR: 5.53; 95%CI (2.62–13.21)], hypertrygliceridemia [OR: 1.82; 95%CI (1.18–2.81)], low-HDL cholesterol [OR: 1.62; 95%CI (1.05–2.49)], SBP's.d values above 8,49mmHg [OR: 2.14; 95%CI (1.16–3.95)], UACR 30–300 mg/g [OR: 3.46; 95%CI (1.43–8.36)], LVH on ECG [OR: 2.14; 95%CI (1.79–7.34)], eGRFCKD-EPI < 60–90 ml/min/1.73m2 [OR: 1.49; 95%CI (1 -2.23)], lack of BP treatment control [OR: 5.53; 95%CI (2.62–13.21)] and high/very high CV risk category by SCORE [OR: 1.69; 95%CI (1.02–2.83)].

Conclusions: Age above 40 years, atherogenic dislipidemia, increased SBP variability, the lack of optimal BP treatment control and the presence of subclinical organ damage, may be considered as predictors of an increased arterial stiffness in hypertensive patients, placing these patients at an increased risk of major CV events.

7C.06 SOLUBLE RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS AND INCREASED AORTIC STIFFNESS IN A GENERAL POPULATION

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Objective: It has been suggested that accumulation of advanced glycation end-products (AGEś) are involved in several pathophysiological processes in vessel wall. We hypothesized that low levels of the soluble receptor for AGEś (sRAGE) might be associated with increased arterial stiffness as manifestation of vascular ageing in general population.

Design and method: In a cross-sectional design, we analyzed 1077 subjects from the Czech post-MONICA study. Aortic pulse wave velocity (aPWV) were measured using a Sphygmocor device. sRAGE concentrations were assessed in freshly frozen samples by ELISA methods(R&D Systems)

Results: Aortic PWV significantly ($p < 0.0001$) increased across the sRAGE quartiles. 1 m/sec of aortic aPWV was associated with 37% increased risk of low sRAGE (<918 pg/mL, bottom quartile) with p value=0.018. In a categorized manner, subjects in the bottom quartile of sRAGE had more than two-times higher risk of raised aortic PWV (= > 9.3 m/sec), but only in non-diabetic hypertensive patients (corresponding odds ratio, adjusted for all potential confounders was 2.05 (95%CI: 1.26-3.32), $p = 0.004$. In contrast, low sRAGE was by similar regression models rejected as independent predictor of raised aortic aPWV in normotensive or diabetic subject.

Conclusions: Low circulating sRAGE was independently associated with increased arterial stiffness in general population- based sample, but only in hypertensive non-diabetic patients.

7C.07 ASSOCIATION OF SERUM FREE FATTY ACID LEVEL WITH REDUCED REFLECTION PRESSURE WAVE MAGNITUDE AND CENTRAL BLOOD PRESSURE: THE NAGAHAMA STUDY

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Objective: Central blood pressure (BP) has been suggested to be a better predictor of cardiovascular disease risk than brachial BP. Arterial stiffness increases central BP by early returning of the reflection pressure wave from peripheral arteries. Curiously, type 2 diabetes and insulin resistance have been favorably associated with central hemodynamics. Major initiators of insulin resistance—such as serum free fatty acid (FFA)—are thus suspected of potentially being involved in central hemodynamics. To confirm that insulin signaling is an important modulator of central hemodynamics, we investigated this hypothesis in a large-scale general population.

Design and method: Brachial BP and radial arterial waveform were measured simultaneously in 9,393 middle-aged to elderly individuals. The augmentation index (AIx) was calculated from the radial waveform as the ratio of the height of the late systolic peak to that of the first peak. Central systolic BP was defined as the absolute pressure of the late systolic peak of the waveform. Differences in central and brachial pulse pressure (PP) were considered to represent PP amplification.

Results: PP amplification differed significantly among serum FFA level quartiles (Q1, 7.8±5.3; Q2, 8.6±5.0; Q3, 9.3±5.7; Q4, 10.3±6.1 mmHg, $P<0.001$). As type 2 diabetes was also positively associated with PP amplification (diabetes, 10.5±6.2; control 8.9±5.6 mmHg, $P<0.001$), the maximum difference reached 4.9 mmHg in combination analysis of FFA quartile and diabetes status. In contrast, AIx exhibited an inverse association with FFA quartile (Q1, 83.8±12.8; Q2, 82.2±12.9; Q3, 81.1±13.3; Q4, 79.3±13.4 %, $P<0.001$). Multivariate analysis adjusted for major covariates indicated that higher serum FFA was an independent determinant for higher PP amplification (β=0.145, $P<0.001$) and lower AIx (β=-0.122, $P<0.001$) and central systolic BP (β=-0.044, $P<0.001$), while the association between FFA and PP amplification significantly decreased (β=0.022, $P<0.001$) after further adjustment for AIx.

Conclusions: Serum FFA is an overlooked factor favorably influencing central hemodynamics. A low-magnitude reflection pressure wave might be involved in this paradoxical relationship.

7C.08 STIFFNESS MODIFICATIONS ALONG AORTIC ARCH ARE DIFFERENT IN HYPERTENSIVES AND CONTROLS

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Objective: Aortic Arch (AoA) stiffness has a major impact on blood pressure (BP). Our objectives were to assess the interplay between age, BP, stiffness and anatomy in normo and hypertensives.

Design and method: AoA Cardiovascular MRI was performed. Ascending (AA), descending (DA) aortic diameters were calculated using automated segmentation of axial view acquired SSFP cine acquisition. AA and DA strains were calculated as (Systolic–Diastolic)/Diastolic areas and were used to calculate distensibility (Di): Di =strain/cPP where cPP is the central pulse pressure obtained by tonometry (sphygmocor §). AoA-width (W) was the distance between the centre of AA and DA cross-sections. AoA height (H) defined the length of the orthogonal projection of the AoA centreline inflection point, positioned at the arch top, on the width of the AoA arch. AoA-length (L) was estimated using dedicated software as the distance between AA and DA locations used for strain measurements. Central BP was used to define BP levels. To evaluate relative changes between indices in the AA and in the DA, AA/DA diameters, strains and Di ratios were calculated.

	Normotensives	Hypertensives	Across groups p value
Aorta Structure			
Ascending Aorta diastolic diameter. -cm	2.57 ± 0.06	2.17 ± 0.04	<0.0001
Descending Aorta diastolic diameter. -cm	2.05 ± 0.06	2.35 ± 0.04	<0.0001
Aortic Arch Length. - cm	118.4 ± 4.9	134.1 ± 3.2	0.0090
Aortic Arch Width. -cm	64.1 ± 1.9	73.4 ± 1.3	0.0002
Aortic Arch Height. -cm	39.7 ± 2.0	43.5 ± 1.3	0.1200
Aorta Function			
Ascending Aorta strain	0.19 ± 0.01	0.11 ± 0.01	<0.0001
Descending Aorta strain	0.19 ± 0.01	0.14 ± 0.01	0.0001
Ascending Aorta Distensibility. - $kPa^{-1}.10^{-3}$	43.4 ± 3.7	21.3 ± 2.4	<0.0001
Descending Aorta Distensibility. - $kPa^{-1}.10^{-3}$	41.7 ± 2.6	26.3 ± 1.7	<0.0001
Ratios			
AA/AD Diameter ratio	1.93 ± 0.09	1.86 ± 0.05	0.4700
AA/AD Strain ratio	1.01 ± 0.08	0.76 ± 0.05	0.0090
AA/AD Distensibility ratio	1.01 ± 0.08	0.76 ± 0.05	0.0100
AA is ascending Aorta, DA is descending Aorta ,			

Results: Population included 80 subjects (mean age 52±13; 53% male): 23 normo and 57 treated hypertensives (28 controlled and 29 uncontrolled). Male proportion was 51%. Demographics were comparable in the 2 groups but all stiffness indices differed as well as L, W and all AA/DA stiffness indices ratios (table 1). Paired t-test in hypertensives showed that all AA and DA indices differed whereas in normotensives only diameters differed. In univariate analysis, AA/DA-diameters, AA/ DA-strain and AA/DA-Dis ratios all correlated to age, BP, height and gender. Moreover, stiffness ratios correlated to all anatomic indices especially AoA-L. Multivariate analysis with adjustment for age, gender, height, cSBP and AoA-L was performed in each group. In normotensives, AoA-L were independent correlates of AA/ DA stiffness ratios whereas in hypertensives, age and central systolic BP were significant determinant of relative stiffness changes between AA and DA.

Conclusions: Stiffness modifications along the aortic arch correlate to morphologic parameters in normotensives whereas only age and BP were independent correlates in hypertensives

7C.09 COMPARISON OF EFFECTS OF PERIPHERAL VASCULATURE ON TONOMETRIC RADIAL PULSE AND CUFF-BASED BRACHIAL PULSE WAVEFORM AS USED IN ESTIMATION OF CENTRAL AORTIC PRESSURE

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Objective: Estimation of central aortic pressure requires reliable acquisition of a peripheral pulse waveform either using radial tonometry or volumetric displacement within a brachial cuff. This study tests whether the radial and brachial waveforms are influenced by changes in properties of the peripheral vasculature of the hand, such an influence potentially compromising central aortic pressure estimation.

Design and method: In 15 subjects (37 ± 15 years, 7 female), brachial waveform acquired by volumetric displacement (cuff-based) and radial waveform acquired by tonometry were simultaneously measured whilst a cuff around the hand on the same arm was inflated to pressures of 30, 15, 0, −15, −30, −60 mmHg with respect to mean arterial pressure to alter peripheral resistance and compliance. Aortic parameters were compared to measurements at baseline (no hand cuff pressure) using repeated measures ANOVA with post-hoc, Bonferroni-corrected, paired t-tests.

Results: Altering peripheral resistance and compliance significantly changed computed mean arterial pressure (MAP), aortic systolic pressure (aSP), pulse pressure (aPP), augmentation pressure (aAP), augmentation index (aAIx) and pulse pressure amplification (PPA) relative to baseline conditions when using tonometric radial waveforms (Table, describing maximum change). Parameters derived from the cuff-based waveform assessment did not change with alterations in the peripheral vasculature. There was no significant change in brachial systolic and diastolic values throughout the experiment.

	ΔMAP (mmHg)	ΔaSP (mmHg)	ΔaPP (mmHg)	ΔaAP (mmHg)	ΔaAIx (%)	ΔPPA (%)
radial	5.7±1.3*	7.7±1.4**	6.2±1.4**	8.8±1.0***	25±1***	-26±2**
	(-15)	(-30)	(-30)	(0)	(0)	(30)
brachial	1.3±1.0	2.2±1.2	1.4±2.0	-1.8±1.1	-5±1	5±3
	(-30)	(-30)	(-60)	(-15)	(0)	(0)

Values in brackets give the transmural pressure in mmHg for which the maximum change occurred. *p<0.05, **p<0.01, ***p<0.001

Conclusions: Localised changes in peripheral resistance and compliance affect the radial waveform (tonometer-based acquisition) but not the brachial pressure waveform (cuff-based acquisition) as judged by significant effects on the computed central aortic parameters from radial but not brachial waveforms, the largest discrepancies occurring in aAIx and in PPA. This suggests that estimation of central aortic pressure from brachial cuff waveforms is less sensitive to disturbances in the peripheral vasculature of the upper limb that alter the peripheral arterial pulse morphology

7C.10 PROTHROMBOTIC MARKERS ARE RELATED TO CAROTID STIFFNESS IN ESSENTIAL HYPERTENSIVE PATIENTS

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Objective: A prothrombotic state is associated with presence and severity of organ damage in hypertensive patients. In these patients, evidence of subclinical carotid damage anticipates major cardiovascular events. The aim of this study was to investigate the association of prothrombotic markers with carotid stiffness in hypertension.

Design and method: In 116 hypertensive patients (age 49±13 years; 54 males) we assessed common carotid artery stiffness by B-mode ultrasonography and measured plasma fibrinogen, D-dimer, plasminogen-activator inhibitor-1 (PAI-1), homocysteine, lipoprotein(a), and C-reactive protein.

Results: No significant differences were observed in fibrinogen, D-dimer, lipoprotein(a), homocysteine, and C-reactive protein levels between patients with values below or above the median of the distribution of carotid distensibility, compliance, coefficient of distensibility, coefficient of compliance, Young elastic modulus, and beta-stiffness. Only PAI-1 levels were borderline higher in patients with high values of the Young elastic modulus than in patients with low values (P=0.042). The Young elastic modulus was significantly correlated with age and PAI-1 levels (r=0.286, P=0.036), whereas no further significant correlation between non-traditional cardiovascular risk factors and indices of carotid stiffness was observed. Stepwise multivariate regression analysis indicated that Young elastic modulus was independently associated with age and PAI-1 (B=0.289, P=0.028).

Conclusions: The findings of this study do not support the involvement of a prothrombotic state and other non-traditional cardiovascular risk factors related to the hemostatic system in carotid artery stiffening of hypertensive patients.

ORAL SESSION

ORAL SESSION 7D
MICROCIRCULATION AND SMALL VESSELS

7D.01 ESSENTIAL HYPERTENSION INDUCES EARLY FUNCTIONAL AND STRUCTURAL VASCULAR AGEING IN SMALL RESISTANCE ARTERIES

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Objective: We evaluated cross-sectionally whether vascular remodeling is physiologically present in normal aging, and whether hypertension causes an acceleration of the aging process for vascular function and structure.

Design and method: 40 essential hypertensive patients (EH, age 44.9 ± 13.2 years; blood pressure, BP, 157 ± 8/99 ± 3 mmHg) and 36 normotensive control individuals (Ctrl, age 44.7 ± 12.7 years; BP: 128 ± 7/80 ± 4 mmHg) underwent laparoscopic surgery with subcutaneous adipose tissue biopsy. Small resistance arteries were studied by pressure micromiography. Endothelium-dependent and –independent vasodilation were evaluated by dose-response curve to Acetylcholine (ACh) and sodium nitroprusside (SNP). Maximum %inhibition by L-NAME on response to Ach was calculated. Structural alterations were assessed by media-lumen ratio (M/L).

Results: EH showed a reduced vasodilation to Ach ($P < 0.001$), but not to SNP, compared to Ctrl. In both groups, %inhibition by L-NAME on response to ACh was inversely related to age (EH, r:-0.75; $P < 0.0001$; Ctrl, r:-0.49; $P < 0.0001$). NO availability was significantly reduced in EH as compared to Ctrl for each age group (<30 years: 22 ± 6% vs 30 ± 9%, $P < 0.05$; 31–45 years: 17 ± 3% vs 30 ± 3%, $P < 0.0001$; 46–60 years: 9 ± 4% vs 21 ± 6%, $P < 0.0001$; >60 years: 4 ± 3% vs 13 ± 3%, $P < 0.05$). Age-hypertension interaction (Repeated measures ANOVA) was not significant ($p = 0.25$).

EH showed an increased M/L ($P < 0.001$) compared to Ctrl. In both groups, M/L was positively related to age. (EH, r:0.82; $P < 0.0001$; Ctrl, r:0.50; $P < 0.0001$). M/L was similar in EH and Ctrl for individuals < 30 years, but greater in EH than Ctrl for the other age groups (31–45 years: 6.5 ± 0.4% vs 5.6 ± 0.4%, $P < 0.0001$; 46–60 years: 7.4 ± 0.5% vs 5.8 ± 0.2%, $P < 0.0001$; >60 years: 7.9 ± 0.3% vs 6.3 ± 0.5%, $P < 0.0001$). There was a significant age-hypertension interaction (Repeated measures ANOVA $p = 0.0009$).

Conclusions: In small resistance arteries, aging is physiologically characterized by progressive reduction in NO availability and increased M/L. In hypertensive patients, NO availability is early reduced in comparison to Ctrl, but the progression rate with age appears to be similar. Conversely, structural alterations are influenced by hypertension only after 30 years of age, but the progression rate with age is steeper in the presence of hypertension.

7D.02 EFFECT OF A SHORT-TERM ANTIHYPERTENSIVE TREATMENT ON RETINAL ARTERIOLES EVALUATED WITH ADAPTIVE OPTICS RETINAL CAMERA

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Objective: Long-term administration of antihypertensive treatment can reduce subcutaneous small-resistance arteries structural alterations in hypertensive patients and also correct arteriolar remodeling in the retina. A recently developed adaptive optics (AO) fundus camera enables noninvasive high reproducible repeated measurements of retinal arteriolar morphology with a micrometer resolution. Our objective was to assess arteriolar changes after a short-term antihypertensive treatment prescription on the very same retinal arteriole segment.

Design and method: Two groups of non-diabetic hypertensive patients were included: group 1: treated or untreated subjects with uncontrolled blood pressure (BP) and group 2: treated subjects with controlled BP. In group 1, one antihypertensive drug was added to the prescription (ARB or ACEI or Calcium antagonist) and only subjects with an observed Systolic BP decrease >10 mmHg were selected for follow-up analysis. Wall thickness (WT) and lumen diameter (LD) were measured directly using the new noninvasive RTX1® AO camera (Imagine-Eyes, Orsay, France) and a dedicated semi-automated analysis software. They were used to calculate Wall-to-Lumen Ratio (WLR) and Wall Cross Sectional Area (WCSA). AO examination was performed by the same trained orthoptist on the same arteriolar branch and at the same distance from the optical disk (about 1 mm) at baseline and after one month.

Results: We included 26 patients in group 1 and 14 in group 2 (50 ± 13 years, 57% men). Second visit was performed after 35.8 ± 14 days. BP and retinal arterioles characteristics at baseline and at follow-up are depicted in table 1. In group 1, BP and WLR significantly dropped when LD increased and seemed to be the principal determinant of WLR decrease. No changes in retinal arterioles or in BP were observed in group 2. Univariate analysis showed significant regression between WLR and systolic BP absolute decrease ($R^2 = 0.18$, $p = 0.01$).

Conclusions: AO enables the visualization of retinal arteriolar morphology modifications after short-term antihypertensive treatment in case of BP significant drop. Although WLR reduction could be ascribed to a eutrophic remodeling process, the observed LD increase with no change in WCSA suggests a short-term effect of antihypertensive treatment on arteriolar tonus.

	Group 1		Group 2	
	Baseline	1 month Follow up	Baseline	1 month Follow up
Blood Pressure				
Systolic BP.- mmHg	154.8 ± 4.9	126.6 ± 4.9 ‡	120.8 ± 5.1	119.4 ± 5.3
Diastolic BP.- mmHg	87.6 ± 71.2	76 ± 2.8	71.2 ± 3.3	71.9 ± 3.0
Retinal Microvasculature				
WLR	0.329 ± 0.012	0.294 ± 0.01 †	0.312 ± 0.013	0.301 ± 0.01
Lumen diameter.- µm	73.09 ± 2.51	76.5 ± 2.37 *	76.36 ± 2.59	77.03 ± 2.45
Wall Thickness.- µm	23.8 ± 0.99	22.08 ± 1.12 *	23.99 ± 1.02	23.12 ± 1.16
Wall Cross Sectionnal Area. -µm²	3206 ± 222	3100 ± 224	3379 ± 229	3292 ± 232

Data are expressed as Mean ±SD. BP is Blood Pressure. *p<.05 †p<.01 ‡<.001 between baseline and follow-up with bilateral Wilcoxon test on matched pairs

7D.03 RELATIONSHIP BETWEEN AGE AND STRUCTURAL ALTERATIONS IN SUBCUTANEOUS SMALL RESISTANCE ARTERIES IN HYPERTENSIVE PATIENTS

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Objective: It was proposed that early vascular ageing may be an important mechanism of vascular damage in large conductance arteries. However it is not known whether aging may also affect small resistance artery morphology.

Design and method: For this reason, we investigated 100 patients with essential hypertension. Secondary forms of hypertension were excluded according to standard clinical evaluations and biochemical or instrumental assessments. In all patients, an evaluation of small resistance arteries morphology was performed by a wire micromyographic approach (Mulvany's technique). A small amount of subcutaneous tissue was obtained by local biopsy or during election surgery and subcutaneous small resistance arteries were dissected and mounted on a myograph; the media to lumen ratio (M/L) was then measured.

Results: The age range of our population was 22–81 years, with a mean value of 57 ± 12 years; 14% of them were current smokers, 32% had alterations in lipid patterns, none of them had diabetes mellitus, 58 were males and average blood pressure values were 156/95 ± 19/12 mmHg.
We found a significant correlation between M/L and age ($r = 0.30$, $p = 0.002$): the statistical significance of the correlation persisted after correction for counfounding variables (gender, serum cholesterol, smoking status, serum glucose, systolic or diastolic blood pressure values). A statistically significant inverse correlation was also observed between internal diameter and age ($r = -0.20$, $p = 0.046$), while the correlation between age and media thickness did not reach statistical significance ($r = 0.09$, $p = 0.37$).

Conclusions: Our data suggest that aging may affect microvascular structure in hypertensive patients. It is also possible that hypertension may anticipate the effects of physiological aging, and this should be explored in a relatively large population of normotensive subjects.

7D.04 ACUTE SALT LOADING AFFECTS VASCULAR FUNCTION WITHOUT SIGNIFICANT CHANGE IN BODY FLUID STATUS AND BODY COMPOSITION IN YOUNG HEALTHY WOMEN

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Objective: Our previous study demonstrated that one week of salt loading significantly impaired skin microvascular reactivity without changes in blood pressure (BP) levels. The aim of this study was to evaluate whether one week of high-salt (HS) diet changes body fluid status and body composition subsequently affecting vascular reactivity.

Design and method: 10 healthy women (age range 20–23) took a 7-days low-salt (LS) diet (<40mmol Na/day) and 7-days HS diet (~240mmol of Na/day). Salt resistance, defined as a <5 mmHg change in BP determined while on the LS and HS diets was confirmed in all subjects. Skin microvascular post occlusive reactive hyperemic (PORH) blood flow (indicator of endothelial function) was assessed by laser Doppler flowmetry (LDF) before and after each diet protocol. Plasma Renin Activity (PRA), plasma aldosterone, plasma and 24h-urine sodium, potassium, urea and creatinine levels were measured before and after diets. Body composition was assessed with a four-terminal portable impedance analyzer (Maltron Bioscan 920-II). Body Mass Index (BMI), Fat Free Mass% (FFM%), Fat Mass% (FM%), Total Body Water% (TBW%), Extracellular Water% (ECW%), Intracellular Water (ICW%), ECW/ICW, Plasma Fluid (PF), Interstitial Fluid (IF) and Body Density Mass (BDM) were calculated.

Results: Changes in 24 h urinary sodium, PRA and plasma aldosterone levels confirmed subjects conformed to the diet. There was no change in BP and HR before and after both diet protocols. HS diet caused significant impairment in microvascular reactivity (PORH) (R-O LS diet 156 ± 23% vs. HS diet 100 ± 12%, P = 0.040). One week HS diet did not induce any significant change in body composition parameters BMI, FFM%, FM% and BDM, compared to LS diet. Body fluid components (TBW%, ECW%, ICW%, ECW/ICW, PF and IF) were not different in LS compared to HS group.

Conclusions: This study confirmed that even one week of HS diet significantly altered microvascular reactivity in young healthy normotensive and salt-resistant women, without changes in BP. Furthermore, our results indicate that vascular changes after HS diet are independent of body composition and body fluid status just as they are pressure independent, but are consequence of unique effect of HS on endothelial function.

7D.05 MATERNAL OBESITY ATTENUATES THE ANTI-CONTRACTILE EFFECT OF PERIVASCULAR ADIPOSE TISSUE IN OFFSPRING

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Objective: Maternal obesity pre-programmes offspring to develop obesity, glucose intolerance and associated cardiovascular disease later in life although the underlying mechanism is currently unknown. This study investigated the effect of a maternal high fat diet on endothelial and perivascular adipose tissue (PVAT) regulation of resistance artery tone.

Design and method: 8 week old female SD rats were fed a 10% fat diet (controls) or 45% fat obesogenic diet (HFD) for 12 weeks before mating then continued on their respective diets during pregnancy and lactation. PVAT-intact or -denuded mesenteric arteries from dams and pups (250–300 μm internal diameter) were mounted on a wire myograph. Cumulative concentration-response curves were constructed to thromboxane A2 receptor agonist U46619 (10nM-3 μM) ± 10 μM A769662, an activator of AMP-activated kinase (AMPK), and/or 100 μM L-NMMA, a nitric oxide synthase (NOS) inhibitor.

Results: Body weight (BW) and systolic (SBP) and diastolic (DBP) blood pressure were significantly increased in HFD dams (BW: $p < 0.05$, SBP: $p < 0.001$, DBP: $p < 0.01$) and their offspring at 24 weeks (BW < 0.0001, SBP: $p < 0.0001$, DBP: $p < 0.0001$) compared to controls but no differences were observed in offspring at 12 weeks. PVAT exerted an anti-contractile effect in artery segments from control dams and their offspring at 12 and 24 weeks ($p < 0.01$, $p < 0.001$, $p < 0.05$), an effect which was lost in both dams fed HFD and their offspring. AMPK activation decreased contractility of both PVAT-denuded and intact control vessels in the presence and absence of a NOS inhibitor in control dams ($p < 0.0001$) and their offspring ($p < 0.0001$); this effect was decreased in PVAT-intact vessels of HFD dams and their offspring.

Conclusions: In summary, the attenuated anti-contractile effects of PVAT in HFD dams and their offspring may be modulated by AMPK; however it is not totally dependent on nitric oxide release.

7D.06 EFFECTS OF AN ACUTE AND CHRONIC SALT LOAD ON MICROVASCULAR PERMEABILITY IN HEALTHY SUBJECTS

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Objective: Abnormal microvascular structure and function have been related to hypertension. Increasing evidence links Na+ to microvascular changes. Whether a chronic dietary Na+ load or an acute IV Na+ load differs in its microvascular effects is unknown. We therefore studied both effects in normotensive subjects on the microcirculation.

Design and method: Twelve healthy male subjects pursued a low-sodium diet (LSD,<50 mmol Na+/d) and a high-sodium diet(HSD,>200 mmol Na+/d) for 8 days in randomized order, separated by a crossover period. On day 8 of LSD hypertonic IV saline (5mmol Na+/L body water) was administered in 30 minutes. Microvascular permeability after both diets and after IV saline was determined with transcapillary escape rate of 125I-albumin(TERalb) after IV administration of 100kBq 125I-albumin. Blood samples were drawn at fixed time points until 60 min. Plasma radioactivity was measured with an automatic γ-counter. TERalb was expressed as percentage decline in plasma radioactivity per hour (%cpm/g/h) using regression analysis. Plasma volume was determined by calculating the y-intercept of the TERalb disappearance curve, corrected for injected dose of tracer. Sublingual Sidestream Darkfield imaging was performed to assess perfused boundary region (PBR), reflecting endothelial glycocalyx thickness, and RBC filling and microvascular density as measures of microvascular perfusion (Glycocheck software). Blood pressure (BP), heart rate (HR), cardiac output (CO) and systemic vascular resistance (SVR) were measured in supine position with Nexfin.

Results: An overview of results is presented in the table. All subjects adhered to both diets. Body weight increased significantly after HSD. TERalb and plasma volume did not differ between LSD and HSD, but increased significantly after saline infusion. PBR showed no differences between LSD and HSD, or after saline infusion. RBC filling and microvascular density did not differ between diets or after saline infusion. BP, HR, CO and SVR were similar after all conditions.

	LSD	HSD	Saline infusion
Urinary Na^+ (mmol/24h)	19±10	341±104	-
Body weight (kg)*	74.0±6.6	76.5±6.7†	74.5±6.6‡
Systolic BP (mmHg)	126.3±6.6	131.3±11.1	124.9±11.7
Diastolic BP (mmHg)	72.5±4.1	74.8±5.3	72.0±7.0
Pulse Pressure (mmHg)	53.8±6.1	56.6±6.8	52.9±6.2
HR (bpm)	56.1±7.2	57.8±10.4	54.9±7.7
CO (L/min)	6.6±1.0	6.9±1.3	6.4±1.0
SVR ($dyn \cdot s \cdot cm^{-5}$)	1125±173	1127±204	1149±218
TERalb (%cpm/g/h)	6.5±2.7	7.4±4.0	10.0±3.1¥
Plasma volume (mL)	2953±685	3068±620	3182±710$
PBR (μm)	1.96±0.19	1.94±0.23	1.92±0.17
RBC filling (%)	74.2±3.8	74.7±5.3	75.5±2.8
Valid microvascular density ($\mu m/mm^2$)	636.5±158.1	695.2±138.7	680.4±63.2

*P for trend <0.001
†P<0.001 HSD vs. LSD
‡ P<0.001Saline vs. LSD
¥ P=0.02 Saline vs. LSD
$ P=0.02 Saline vs. LSD

Conclusions: Acute, but not chronic Na+ loading in healthy subjects resulted in higher microvascular permeability that coincided with increased plasma volume. These results suggest that deleterious microvascular effects of an acute Na+ load may develop by hydrostatic, or hypertonic, or direct effects of Na+ to the endothelium.

7D.07 RETINAL ARTERIOLAR STRUCTURE IN PATIENTS WITH PHEOCHROMOCYTOMA

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Objective: The aim of the ongoing study is to analyze retinal arteriolar structure in patients with pheochromocytoma (Pheo), a form of secondary hypertension characterized by excessive catecholamine secretion as compared with well-matched patients with essential hypertension (EHT).

	AD (μm)	LD (μm)	WT (μm)	WLR	WCSA (μm²)	RCF (AU)
Pheo	111.0±19.0	78.0±8.8	16.5±6.3	0.42±0.14	5115±2644	283±70
EHT	99.6±11.2	73.3±6.2	13.1±3.6	0.36±0.09	3636±1319	286±52
p	0.015	0.037	0.029	0.083	0.020	0.853

Table. Retinal arterioles' morphology in patients with pheochromocytoma (Pheo) and hypertensive controls (EHT).

Design and method: We examined 24 (15f/9m) patients with Pheo (mean age 46.3 ± 11.8 years) and 24 (15f/9m) age, gender, body mass index, glycemic status and blood pressure levels matched patients (46.7 ± 12.0 years) with (EHT). In all patients evaluation of plasma free normetanephrine (NMN) and metanephrine (MN) concentrations by liquid chromatography with tandem mass spectrometry was performed. Diagnosis of pheochromocytoma was made based on increased free NMN and/or MN concentration and confirmed on pathological examination. Retinal arterioles morphology were assessed by Heidelberg Retina Flowmetry using scanning laser Doppler flowmetry (SLDF). Outer diameter (AD) and lumen diameter (LD) were measured with automatic full-field perfusion imaging analysis (AFFPIA). Wall-to-lumen ratio (WLR), wall thickness (WT) and wall cross-sectional area (WCSA) of retinal arterioles were calculated. Retinal capillary blood flow (RCF) was also assessed by SLDF.

Results: Pheo and EHT groups were well matched for age, gender, BMI, office and ambulatory blood pressure levels as well as for glycemic status and number of hypertensive medication ($p > 0.05$ for all comparisons). Patients with pheochromocytoma were characterized by higher AD, LD, WT and WCSA as compared with EHT (Table). A tendency towards higher WLR in patients with pheochromocytoma as compared to EHT was also noted (Table). There was no difference in RCF between patients with pheochromocytoma and EHT.

Conclusions: Patients with pheochromocytoma as compared with matched patients with essential hypertension are characterized by higher outer wall diameter, lumen diameter, higher wall thickness and higher wall cross-sectional area of retinal arterioles. This may indicate potential deleterious effect of high catecholamine levels on small caliber arterioles evaluated non-invasively by SLDF.

7D.08 DETECTING HYPERTENSIVE RETINOPATHY USING RETINAL VASCULAR GEOMETRY

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Objective: Identification of subtle vascular alterations of the retina may serve as an early index of hypertension-induced target organ damage, in terms of global cardiovascular risk assessment. Evaluation of retinal vessels can be achieved promptly, easily and non-invasively using the non-mydriatic fundus camera; as such, the need to identify new, reliable, and easily estimated cardiovascular risk markers derived from the retinal vasculature is growing rapidly. Apart from the retinal vascular diameters, research has recently focused on the evaluation and the quantitative estimation of other signs of retinal vascular geometry, such as the bifurcation of the retinal vessels.

Design and method: We studied naïve, never-treated patients with recent duration of hypertension, confirmed with 24-hour ambulatory blood pressure (BP) and a control group consisting of healthy volunteers. All patients underwent fundus photography with a non mydriatic NIDEK AFC-230/210 camera. Innovative software was developed to estimate retinal vascular geometry, using novel advances in retinal digital image analysis which allow precise measurements of features of the whole vascular network spread across the retina. The retinal bifurcation geometry was expressed with the asymmetry ratio (α), area ratio (β) and the bifurcation index (λ).

Results: In total 69 participants, 48 hypertensives and 21 matched normotensives were included in this pilot collaborative study. Hypertensives exhibited all measured tortuosity indices significantly increased (α: 0.674 vs 0.624, $p = 0.001$, β: 1.480 vs 1.431, $p = 0.008$ and λ:0.804 vs 0.771, $p = 0.001$ respectively). Correlations between the above parameters and the components of office and ambulatory BP are depicted in table 1. The strongest correlation was found with office systolic BP, followed by the nighttime systolic measurements.

Table 1. Association between asymmetry ratio (α), area ratio (β), bifurcation index (λ) and office and 24-hour ambulatory blood pressure parameters.

	Alpha (α)	Beta (β)	Lamda (λ)
OFFICE SBP	0.404***	0.437***	0.365**
OFFICE DBP	0.295*	0.284*	0.268*
24Hour SBP	0.260*	0.264*	0.235
24Hour DBP	0.131	0.149	0.098
Day-Time SBP	0.244*	0.235	0.214
Day-Time DBP	0.167	0.140	0.130
Night-Time SBP	0.273*	0.319**	0.258*
Night-Time DBP	0.123	0.217	0.101

Adjusted for age, sex, smoking and body mass index.
SBP: Systolic blood pressure, DBP: Diastolic blood pressure
*p<0.05, **p<0.01, ***p<0.001

Conclusions: This is the first study showing that even in "naïve" hypertensive patients, all tortuosity indices, estimated by innovative software, were increased compared to normotensive controls. All studied tortuosity indices were significantly associated with both office and 24-hour ambulatory BP. The verification of these promising novel indices of retinal vascular geometry in terms of cardiovascular disease prediction should be the subject of future studies.

7D.09 REDUCED VIT D AND ELEVATED URICEMIA INDUCE CAPILLARY RAREFACTION BEFORE MACROVASCULAR DAMAGE IN PATIENTS WITH METABOLIC SYNDROME AT THE VERY EARLY STAGES OF HYPERTENSION

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Objective: Reduced (L) Vit D (D) and high (H) uric acid (U) levels have been associate with increased cardiovascular risk. Aim of the study was to highlight their association with the subclinical vascular damage in untreated recently diagnosed very mild hypertensives with a similar number of metabolic syndrome factors (nATPIII).

Design and method: By medical visit and identification of the metabolic syndrome factors, 238 very mild hypertensives (136 ± 15/84 ± 9 mmHg), 62 controls with normal (N) D and U, 96 with LD, 40 with HU and 40 with both the conditions (LDHU) with similar metabolic assessment, underwent measures of carotid-femoral pulse wave velocity (PWV), ankle-brachial index (ABI), carotid intima-media thickness (IMT), as indices of functional and structural arterial damage, and video-capillaroscopy of the middle and distal phalangeal skin of the 2nd, 3rd and 4th finger of the non-dominant hand during baseline (CAP) and venous congestion (CVC) obtaining capillary recruitment (REC) as indices of functional and structural microcirculatory damage.

Results: Patients showed a similar hypertensive state during the medical visit and ABPM but different capillary indices.

(m ± s:d.*:p<.05, **:p < .01, ***:p < .001 vs NDNU; °:p < .05, °°:p < .01, °°°:p < .001 vs LDNU;^p < .05, ^^:p < .01, ^^^:p < .001 vs NDHU).

pts/var	VitD	Uricemia	nATPIII	IMT	ABI	PWV
NDNU	32.7±3.7	4.5±0.7	3.4±0.7	0.8±0.2	1.1±0.2	9.6±1.8
LDNU	14.5±5.5***	4.5±0.8	3.6±0.7	0.9±0.2	1.1±0.1	10.2±1.3
NDHU	34.1±9.8°°°	6.9±1.0*** °°°	3.4±0.8	0.8±0.2	1.1±0.1	8.9±3.4
LDHU	15.4±4.1*** ^^^	6.9±0.9*** °°°	4.0±2.3	0.8±0.2	1.1±0.1	9.3±3.6

pts/var	PWV	CAP	CVC	REC
NDNU	9.6±1.8	53.3±8.6	62.4±8.3	9.1±2.8
LDNU	10.2±1.3	43.6±3.6***	48.9±4.1***	5.41±2.1***
NDHU	8.9±3.4	45.1±4.2***	51.6±5.5*** *	6.6±4.2*
LDHU	9.3±3.6	41.9±2.5*** ^^	46.9±2.8*** ^^^	4.9±1.7*** ^

Pearson analysis showed the association between Vit D and CVC (.440*) and REC (.335***) in LDNU and with CVC (631***) and REC (.666*) in LDHU as well as between U and CAP (-.470*) in NDHU and (-606*) in LDHU.

Conclusions: The results suggest that, in very mild hypertensives with metabolic syndrome, reduced Vit D is associate to structural microvascular damage before the onset of structural or functional macrovascular impairment. Hyperuricemia show a lower microcirculatory damage but this is amplified in patients with both the disorders (LDHU),

7D.10 EFFECTS OF MELATONIN ON CONTRACTILE RESPONSES IN SMALL ARTERIES OF AGEING MICE

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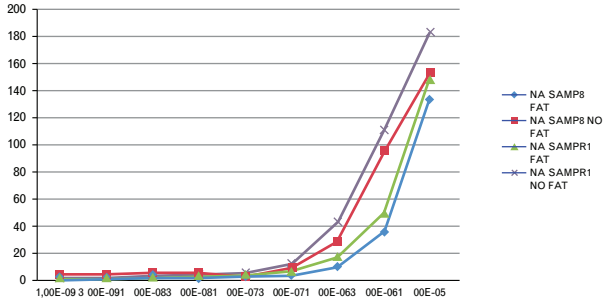
Objective: It has been previously demonstrated that inflammation in adipose tissue may be implicated in vascular dysfunction (Circulation 2009; 119(12):1661–1670). A senescence-accelerated prone mouse (SAMP8) is a model of age-related cognitive decline and vascular dysfunction. Several studies demonstrated that SAMP8 suffers from increased oxidative stress and that accelerated senescence was associated with decreased eNOS and nNOS and increased oxygen radicals synthesis. Aim of the study was to investigate functional responses of small mesenteric arteries in a senescence-accelerated prone mouse (SAMP8) before and after chronic treatment with melatonin.



Design and method: We investigated 7 SAMP8 and 7 SAMR1 normal controls. Mesenteric small resistance arteries were dissected and mounted on a wire myograph, according to Mulvany-Halpern technique (internal diameter about 200 μm). A concentration-response to norepinephrine (NE, from 10–9 to 10-5 Mol/l) was evaluated in vessels with intact prerivascular fat tissue (WF) and in vessels in which perivascular fat tissue was removed (NoF). Investigations were repeated in 7 SAMP8 and 7 SAMR1 after 54 weeks of chronic treatment with melatonin, an endogenous hormone with antioxidant and vasculoprotective properties.

Results: In SAMR1 control mice anticontractile effect of perivascular fat was present (WF vs. NoF: ANOVA $p = 0.04$), while in aging SAMP8 mice the effect was less pronounced (WF vs. NoF: ANOVA p = NS) (see figure). Long-term treatment with melatonin had no effect in SAMR1 either in WF or NoF vessels, while it decreased the contractile response to norepinephrine in noF vessels of SAMP8 (ANOVA $p < 0.001$); the effect of melatonin treatment in WF vessels was not statistically significant.

Conclusions: The anticontractile effect of perivascular fat is impaired in a senescence-accelerated prone mouse, compared with controls. A long-term treatment with melatonin seems to decrease contractile responses to norepinephrine in NOF mesenteric small arteries of SAMP8, thus restoring an anticontractile effect, probably through antioxidant mechanisms.

7D.11 RETINAL ARTERIOLAR STRUCTURE IN PATIENTS WITH PRIMARY ALDOSTERONISM

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Objective: Since retinal arteriolar structure has not been evaluated in patients with secondary hypertension we addressed a question if retinal arteriolar structure in patients with primary aldosteronism (PA) is altered as compared with well-matched patients with essential hypertension (EHT).

	AD (μm)	LD (μm)	WT (μm)	WLR	WCSA (μm²)	RCF (AU)
PA	107.9±13.8	75.2±9.9	16.3±3.9	0.44±0.11	4772±1516	301±72
EHT	99.5±12.7	72.6±5.8	13.5±4.5	0.37±0.11	3749±1603	275±61
P	0.017	0.211	0.011	0.019	0.014	0.131

Design and method: We examined 30 (18m/12f) patients with PA (54.1 ± 9.5 years) and 30 (18m/12f) age, gender, body mass index, glycemic status, blood pressure levels and number of medication ($p > 0.05$) matched patients (55.8 ± 8.4 years) with EHT. All patients with PA underwent adrenal venous sampling to differentiate between aldosterone producing adenoma (APA) and bilateral adrenal hyperplasia (BAH). Retinal microperfusion (RCF) and retinal arterioles' morphology were assessed by Heidelberg Retina Flowmetry using scanning laser Doppler flowmetry (SLDF). The parameters: outer diameter (AD) and lumen diameter (LD) were determined by automatic full-field perfusion imaging analysis (AFFPIA). Wall/lumen ratio (WLR), wall thickness (WT), and wall cross-sectional area (WCSA) were calculated.

Results: Patients with PA were characterized by higher AD, WT, WLR and WCSA as compared with EHT (Table). There was no significant difference in LD, as well as in RCF between the groups (Table). Parameters describing retinal arterioles' morphology were not correlated to office and ambulatory blood pressure both in the PA group and in the EHT group. There was no significant difference in parameters describing retinal morphology between BAH and APA groups.

Conclusions: Patients with primary aldosteronism as compared to matched hypertensive controls are characterized by higher outer wall diameter, wall thickness, wall-to-lumen ratio and wall cross sectional area of retinal arterioles reflecting hypertrophic vascular remodeling. This may indicate the detrimental effect of excessive aldosterone on small retinal arterioles evaluated non-invasively by SLDF method.

7D.12 TELMISARTAN MONOTHERAPY EFFECTS ON MICROCIRCULATION IN PATIENTS WITH UNCOMPLICATED ARTERIAL HYPERTENSION

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Objective: To evaluate telmisartan monotherapy effects on structural and functional characteristics of small-caliber vessels in patients with uncomplicated arterial hypertension (AH).

Design and method: 20 patients (age $50,2 \pm 12,8$ years; male - 65%) with untreated uncomplicated grade I-II AH are included into the study. All patients were treated by telmisartan 80 mg during 8 weeks. At baseline and after 8 weeks the parameters of microcirculation were measured. The parameters of microcirculation were evaluated by laser Doppler flowmetry: index of microcirculation (IM, perf.units), which characterizes basal blood flow; occlusion test - capillary blood flow reserve (CBFR), which characterizes the reversibility of remodeling microvasculature; difference index of microcirculation (DIM), which indicates the degree of reduction in blood flow during occlusion; half-recovery time of capillary blood flow (T1/2,s), which characterizes the reactivity of the vascular bed; index of increase in capillary blood flow (IICBF, perf.units), which indicates an increase in vasoconstriction. Data presented as $M \pm m$. Wilcoxon criteria for by-pair comparisons was used. $p < 0,05$ was considered significant.

Results: After 8 weeks of treatment BP decreased from $154,4 \pm 2,5/98,4 \pm 1,8$ mmHg to $136,2 \pm 3,1/84,9 \pm 2,5$ mmHg ($p = 0,0077$). 55% of surveyed have reached target BP levels < 140/90 mmHg. 25% responded to treatment determined as decrease in systolic BP >20 mmHg or diastolic BP>10 mmHg.
Significant increase ($p < 0,05$) of IM from $2,93 \pm 0,39$ perf.units to $4,22 \pm 0,75$ perf.units was observed. CBFR decreased from $391,1 \pm 25,5\%$ to $295,4 \pm 29,2\%$ ($p < 0,05$). According to the occlusion test were observed recovery of normal type reactions to arterial occlusion: DIM increased from $1,63 \pm 0,30$ perf.units to $2,27 \pm 0,68$ perf.units ($p < 0,05$). IICBF and T1/2 were not significantly changed.

Conclusions: Telmisartan monotherapy (dose – 80 mg), 8-weeks course, contributes to restore normal hemodynamic type of microcirculation, normalizes microcirculation response to arterial occlusion and improves capillary blood flow reserve.

ORAL SESSION

ORAL SESSION 8A
HEART AND HAEMODYNAMICS

8A.01 INTERRELATIONSHIPS BETWEEN THE DEVELOPMENT OF HYPERTENSION AND LONGITUDINAL CHANGES OF ARTERIAL STIFFNESS/RENAL FUNCTION, AND PROPER BODY WEIGHT MAINTENANCE

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Objective: The mechanisms of the development of hypertension have not been fully clarified, as conflicting results have been reported on the long term relationships among blood pressure (BP), arterial stiffness, and renal dysfunction. Currently, repeated measure model is regarded as a powerful model for longitudinal data. This prospective study was conducted to examine either the progression of arterial stiffening or renal dysfunction has more close association with the development of hypertension, and to examine interrelationships among BP, arterial stiffness, and renal function, using repeated measure model. We also examined whether proper body weight maintenance affects their interrelationships.

Design and method: Middle aged non-hypertensive Japanese men who underwent annual health screening check were prospectively followed up to 11 years from 2002. Arterial stiffness and renal function were measured as brachial-ankle pulse wave velocity (baPWV) and eGFR. A total 3,241 subjects (mean age; 41 $\pm$ 9 years) were enrolled in this study. We performed linear mixed models adjusted for conventional risk factors for hypertension to examine longitudinal relationships among baPWV, BP, and eGFR. Subgroup analysis stratified by proper body weight maintenance (keeping BMI $<$25.0 kg/m^2) was also performed.

Results: The mean change of baPWV, systolic BP, and eGFR during follow up were, 67 $\pm$ 131cm/sec, 2 $\pm$ 12mmHg, and -10 $\pm$11 ml/min/1.73 m^2, respectively. The results from linear mixed model revealed that baPWV was a significant estimate for annual change of systolic BP independent of eGFR, and systolic BP was a significant estimate for annual change of baPWV as well (both $p<0.05$). On contrary, eGFR was not associated with annual changes of either baPWV or BP. These associations were not modified regardless of proper body weight maintenance.

Conclusions: In middle-aged Japanese non-hypertensive men, our resuts suggested; 1. The progression of arterial stiffening, rather than that of renal dysfunction, may be a key player for the development of hypertension; 2. The development of hypertension and the progression of arterial stiffening mat have vicious cycle apart from progression of renal dysfunction; 3. The proper body weight maintenance may not be associated with breaking off this vicious cycle.

8A.02 THE ASSOCIATION OF LEFT VENTRICULAR AND ATRIAL STRUCTURE WITH BODY COMPOSITION: IMPACT AND PITFALLS OF SCALING IN POPULATION BASED STUDIES

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Objective: Several allometric methods for indexing cardiac structures to body size have been proposed but the optimal way for normalization of cardiac structures is still controversial. We aimed to estimate the allometric exponents that best describe the relationships between cardiac dimensions and body size and propose normative values. We also explored how different scaling metrics influence the associations of left heart size with cardiovascular risk factors and outcome in the general population.

Design and method: We measured left ventricular end-diastolic dimension (LVEDD), end-diastolic volume (LVEDV), left ventricular mass (LVM) and left atrial volume (LAV) in randomly recruited population cohorts (n = 1509; 52.8% women; mean age, 47.8 years). After determining optimal scaling metrics in a healthy reference population (n = 656) and proposing normative values, we analyzed how the different scaling metrics influence predictive models for left ventricular hypertrophy (LVH) and left atrial enlargement (LAE) as well as cardiovascular outcome.

Results: The allometric exponents that described the relationships between LVEDD and body size were 1, 0.5 and 0.33 for body height (BH), body surface area (BSA) and estimated lean body mass (eLBM), respectively. With regards to LVEDV, LVM and LAV the allometric exponents for BH were 2.9, 2.7 and 2.0, respectively; for BSA they ranged from 1.7 to 1.8; for eLBM all exponents were around 1. These exponents were used to appropriately scale the cardiac dimensions to body size and derived sex-specific cut-off limits for different indexed cardiac dimensions. Indexation of LVM to height2.7 better detected LVH in overweight and obese subjects. The hazard ratios of cardiovascular outcome were highest for LVH defined by LVM/height2.7.

Conclusions: Our current study resulted in a proposal for thresholds for various indexed cardiac dimensions. LVM indexed to height has the advantage of being more sensitive in detection of LVH associated with obesity and slightly better for prediction of outcome.

8A.03 CONTINUOUS MONITORING OF HEMODYNAMICS IN THE SHORT ARM HUMAN CENTRIFUGE: A FEASIBILITY STUDY

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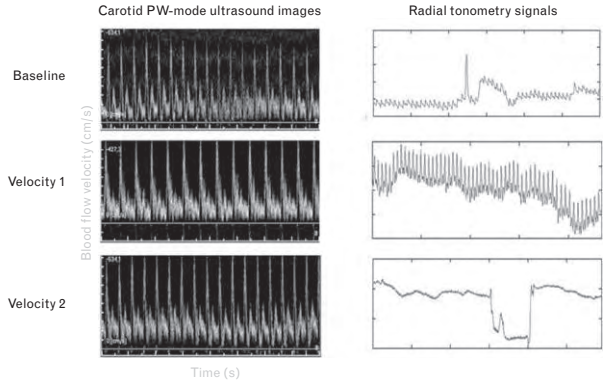
Objective: The aim was to test the technical feasibility of a set up combining tonometry and ultrasound,designated as Continuous Physiological and Medical Monitoring (CPMM), for cardiovascular assessment on humans and to evaluate the ability to assess physiological changes induced by artificial gravity in the short arm human centrifuge (SAHC, Verhaert, Belgium) for detecting and preventing potential disorders induced by weightlessness.

Design and method: The project was developed under an European Space Agency (ESA) contract (4000101988/10/NL/EM) and with its support, by the company Verhaert in consortium with the Institute for Space Medicine and Physiology (MEDES) and Ghent University. Measurements were performed at MEDES facilities in 4 young (presumably) healthy volunteers (3 males). For two volunteers, the protocol was divided in three periods: acceleration, steady rotation velocity and deceleration, obtaining carotid pulsed wave (PW)-Mode ultrasound sequences. For another volunteer (female), carotid PW-Mode ultrasound images and brachial and radial tonometry signals were acquired at baseline and during steady rotation. For the fourth volunteer, carotid and femoral PW-Mode ultrasound images and brachial, radial and carotid tonometry signals were acquired at baseline and during an initial (velocity1) and a following faster (velocity2) rotation velocity (see figure on the following page).

Results: Carotid PW-Mode ultrasound imaging was obtained in all 4 volunteers during different steps of the protocol. Femoral ultrasound imaging presented more difficulties related mainly to the placement of the probe after baseline, even if in one case results were feasible. Tonometry was, generally, a bigger challenge due to the intrinsic sensitivity of the method. Overall, radial artery tonometry provided the best results, while brachial artery results were acceptable only in one occasion. Carotid tonometry was measured only for one subject with suitable results for processing.

Conclusions: Tonometry measurements were feasible under a spin velocity limit, while PW-Mode ultrasound images were more robust and stable. Although general conclusions must be supported by a larger sample, suitable signals and locations were identified and a user friendly and mobile set-up was tested successfully and it is available for further research to identified and assess mechanisms and reflexes acting in physiological adaptation to various gravity conditions.



8A.04 RISK OF MORTALITY IN RELATION TO AN UPDATED CLASSIFICATION OF LEFT VENTRICULAR GEOMETRIC ABNORMALITIES IN A GENERAL POPULATION: THE PAMELA STUDY

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Objective: We estimated the risk of cardiovascular and all-cause mortality associated with left ventricular (LV) geometric patterns, as defined by a new classification system proposed by the Dallas Heart Study, in 1716 representatives of the general population of Monza enrolled in the Pressioni Monitorate e Loro Associazioni (PAMELA) study.

Design and method: Cut-points for abnormal LV geometric patterns were derived from reference values of the healthy fraction of the PAMELA population by combining LV mass (LVM) index, LV diameter and relative wall thickness. Death certificates were collected over an average 211 months follow-up period.

Results: During follow-up, 89 fatal cardiovascular events and 264 all-cause deaths were recorded. Concentric remodeling (CR) was the most common LV geometric abnormality (9.4%) followed by eccentric non-dilated LVH (6.3%), concentric LVH (4.6%) and dilated LVH (3.5%). Compared to normal LV geometry, concentric LVH (HR = 4.04, 95% CI: 2.05–7.97, $p < 0.0001$), dilated LVH (HR = 3.83, 95% CI: 1.93–7.60, $p = 0.0001$) and eccentric non-dilated LVH (HR = 2.61, 95% CI: 1.39–4.92, $p = 0.003$) predicted the risk of cardiovascular mortality, after adjustment for baseline covariates, including ambulatory blood pressure. Similar findings were observed for all-cause mortality. Only concentric LVH maintained a significant prognostic value for both outcomes after adjustment for baseline differences in LVM index.

Conclusions: The new classification system of LV geometric patterns, may improve mortality risk stratification in a general population. The risk is markedly dependent on LVM values; only concentric LVH provides a prognostic information beyond that conveyed by cardiac mass.

8A.05 AGE-DEPENDENT ASSOCIATION OF 24-HOUR PERIPHERAL OR CENTRAL PULSE PRESSURE WITH STROKE VOLUME

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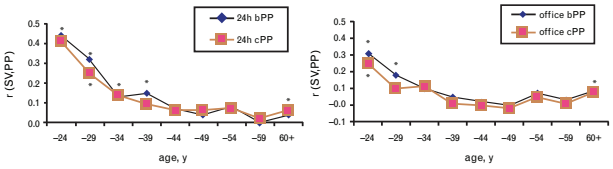
Objective: Pulse pressure (PP) is a complex physiologic trait affected by many variables, including left ventricular contractility (reflected by stroke volume), arterial stiffness, and central-to-brachial amplification. The impact of age on the relationship between stroke volume and central or brachial PP has not been investigated.

Design and method: 3765 adult subjects with untreated essential hypertension (men 56%, age 50 ± 12 years) underwent 24-hour ambulatory BP monitoring (SpaceLabs) and 2D-guided M-mode echocardiography. In a subset of 982 subjects in whom central PP was measured by applying a transfer function to radial pulse wave (SphygmoCor), we also estimated central office (or 24 h) PP by regression equations based on office (or 24 h) PP and mean arterial pressure, heart rate, age, height and sex ($R^2 = 0.92$ between estimated and measured central PP). The same equations were then applied to the original population to obtain estimated central PP.

Results: Stroke volume had a significant direct association with both brachial and central 24 h PP up to the age of 39 years (Figure). The above relationship weakened with age and became mostly non-significant after the age of 40 (all $r < 0.10$). Similar, although weaker, trends were observed for office PP (both brachial and central).



Conclusions: 24-h PP has a strong direct association with left ventricular stroke volume in the young only, and might more exclusively depend on arterial stiffness later in life. Since the above relationship was also observed with estimated central PP, it may not depend on PP amplification. The 'young' and 'old' pathophysiological patterns of PP may help to explain the increasingly adverse prognostic value of PP observed with advancing age.

8A.06 DIFFERENTIAL IMPACT OF ANEMIA ON LEFT VENTRICULAR FILLING PRESSURE BETWEEN SUBJECTS WITH AND WITHOUT HYPERTENSION. RESULTS FROM A MULTICENTER, COHORT STUDY

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Objective: It has been reported that anemia is associated with elevated left ventricular (LV) filling pressure and structural changes in hypertensive patients. However, effect of mild to moderate anemia on LV structure or function in non-hypertensive population is not well known. The aim of the study was to evaluate impact of anemia on LV functional changes in patients with and without hypertension among participants in Chest Pain in Korean Women's Registry.

Figure. Correlation between homoglobin level and E/e' in patients with and without hypertension

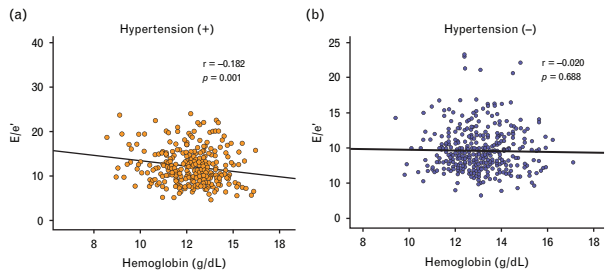
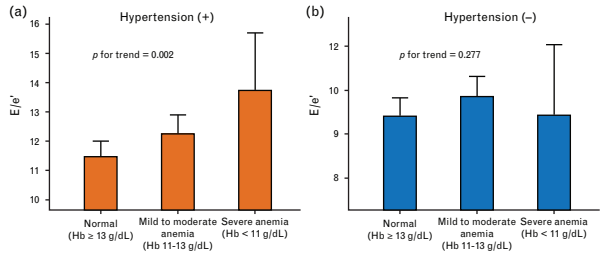


Figure. Change in E/e' according to the presence of anemia in patients with and without hypertension



Design and method: Chest Pain in Korean Women's Registry is a large, multicenter registry including demographic data, symptom, psychosocial variables, coronary angiographic and echocardiographic data and a variety of blood determinations. As a part of the core data, 916 patients with preserved LV ejection fraction constituted the study population. Echocardiographic data were obtained including LV mass index, early mitral inflow (E) velocity and early mitral annular (e') velocity. E/e', a parameter for the LV filling pressure, was calculated.

Results: Hypertension was observed in 407 patients (44%). Coronary artery disease (CAD) was diagnosed in 353 patients (39%). There were signifi-

cant differences in prevalence of CAD, age, serum creatinine, blood pressure, left atrial size, LV mass index, E velocity, e' velocity and E/e' between the patients with and without hypertension. There was negative correlation between hemoglobin level and E/e' in hypertensive patients ($r = -0.182$, $p = 0.001$), but there was no significant relation between the variables in non-hypertensive patients. In addition, E/e' proportionally increased according to normal, mild to moderate anemia and severe anemia only in hypertensive patients (p for trend = 0.002). On multivariate analysis, E/e' demonstrated independent correlation with presence of anemia in hypertensive patients, even after adjusting age, diabetes mellitus,CAD, creatinine and total cholesterol in hypertensive patients ($p = 0.019$).

Conclusions: Anemia is associated with raised LV filling pressure only in patients with hypertension, but not in those without hypertension from the large registry of women with high prevalence of CAD.

8A.07 NON-INVASIVE ASSESSMENT OF HAEMODYNAMICS IN RESISTANT HYPERTENSION: THE ROLE OF RENAL HAEMODYNAMICS

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Objective: Hypertension is a multisystem disease in which the kidney plays a key role in long term regulation of blood pressure and the development of hypertension. The aim of this study was to evaluate the role of intrarenal resistance indices in the renal interlobular arteries measured by Doppler ultrasound in resistant hypertensive patients.

Design and method: We studied 50 patients with resistant hypertension (RH) [age: 61 ± 11 years, 31 males, office blood pressure (BP): $163/89 \pm 24/15$ mmHg, under 4.2 ± 0.5 drugs] and 50 hypertensive patients controlled on three or less drugs [age: 59 ± 9 years, 26 males, BP: $131/79 \pm 9/8$ mmHg, under 2.2 ± 0.3 drugs] that underwent transthoracic echocardiographic study for determination of mitral annular early diastolic velocity (E/e') and blood sampling for assessment of metabolic profile. Moreover, data on renal resistive index (RRI), obtained by Doppler ultrasound sampling of the intrarenal arteries, were retrospectively analyzed.

Results: Hypertensives with RH compared to those without RH exhibited higher RRI by 0.078 ($p < 0.001$) and E/e' values by 3.1 ($p < 0.001$). In the entire study population, RRI was negatively related to office diastolic BP ($r = -0.239$, $p < 0.05$), while it was positively associated with office systolic BP ($r = 0.310$, $p < 0.05$), office PP ($r = 0.583$, $p < 0.01$), age ($r = 0.322$, $r < 0.001$), and LVMI (height) ($r = 0.283$, $p < 0.001$). Systolic BP (beta 0.864, $p < 0.001$) and diastolic BP (beta -0.907, $p < 0.001$) were the only independent predictors of RRI in linear regression analysis, while according to multivariate logistic regression analysis, the major factors influencing whether a person reported having RH were RRI, E/e', duration of hypertension, and age.

Conclusions: Increased renal and cardiac haemodynamics, as reflected by increased vascular resistance of intrarenal arteries and E/e', are associated closely with the presence of RH. These findings imply that RRI and E/e' values should be taken into account for the prediction of insufficient control of BP in hypertensive patients.

ORAL SESSION

ORAL SESSION 8B
RESISTANT HYPERTENSION

8B.01 META-ANALYSIS OF FIVE PROSPECTIVE AND RANDOMIZED CONTROLLED TRIALS OF RENAL SYMPATHETIC DENERVATION ON OFFICE AND AMBULATORY SYSTOLIC BLOOD PRESSURE IN TREATMENT RESISTANT HYPERTENSION

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Objective: Renal sympathetic denervation (RDN) has been and is still proposed as a new treatment modality in patients with treatment resistant hypertension (TRH), a condition defined as persistent blood pressure (BP) elevation despite prescription of at least 3 antihypertensive drugs, including a diuretic. However, the randomized controlled evidence that RDN effectively lowers BP is scarce and contradictory. This study investigated the current effectiveness of RDN for TRH.

Design and method: We performed a systematic review and meta-analysis of the randomized controlled trials (RCT) that reported office and ambulatory systolic BP in RDN and control (sham control or drug adjustment) groups at 6 months of follow-up in patients with TRH. Pooled effect sizes were derived, using a random-effects model.

Results: The literature search identified five RCTs with 867 randomized patients. In the pooled analysis, RDN was not associated with a significant decrease, either in office systolic BP (weighted mean difference (WMD): - 4.21 mmHg, 95% confidence interval: -17.12 to 8.69, p = 0.52), or in 24-h ambulatory systolic BP (WMD: -1.94 mmHg, 95% confidence interval: -6.05 to 2.17 mmHg, p = 0.36) compared to control at 6-months of follow-up.

Characteristics of five prospective and randomized studies investigating blood pressure lowering effects of RDN with Symplicity catheters

Variable	SYMPLICITY HTN-2		OSLO RDN		SYMPLICITY HTN-3		PRAGUE-15		DENER-HTN	
Year	2010		2014		2014		2014		2014	
Design	Open		Open		SHAM single-blind		Open		Open	
Drug adherence	Patient diary		Witnessed intake of drugs		Patient diary		Plasma drug concentrations		Questionnaire	
	RDN	Control	RDN	Control	RDN	Control	RDN	Control	RDN	Control
N° of patients	52	54	9	10	364	171	52	54	48	53
N° of drugs at baseline	5.2	5.3	5.1	5.0	5.1	5.2	5.1	5.4	5	5
Intervention	RDN	Fixed drugs	RDN	Drug adjusting	RDN	Fixed drugs	RDN	Drug adjusting	RDN+Drug adjusting	Drug adjusting
Office SBP										
Baseline, mmHg	178	178	156	160	180	180	159	155	160	156
24-h ambulatory SBP										
Baseline, mmHg	?*	?*	149	151	159	160	149	147	151.6	146.8

Conclusions: In patients with TRH, the overall BP lowering effect of RDN is not superior to control. Accordingly, RDN should not be considered as a treatment modality of RHT in clinical practice. Future research should identify the characteristics of patients who might respond to RDN, effective ablation dose and measure that could confirm that RDN do occur.

8B.02 EFFECTS OF LONG-TERM BAROREFLEX ACTIVATION IN CONGESTIVE HEART FAILURE

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Objective: It is well known that congestive heart failure (CHF) is characterized by an increased adrenergic tone and by an impaired baroreflex sympathetic and vagal control. In recent years have been developed additional therapeutic options, baroreflex activation therapy (BAT), capable to antagonize the sympathetic overactivity. It has been reported in CHF patients a significant reduction in muscle sympathetic nerve activity (MSNA) after 6 months BAT. Whether the effects on sympathetic and clinical variables were maintained chronically is unknown.

Design and method: Eleven CHF patients (NYHA class III, left ventricular ejection fraction < 40%, with optimized and stable medical therapy and no active resinchronization therapy) have been evaluated at baseline and after 6 and 24 months BAT follow-up. During each step we collected clinical parameters, HYHA class, six-minute hall walk distance (6MHW), quality of life from the Minnesota Living with Heart Failure Questionnaire score (QOL), LVEF (3D echo), B-type natriuretic peptide (BNP), estimated glomerular filtration rate (eGFR), MSNA by microneurography, and baro reflex sensitivity (variated Kienbaum's method).

Results: Two patients died during long-term follow-up (pneumoniae and acute HF). In the surviving 9 the beneficial effects observed at 6 months (MSNA -28%; BRS +100%; 6MWD +22.7%; LVEF +10%; QOL +37.2%) were maintained 21.5 ± 4.2 months (MSNA -31.6%,p < 0.001; BRS +100%,p < 0.001; 6MWD +19%,p = 0.01; LVEF +2.4%,p < 0.01; QOL +42.7%p < 0.01). A slight but not significant reduction was observed in blood pressure, heart rate, BNP and eGFR values. Hospitalization was not necessary after BAT.

Conclusions: BAT provides long-term reduction in sympathetic activity and improvement in baroreflex sensitivity. This is accompanied by an improvement in clinical status, quality of life and functional capacity and by a reduction in rates of hospitalization.

8B.03 ATHEROMA PROGRESSION IN RENAL ARTERIES AFTER CATHETER-BASED RENAL ARTERY DENERVATION USING SERIAL VOLUMETRIC COMPUTED TOMOGRAPHY ANALYSIS: ANALYSIS FROM THE ENLIGHTN 1 TRIAL

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Objective: We analysed the renal artery wall using serial high resolution CT image analysis before and at 6 months after renal artery denervation in the EnligHTN 1 trial.

Design and method: The EnligHTN-I study was a prospective, multi-center, non-randomized study to evaluate the clinical efficacy of the EnligHTN™ multi-electrode radiofrequency ablation catheter in resistant hypertensive patients. 40 patients with serial renal artery CT imaging were analyzed. Cross-sectional images of renal arteries at 1-mm interval were acquired by a commercially available software (3-mensio, Structural heart, ver 5.1). The luminal and outer wall boundaries of renal arteries were manually traced at 1 mm interval. Total atheroma volume (TAV) was calculated by summation of the plaque area which was the difference between the lumen and vessel wall areas. Percent atheroma volume (PAV) was calculated as the proportion of vessel wall volume occupied by plaque volume.

Results: On serial evaluation, greater progression of PAV and TAV was observed in the proximal zone (Change in PAV, 6.9 ± 0.6 vs. 4.4 ± 0.6; p = 0.01, change in TAV, 76.9 ± 12.9 vs. 17.9 ± 12.9, p = 0.002). Receiver-operating characteristics analysis demonstrated that baseline PAV in the ablation zone > 38.1% was an optimal cut-off value to predict its substantial progression at 6 months after the procedure (AUC = 0.83, sensitivity 90.0%, specificity 74.3%). Interestingly, the change in PAV and lumen areas were associated with reduction in office BP in the distal segment (p = 0.0142 and 0.0226 respectively), but not in the poroximal segment. This could suggest that ablations occurring in the more distal segment may be more effective

at inducing renal denervation and therefore inducing a BP reduction, than the more proximal segment.

Conclusions: Renal artery denervation with the EnligHTN multi-electrode catheter was associated with subsequent vessel wall thickening of the renal arteries. Proximal position and larger atheroma volume at baseline were predictors for a greater increase in vessel wall thickness. By performing ablations more distally and avoiding those with more significant atherosclerotic disease may well reduce the risk of renal artery stenosis after renal artery denervation and potentially lead to a more efficacious renal denervation procedure.

8B.04 RENAL ARTERY DENERVATION FOR TREATMENT OF HYPERTENSIVE PATIENTS WITH OR WITHOUT OBSTRUCTIVE SLEEP APNEA AND RESISTANT HYPERTENSION: RESULTS FROM THE GLOBAL SYMPLICITY REGISTRY

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Objective: Obstructive sleep apnea (OSA) is associated with sympathetic nervous system activation and the development of hypertension. The Global SYMPLICITY Registry is prospectively enrolling real world patients with uncontrolled hypertension including patients with OSA. This analysis compares baseline characteristics and blood pressure (BP) lowering effects of renal denervation in patients with and without OSA.

Design and method: The Global SYMPLICITY Registry is a prospective, multicentre international registry designed to evaluate the safety and effectiveness of renal denervation in a broad population of patients with uncontrolled hypertension. Baseline characteristics antihypertensive medication use, office and 24-hour ambulatory BP are compared between patients with and without OSA.

Results: In a 998 patients with complete 6 month follow-up OSA was reported in 116 patients. OSA patients were more likely to be male than patients without OSA ($n = 752$) (83% vs 56%, $p < 0.0001$), had a larger body mass index (34 ± 6 kg/m2 vs 30 ± 5 kg/m2, $p < 0.0001$) and significantly more, left ventricular hypertrophy (25% vs 15%, $p = 0.008$) atrial fibrillation (19% vs 11%, $p = 0.020$) and diabetes (52% vs 39%, $p = 0.008$). OSA patients were taking more antihypertensive medications (4.9 ± 1.4 vs 4.4 ± 1.3, $p < 0.001$); a higher proportion of aldosterone antagonists (39% vs 20%, $p < 0.0001$), vasodilators (24% vs 13%, $p = 0.001$) and alpha 2 agonists (54% vs 36%, $p < 0.001$). Baseline office systolic BP was 166 ± 23 mm Hg for OSA patients and 163 ± 24 mm Hg for non-OSA patients. At 6 months the office systolic BP was reduced -15.5 ± 24.4 mm Hg in the OSA group and -11.3 ± 25.0 mm Hg in the non-OSA group (both $p < 0.0001$; $p = 0.136$ for difference between the groups). Baseline ambulatory 24-hr systolic BP was 156 ± 20 mm Hg in OSA patients and 152 ± 17 in non-OSA patients. At 6 months 24-hour systolic BP declined -4.6 ± 17.1 mm Hg ($n = 73$, $p = 0.023$) in the OSA group and -7.1 ± 17.6 mm Hg ($p < 0.0001$) in the non-OSA group ($p = 0.450$ for the between group difference).

Conclusions: Renal denervation resulted in significant 6-month BP reductions in patients with and without OSA but there was not a significant difference in the BP change between the 2 groups. Data from a larger cohort of 2100 patients will be presented.

8B.05 FAILURE OF RENAL DENERVATION IN SYMPLICITY HTN-3 IS A PREDICTABLE RESULT OF ANATOMICALLY INADEQUATE OPERATIVE TECHNIQUE AND NOT THE TRUE LIMITATIONS OF THE TECHNOLOGY

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Objective: Actual procedure of renal denervation (RD) in Symplicity HTN-3 study - 4–6 point ablations equally distributed along the length and circumference of main trunk of renal artery (RA) - may only be effective if renal nerves are likewise equally distributed along and around the RA strictly following its course. However, a number of surgical studies demonstrated that renal nerves form a fan-shaped triangle plexus converging toward hilum, i.e. proximally the nerves go at a distance from RA obliquely to its course and join it in the middle/distal portion so that number of fibers available for endovascular ablation is small in proximal portion of RA but rises to maximum in its distal part.
To evaluate whether ablation of sympathetic nerves in distal part of RA is more effective than conventional RD treatment equally distributed in its main trunk.

Design and method: We initiated randomized (1:1) controlled study in which we compare the modified operative technique (ablations performed in distal part and major branches of RA) with conventional RD in patients with resistant hypertension using Symplicity device.

Results: At the time of this analysis 26 patients (13 treated by modified technique and 13 – by conventional RD) completed 6 months follow up. The only complication was 1 post-punctional pseudoaneurysm.
Ambulatory BP decreased significantly in the group of modified technique: -21.3/-11.5 (SD 20.5/11.2) mmHg (mean 24-hr BP, systolic/diastolic respectively), $p = 0.003/0.003$ and only slightly in the group of standard RD: -6.2/-4.5 (SD 16.4/8.3) $p = 0.19/0.07$. The difference in the effects was statistically significant for mean 24-h systolic BP ($p = 0.049$) and close to significance for mean 24-h diastolic BP ($p = 0.085$). Office BP lowering did not differ significantly between groups: -25.3/-10.8 vs -22.1/-12.1 respectively.

Conclusions: Radiofrequency denervation of distal part and segmental branches of renal artery based on the surgical findings of distal convergence of renal nerves seems to be significantly more effective than existed mode of RD presuming equal nerve availability along the artery. This may indicate anatomical inadequacy of the existed mode of RD explaining its failure in Symplicity HTN-3 trial.

8B.06 BAROREFLEX ACTIVATION THERAPY CONSISTENTLY MAINTAINS BLOOD PRESSURE REDUCTION IN A LARGE RESISTANT HYPERTENSION COHORT FOR AT LEAST 6 YEARS

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Objective: Previous reports have indicated that blood pressure (BP) reductions imparted by baroreflex activation therapy (BAT) in patients with resistant hypertension (rHTN) are maintained for at least 5 years. Because such reports have focused only on patients who remain active, it is possible that selection bias could overstate the impact of BAT. The purpose of this investigation is to comprehensively describe long-term BP reductions in rHTN patients receiving BAT using all data currently available.

Design and method: Following collection of the pre-specified 12-month endpoints, patients were followed every 6 months. BP data were collected at each follow-up using a protocol-defined technique to minimize bias.

Results: Original trial enrollment consisted of 322 patients. Of those, 182 presently remain active while 140 are inactive due to withdrawal from the study (112) or death (28). Consistent with earlier reports, BP reductions were > 30/15 mmHg for at least 6 years. Long-term therapy safety was excellent with low rates of stroke, myocardial infarction and hypertensive urgency.

	Baseline (N=322)	Δ1 Year (N=294)	Δ2 Years (N=255)	Δ3 Years (N=238)	Δ4 Years (N=214)	Δ5 Years (N=114)	Δ6 Years (N=34)
SBP (mmHg)	178.1±22.6	−34.3±1.7§	−31.9±2.0§	−34.3±2.2§	−31.6±2.1§	−37.6±2.8§	−33.0±5.6§
DBP (mmHg)	103.1±15.4	−15.5±1.0§	−15.2±1.1§	−17.0±1.2§	−15.9±1.2§	−20.1±1.6§	−15.1±3.1§

Baseline: Mean ± SD Changes: Mean ± SE §$p < 0.001$

Conclusions: BAT-induced BP reductions in rHTN patients were remarkably consistent over time, maintaining high levels of clinical and statistical significance. Previous reports of only active patients faithfully represent the true course of BP response to BAT in a large rHTN cohort.

8B.07 RESULTS FROM THE UK RENAL DENERVATION AFFILIATION- 246 CASES FROM 17 CENTRES

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Objective: To describe the UK experience with Renal Denervation (RDN).

Design and method: RDN may lower blood pressure (BP) in people with resistant hypertension.
The UK Renal Denervation Affiliation is an independent, investigator-led initiative. Each centre had done >5 cases. A standardised dataset was collected retrospectively, anonymised and submitted to the coordinating centre for analysis.

Results: Results from 246 cases from 16 centres are reported. Average cases per centre was 15. Five different ablation technologies were used: unipolar catheters in 198 and multipolar in 48.
Mean age was 56.7 years, 53% female, 87% Caucasian and 27% diabetes. Previous stroke/TIA - 24%; myocardial infarction - 15%; proteinuria - 26%.
Patients were screened by a mean of 1.6 specialists with an interest in hypertension. 86% attended specialist hypertension clinics.
On average 4.7 drugs were used before RDN; 95% were on 3+ drugs; 90% were on RAS blockers, 90% diuretics and 56% aldosterone antagonists at time of RDN.
Pre-RDN mean office BP was 186/102 mmHg. Ambulatory blood pressure monitoring (ABP) data were available for 179 patients (73%). Average pre-RDN ABP was: daytime - 170/98; night - 154/86.
Average follow-up was 10.7 months. Mean Office BP post-RDN was 164/93, a fall of 22/9 mmHg ($P < 0.001$). In 24%, office SBP fell 40+ mmHg. On average, 0.8 drugs were withdrawn per patient and 0.3 drugs added between RDN and follow-up.
Mean daytime ABP after RDN was 158/92 and nighttime ABP 145/81 - fall in daytime ABP was 12/6 ($p < 0.001$). 18% had a drop in day systolic ABP of >20 mmHg.
A decrease in GFR >25% was seen at 10 months in 5% patients. Otherwise, no significant complications were seen.

Conclusions: In a cohort of 246 patients from 16 UK centres who had undergone renal denervation, a significant fall in blood pressure was observed. Office BP fell by 22/9 mmHg. Daytime ambulatory BP fell by 12/6 mmHg.
Carefully selected patients with resistant hypertension exhibited significant BP reduction following RDN. This was a group with severe hypertension who had been well characterised in specialist hypertension clinics. Drug additions/withdrawals did not appear to explain the BP fall.

8B.08 SUSTAINED BENEFICIAL EFFECTS OF MULTI-ELECTRODE RENAL DENERVATION ON CARDIAC ADAPTATIONS IN RESISTANT HYPERTENSION: A 24-MONTHS FOLLOW-UP STUDY

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Objective: In this study we investigated whether multi-electrode catheter-based renal sympathetic denervation (RDN) has favorable effects on left ventricular (LV) structural and functional indices in patients with resistant hypertension after a follow-up of 24 months.

Design and method: Twenty patients with resistant hypertension [age: 57 ± 10 years, 13 males, office blood pressure (BP): $182/97 \pm 19/18$ mmHg under 4.5 ± 0.6 drugs] who underwent RDN were followed-up for 24 months. A full transthoracic echocardiographic study was performed in all patients and LV mass was calculated using the Devereux formula and was indexed for body surface area and height.

Results: Average office BP was reduced to $148 \pm 21/85 \pm 14$ mmHg at 12 months and to $143 \pm 23/80 \pm 14$ mmHg at 24 months ($p < 0.001$ for all). In the RDN group, LV mass index was significantly reduced from 136 ± 20.1 g/m2 (56.5 ± 8.7 g/m2.7) to 121 ± 16.6 g/m2 (50.6 ± 6 g/m2.7) at 12 months and to 115.6 ± 23.3 g/m2 (48.8 ± 9.3 g/m2.7) at 24 months ($p < 0.01$ for all). RDN decreased mean interventricular septum thickness from 12.1 ± 1.2 mm to 11.4 ± 0.9 mm at 12 months and to 11.3 ± 0.9 mm at 24 months ($p < 0.05$ for all). After RDN, the number of patients with concentric LV hypertrophy (i.e. relative wall thickness > 0.42 and LV mass > 48 g/m2.7 for male and > 44 g/m2.7 for female) decreased from 16 patients (80%) at baseline to 10 patients (50%) at 12 months, and to 7 patients (36.8%) at 24 months. Regarding diastolic function RDN caused an increase in mitral valve É / Á ratio from 0.62 ± 0.28 to 0.70 ± 0.25 at 12 months and to 0.84 ± 0.32 at 24 months ($p < 0.05$ for all) and a decrease in the E / É ratio from 14.8 ± 6.1 to 11.8 ± 3.7 at 12 months and to 9.7 ± 4 ($p < 0.05$ for all).

Conclusions: This the first study to show that multi-electrode RDN system results in a significant and sustained improvement of diastolic function and attenuation of LV mass index in increased cardiovascular risk resistant hypertensive patients after a follow-up of 24 months. These results suggest pleiotropic cardiovascular benefits of RDN therapy in the setting of resistant hypertension.

8B.09 RIGHT-SIDED DOMINANCE OF CAROTID BARORECEPTOR REFLEXES IN PATIENTS WITH RESISTANT HYPERTENSION

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Objective: Carotid baroreflex activation therapy (BAT) is a renewed therapy to treat resistant hypertension. Currently, the activation electrodes are implanted unilaterally, preferably at the right carotid sinus. However, information on the carotid baroreflex side dominance is still lacking in hypertensive patients. The aim of this study is to explore carotid baroreflex asymmetry in patients with resistant hypertension.

Table. Mean drop in cardiovascular parameters during left and right carotid sinus massage

Group	SBP? left	SBP? right	HR? left	HR? right	TPR? left	TPR? right
Healthy	11±9	9±5	10±6	9±5	147±176	156±79
HT	14±9	21±10	9±5	13±9	259±202	361±241
HT+BAT	18±10	30±12	10±5	21±11	343±299	558±295

Control= healthy non-hypertensive humans. HT= patients with resistant hypertension. HT+BAT= patients with resistant hypertension and baroreflex activation therapy.

Design and method: To this aim we performed carotid sinus massage (CSM) in 19 patients, who receive BAT for drug-resistant hypertension. CSM was repeated twice at the left and right carotid sinus in a random order and the greatest reflex is presented. The procedure was also performed in 19 patients with resistant hypertension and without BAT. In addition, a group consisting of 19 healthy, age-matched persons also underwent CSM to serve as a control. The same investigator performed CSM in all participants. An independent investigator repeated the procedure in the healthy control group. Systolic blood pressure, heart rate and total peripheral resistance were recorded before and during CSM.

Results: The patients showed a greater drop in systolic blood pressure, heart rate and total peripheral resistance during right than during left CSM (see Table, $p < 0.05$), while the healthy controls demonstrated an equal drop in systolic blood pressure, heart rate and total peripheral resistance during left and right CSM. Remarkably, the patients had a greater drop in those parameters during CSM when compared to the healthy controls.

Conclusions: The carotid baroreflexes in hypertensive patients showed side-dominance towards the right carotid sinus. However, no side dominancy has been demonstrated in healthy humans suggesting that this asymmetry may occur in the course of the hypertensive disease.

ORAL SESSION

ORAL SESSION 8C
CLINICAL ASPECTS

8C.01 SFLT-1 AND PLGF MEASUREMENTS AND THEIR RATIO FOR THE DIAGNOSIS AND PROGNOSIS OF PREECLAMPSIA IN A HIGH-RISK COHORT

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Objective: The soluble Fms-like tyrosine kinase 1 (sFlt-1)/placental growth factor (PlGF) ratio has been introduced as a biomarker for diagnosing preeclampsia (PE) and the prediction of adverse pregnancy outcome. In a cohort of pregnant women with PE or at high risk of PE, the additive value of the sFlt-1/PlGF ratio for diagnosing PE and prediction of adverse pregnancy outcomes was investigated.

Design and method: From September 2011 until August 2013 patients with suspected or confirmed clinical PE were recruited at the Erasmus MC. At time of admission, blood for measurement of sFlt-1 and PlGF was obtained. A sFlt-1/PlGF ratio of >85 was considered suggestive for PE. Clinical characteristics and pregnancy outcomes were retrieved from medical records. The clinical diagnosis of PE was made based on the ISSHP criteria, whereas the fullPIERS definition was used for the rating of adverse pregnancy outcomes.

Results: A total of 96 patients were included. Of the patients, 53 (55%) met the clinical criteria of PE at time of blood sampling. In 11% of these patients (n = 6) the ratio was < 85 (false-negative), whereas in 14% (n = 6) of patients without clinical PE the ratio was >85 (false positive), resulting in positive and negative predictive values of 89% and 86% respectively. Three patients without clinical PE, but with a positive ratio, developed superimposed PE and 2 developed an adverse pregnancy outcome. In 2 of the 6 patients with clinical PE but a negative ratio, an adverse pregnancy outcome was encountered. Using a binary regression model with adjustment for gestational age < 34 weeks, clinical PE was associated with a 9 times increased risk for an adverse outcome, while this was 29 times for an elevated ratio (P = 0.036).

Conclusions: The additive value of an increased ratio for diagnosing PE is limited since most patients with clinical PE also have a positive ratio. An elevated ratio is superior to the clinical diagnosis of PE for predicting an adverse pregnancy outcome.

8C.02 THE SERINE PROTEASE PROSTASIN IS ABERRANTLY FILTRATED IN URINE IN PREECLAMPSIA WITH SIMILAR LEVELS IN PLASMA AND PLACENTA TISSUE COMPARED TO NORMAL PREGNANCY

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Objective: The serine protease prostasin (PRSS8, CAP1) and its activator matriptase and inhibitor nexin-1 are necessary for normal placental development in mice. Prostasin is regulated by aldosterone in the kidney and may activate the epithelial sodium channel (ENaC). Preeclampsia is characterized by disturbed placentation, suppression of aldosterone and avid renal sodium retention with hypertension. It was hypothesized that preeclampsia is associated with low prostasin expression in placenta and spillover of prostasin into urine across the defect glomeular barrier.

Design and method: The hypothesis was addressed in a cross-sectional case-control design with 20 healthy pregnant women and 20 women with new onset of preeclampsia (hypertension and 1+ for protein on urine dipstick). Blood and urine samples were obtained in relation to delivery and placental biopsies were taken immediately after delivery (control = 39 and preeclampsia 40 weeks). Prostasin, matriptase, nexin-1 and HAIs were measured by qPCR and western immunoblotting (prostasin, matriptase, nexin-1) and ELISA (prostasin). Aldosterone was measured in plasma and urine by ELISA.

Results: Women with preeclampsia displayed lower levels of aldosterone in plasma and in spot urine normalized for creatinine (p = 0.0001). Placental weight was not different between groups. Prostasin, matriptase, HAI 1 and 2, and nexin mRNA abundances were not different in placental tissue between groups. Prostasin and nexin protein level in placental homogenate was not different between groups. Active matriptase was expressed at very low levels in placenta. Western blotting showed significantly elevated urine excretion of prostasin in preeclamptic patients compared to controls. Plasma prostasin was not different between groups and did not correlate to aldosterone or placental weight. In summary, preeclampsia is associated with increased urine but not plasma or tissue prostasin

Conclusions: It is concluded that placental and plasma prostasin level is not controlled by aldosterone during term pregnancy. In contrast, prostasin is aberrantly filtered and may contribute to renal EnaC activation and suppression of aldosterone in preeclampsia. Potential impact of prostasin-matriptase on placental development is likely to be at the level of activity and not protein abundance.

8C.03 A KEY ROLE FOR ENDOTHELIN-1 IN THE PATHOGENESIS OF PREECLAMPSIA AND THE ASSOCIATED SUPPRESSION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

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Objective: Women with preeclampsia (PE) display low renin-angiotensin-aldosterone system (RAAS) activity and a high anti-angiogenic state, the latter characterized by high levels of soluble Fms-like tyrosine kinase-1(sFlt-1) and reduced levels of placental growth factor (PlGF). In the present study, we hypothesized that the RAAS suppression in PE is the consequence of the disturbed angiogenic balance.

Design and method: In a group of pregnant women with hypertensive disease of pregnancy and a group of healthy pregnant women, matched for gestational age (GA) we measured mean arterial blood pressure (MAP), urinary protein-to-creatinine ratio (PCR), and the plasma levels of sFlt-1, PlGF, albumin, creatinine, endothelin-1 (ET-1), renin (concentration and activity, PRC and PRA), angiotensinogen, and aldosterone. Since initial analysis revealed that these parameters strongly correlated with each other, multiple regression analysis was applied to establish independent determinants of ET-1, PRC, aldosterone and PCR. A sFlt-1/PlGF ratio >85 was considered to be representative for a high anti-angiogenic state.

Results: Of the 103 pregnant women included, 65 had a sFlt-1/PlGF ratio <85 and 38 had a ratio >85. Plasma ET-1 and creatinine levels were increased in women with a high ratio, whereas PRA and the plasma levels of renin, angiotensinogen, aldosterone and albumin were decreased in these women. The PRA-aldosterone relationship was identical in both groups. Multiple regression analysis revealed that PRC correlated independently with MAP and plasma ET-1 (R2 0.30). In turn, plasma ET-1 correlated positively with sFlt-1 and negatively with PRC (R2 0.52). Independent determinants of plasma aldosterone were GA and PRA (R2 0.56). Finally we found that plasma PlGF, plasma ET-1 and MAP determined PCR (R2 0.69).

Conclusions: The high anti-angiogenic state in PE induces ET-1 activation. Together with the increased MAP in PE this factor suppresses renin release, and in parallel (via PRA reduction) aldosterone synthesis. The identical reduction in PRA and aldosterone argues against studies reporting that a high anti-angiogenic state, via a reduction of adrenal capillary density, selectively suppresses aldosterone. Since ET-1 also was a major determinant of PCR, our data reveal a key role for ET-1 in the pathogenesis of PE.

8C.04 POSSIBLE ROLE OF ARTERIAL FUNCTION IN CANCER TREATMENT TARGETING VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR ONCOLOGIC RESPONSE

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Objective: In the last two decades new drugs that oppose the effects of vascular endothelial growth factor receptor (VEGFR), and thus angiogenesis, have considerably improved treatment of solid tumors. These anti-VEGFR drugs, however, are burdened by several side effects, particularly relevant on heart and vessels. Aim of this study was to analyze the changes in cardiovascular structure and function associated with use of anti-VEGFR drugs.

Design and method: 29 patients (27 affected by renal and 2 by thyroid cancer), received treatment with antiVEGFR drugs. Hemodynamic, non invasive arterial investigation (Pulse Wave velocity -cfPWV-, Augmentation Index-Aix- and Aortic Pressure) and echocardiography with global longitudinal strain (gLS) were performed before starting therapy (T0), after 2 (T1) and 6 weeks (T2). Oncologic outcome was determined by the assessment of the neoplastic lesions at CT scans, according to Response Evaluation Criteria in Solid Tumors Guidelines.

Results: A significant increase of both peripheral and central blood pressure (BP) was observed. We documented a significant raise of cfPWV from T0 (9.9 ± 2.5m/sec) to T1 (10.6 ± 2.3m/sec); at T2 cfPWV still increased in patients who continued treatment (10.8 ± 2.3m/sec), while decreased in patients who stopped therapy (9.8 ± 1.9m/sec). At the on-treatment CT scan (available in 22 patients) 12 patients had a stable disease (StD), 5 showed a reduction of the lesions (responders –PR-) and 5 showed a disease progression (PD). PD patients showed a lower cfPWV at T2 than StD-PR patients (cfPWV: 9.3 ± 2.8 Vs 13.3 ± 1.5 m/sec; p value 0.02). Aix at T1 was higher in PD than in StD-PR (Aix: 36 ± 2.8% Vs 24.6 ± 9.2%; p value 0.02).

Conclusions: Anti-VEGFR treatment is associated with a marked increase in both brachial and central BP. Moreover it early induces an aortic reversible stiffening. The evidence that cfPWV and AIx changes are early and sensitive cardio-vascular effects of anti-angiogenic treatment and that disease progression is associated with a concomitant come back to pre-treatment value of cfPWV and a further increase in augmentation index, suggests their possible role on oncologic outcome.

8C.05 EPOXYEICOSATRIENOIC ACIDS ARE INCREASED IN PLACENTAS OF PREECLAMPTIC PREGNANCIES

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Objective: Plasma concentration of epoxyeicosatrienoic acids (EETs) derived from cytochrome P450 (CYP)-dependent metabolism of arachidonic acid is increased in women with preeclampsia (PE) as compared to normal pregnancy (N), and is even higher in fetal plasma (Herse et al. Circulation 2012, Jiang et al. Am J Hypertens 2013). We hypothesized that differences in EET synthesis or metabolism in the feto-placental unit underlie the observed differences in circulating EETs.

Design and method: To evaluate EETs generation as well the expression of the relavant CYP isoforms and of the metabolizing enzyme soluble epoxide hydrolase (sEH), biopsies of placenta were collected from 19 N and 10 PE at the time of surgical delivery. EETs were extracted from tissue homogenates and analyzed by LCMS.

Results: Both cis- and trans- EETs were detected in the placenta in PE and N, with similar mean ratios. Concentration of total EETs was higher in the placenta in PE compared to N (2.37 ± 1.42 ng/mg vs 1.20 ± 0.72 ng/mg, Mean $\pm$ SD, $P < 0.01$), especially the 5,6-, 8,9- and 11,12-EETs, measured in a subgroup of tissue samples ($N = 10$, $PE = 5$), were elevated. By immunohistochemistry, CYP2C8 was not detectable, CYP4A11 showed weak positivity in the mesenchimal axis of some villi (up to 50%) and scattered signal in the others. Also CYP2J2 was detectable in mesenchimal elements of placentas (scattered in 10–40% of villi, up to 50%). sEH showed weak signal in 1–3 cells for each villous, with a regular pattern distribution. CYP2C8, CYP4A11 and CYP2J2 were not detectable in umbilical cord. Western blotting analysis of placenta homogenates revealed a higher expression of sEH in N with respect to PE (3.9 ± 0.9 vs 0.8 ± 0.4 sEH relative expression, $P < 0.05$).

Conclusions: In conclusion, along with the enzymes implicated in their biosynthesis, significant amounts of EETs were found in the placenta and the umbilical cord. Reduced expression of sEH in PE may contribute to increased EET in the placenta. Altered synthesis of EETs occurs in the placenta, reinforcing the hypothesis of their pathogenetic role in PE.

8C.06 COST-EFFECTIVENESS OF TWO SINGLE-PILL TRIPLE ANTIHYPERTENSIVE THERAPIES BASED ON THE AMBULATORY BLOOD PRESSURE MEASUREMENTS

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Objective: To compare the cost-effectiveness of the two single-pill triple antihypertensive therapies available in Greece using the ambulatory blood pressure measurements; the valsartan (V) against the olmesartan (O) combination with amlodipine (A) and hydrochlorothiazide (H).

Design and method: A Markov model with eight health states was constructed. The short-term effect of antihypertensive treatment on blood pressure (BP) was extracted from the only available head-to-head clinical trial and extrapolated through the Hellenic SCORE and Framingham risk equations, estimating long-term survival and quality-adjusted life-years (QALYs) gained. Both deterministic and probabilistic analyses have been performed using ambulatory BP measurements. Costs and outcomes were evaluated over lifetime, divided into annual cycles and discounted at 3.0% with 2014 as reference year. The analysis was conducted by the Greek third-party-payer perspective (EOPYY).

Results: The estimated QALYs gained with V/A/H were 10.72 ± 0.60 vs. 10.68 ± 0.60 for O/A/H ($p < 0.001$). The total lifetime cost with V/A/H was €$11{,}736.16 \pm 234.59$ vs €$11{,}482.67 \pm 240.17$ for O/A/H ($p < 0.001$). The deterministic analysis of the model demonstrated that the incremental cost-effectiveness ratio of the V/A/H vs. O/A/H was far lower than the Greek GDP per-capita (€6,845/QALY), rendering V/A/H as a cost-effective choice. Extensive sensitivity analyses confirmed the robustness of the results. Probabilistic sensitivity analysis demonstrated a more than 85% probability for V/A/H to be cost-effective at a willingness-to-pay threshold of €16,000/QALY.

Conclusions: This study constitutes the first pharmacoeconomic comparison of single-pill triple antihypertensive therapies. The study demonstrated that V/A/H combination was a cost-effective choice for the treatment of moderate to severe hypertension in the Greek health-care setting.

8C.07 DETECTION OF FREE-CIRCULATING DNA IN PATIENTS WITH ALDOSTERONE PRODUCING ADENOMA

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Objective: Tumor cells undergoing apoptosis or necrosis release cell-free DNA fragments (cf-DNA) of different sizes into the bloodstream. Primary aldosteronism (PA) caused by aldosterone-producing adenoma (APA), but not by bilateral hyperplasia (BAH), has somatic mutations in KCNJ5 gene. Hence, the detection of KCNJ5 mutations in cf-DNA from peripheral blood could allow pinpointing PA patients with APA that must be submitted to Adrenal Vein Sampling (AVS). The aim of the study was to investigate the feasibility of using cf-DNA to detect KCNJ5 mutations in plasma of PA patients.

Design and method: Plasma was collected from the right/left adrenal veins from 6 APA patients undergoing AVS. Plasma from 7 patients with stomach cancer and from 6 healthy subjects was used as positive/negative control, respectively, for cf-DNA quality. The integrity index (DII) was calculated as a ratio of 400pb/200pb amplicons.
A DII cut off equal or greater than 1.0 was assumed to denote cf-DNA integrity. DNA sequences entailing the region with KCNJ5 gene mutations (G151R, L168R, T158A) were amplified using PCR real time (qPCR) to obtain long (400 bp) and short (200 bp) fragments.

Results: The DII for KCNJ5 amplicons on average was consistently > 1.0 in gastric cancer samples, 1.0 in healthy subjects whereas it was < 1.0 in APA patients. The cf-DNA concentration of KCNJ5 amplicons was 10-fold higher in gastric cancer patients than in AVS plasma (4.8 ± 1 vs 0.4 ± 0.1 ng/ul $p < 0.01$). The latter showed no significant differences between the APA and the contralateral side (0.41 ± 0.1 vs 0.36 ± 0.1).

Conclusions: These results confirm the feasibility of isolating cf-DNA not only from patients with malignancies, but also with PA. With current technology the cf-DNA amount and integrity that were obtained suggest the feasibility of using this strategy to detect malignancies. However, at present the results obtained in this study do not support the use of this approach to pinpoint PA with APA based on identification of KCNJ5 mutations. Therefore, further work is needed to develop this innovative and non-invasive strategy that could be useful to pinpoint the patients with APA before the AVS.

8C.08 CONTINUOUS POSITIVE AIRWAY PRESSURE IS EFFICIENT TO DECREASE BLOOD PRESSURE IN PATIENTS WITH RESISTANT HYPERTENSION. RESULTS FROM THE RHOOSAS STUDY

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Objective: Most of patients suffering from resistant hypertension (HTN) have obstructive sleep apnea (OSA). Little data are available to confirm or not the efficacy of continuous positive airway pressure (CPAP) on blood pressure (BP) in resistant HTN.

Design and method: We performed a multicentric, comparative (presence or not of OSA), randomized (sham CPAP then active CPAP versus active CPAP right away), simple blind study in patients with essential resistant HTN (confirmed by ABPM). OSA patients (apnea-hypopnea index, AHI, > 15 per hour) previously untreated for OSA received CPAP. Follow-up was of 6 (active CPAP group) or 9 (sham CPAP group) months.

Results: 61 patients were included, mean age 59.6 years, 77% of men, BMI 29.6 kg/m^2, daytime BP 145/85 mmHg, 3.7 antihypertensive drugs. The 36 OSA patients (59%, mean AHI 44.8) were predominantly men (86 vs 64%, $p = 0.043$), with metabolic syndrome (83 vs 60%, $p = 0.042$). After a period of 6 months under active CPAP, BP decreased by 3.4 ($p = 0.161$) and 2.8 ($p = 0.068$) mmHg over 24 hours, by 1.6 (ns) and 1.9 (ns) mmHg during the day and by 5.5 ($p = 0.022$) and 4.0 ($p = 0.015$) mmHg during the night, respectively for systolic and diastolic BP. Dipper profile was improved by active CPAP (64.5 vs 35.5 %, $p = 0.047$, for systolic BP, and 71 vs 58%, $p = 0.084$, for diastolic BP).

Conclusions: Not only OSA must be investigated in resistant HTN but also its treatment must be started. Indeed, besides its interest on sleepiness, CPAP is efficient to decrease nighttime BP in apneic patients suffering from resistant HTN. This explains in part the benefit of CPAP on morbidity-mortality of OSA patients.

8C.09 A CENTRAL ILIAC ARTERIOVENOUS ANASTOMOSIS RESULTS IN DURABLE AND SUBSTANTIAL BLOOD PRESSURE REDUCTION IN A WOMAN WITH UNCONTROLLED HYPERTENSION AND MULTIPLE DRUG INTOLERANCES

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Objective: Intolerance of antihypertensive medications is a major cause of non-adherence to pharmacotherapy leading to poor blood pressure control in the hypertensive population. We investigated the role of a central iliac arteriovenous (AV) anastomosis in a woman with uncontrolled hypertension due to multidrug intolerances.

Design and method: A sixty-one year old Caucasian female with long-standing poorly-controlled hypertension was referred with multiple drug intolerances. She was unable to take Amlodipine, Nifedipine, Lercanidipine, Lisinopril, Candesartan, Bendroflumethiazide, Indapamide, Spironolactone, Amiloride, Doxazosin, Bisoprolol due to unacceptable side effects. After multiple pharmacotherapeutic attempts over a one year period, she could only tolerate Nebivolol 2.5 mg daily, liquid Nifedipine solution 16 mg twice daily and one quarter Glyceryl trinitrate (GTN) 5 mg transdermal patch daily. Despite this BP control remained suboptimal and she was offered treatment with the ROX coupler device having declined renal denervation for personal reasons.

Results: At baseline the office BP (OBP) was 165/92 mmHg and 24 hour ambulatory BP (ABP) confirmed suboptimal control with an average daytime mean of 158/83 mmHg, nocturnal mean 126/65 mmHg. At 6 months after creation of a right-sided iliac AV anastomosis, OBP was reduced by 24/21 mmHg), and 24 hour ABP daytime average by 14/12 mmHg. At this point her BP was sufficiently well controlled to allow discontinuation of the nebivolol and GTN patch with no further change in BP at 1 year follow up. Baseline and 6 month echocardiograms both showed mild LVH with no change in ventricular wall thickness or ejection fraction. There was no significant change in renal function post-AV anastomosis. Right heart catheterisation at 6 months showed normal pressure in the right heart and pulmonary system.

Conclusions: This is the first report of a patient with multiple drug intolerances and uncontrolled hypertension undergoing treatment with a central iliac AV anastomosis resulting in early and sustained OBP lowering to target levels and reduction in daytime mean ABP. This novel therapy appears to target mechanical properties of the circulation and may be of benefit in the management of patients with uncontrolled hypertension including those with multiple medication intolerances.

ORAL SESSION

ORAL SESSION 8D
RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

8D.01 EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME 2 ON RENAL OXIDATIVE STRESS LEVELS IN APOLIPOPROTEIN E-DEFICIENT MICE

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Objective: The renin-angiotensin system (RAS) has been known for more than a century as a cascade that regulates body fluid balance, renal functions and blood pressure. Angiotensin-converting enzyme 2 (ACE2) is now known as a negative regulator of RAS, and activation of the ACE2 is a possible alternative target for new drugs, since some protective influences on renal and cardiovascular function have been revealed. We hypothesized that ACE2 would exert beneficial effects on oxidative stress levels and renal injury in apolipoprotein E (ApoE) -knockout (KO) mice.

Design and method: In this study, we used 12-week-old wild-type, ApoEKO, and ACE2/ApoE double KO mice. The ApoEKO mice were treated with recombinant human ACE2 (hrACE2) with the daily dose of 2 mg/kg. We characterized the functional, structural and molecular signaling changes in mice kidneys.

Results: Compared with the ApoEKO mice, ACE2 deficiency led to greater increases in renal oxidative stress levels and expression of oxidative stress-inducible proteins NADPH oxidase 4 (NOX4) in the ACE2/ApoE double KO mice. These changes were associated with exacerbation of renal tubule ultrastructure injury and greater activation of Akt and ERK1/2 phosphorylated signaling. Conversely, treatment with hrACE2 significantly attenuated renal oxidative stress levels and ultrastructure injury, and prevented the expression of NOX4 and phosphorylated level of Akt and ERK1/2 in ApoEKO mouse kidneys. However, there were no changes in renal expression of NOX2 and Mas receptor among groups.

Conclusions: Deletion of ACE2 triggers greater increases in renal oxidative stress and tubular ultrastructure injury in the ACE2/ApoE double mutant mice with greater activation of Akt-ERK1/2 phosphorylated signaling. While ACE2 overexpression alleviates renal tubular injury in ApoE-mutant mice with suppression of superoxide generation and downregulation of the Akt-ERK phosphorylated signaling. Strategies aimed at enhancing ACE2 action may have important therapeutic potential for atherosclerosis and renal diseases.

8D.02 PERIPHERAL PLASMA 18-OXOCORTISOL CAN DISCRIMINATE UNILATERAL ADENOMA FROM BILATERAL DISEASES IN PRIMARY ALDOSTERONISM PATIENTS

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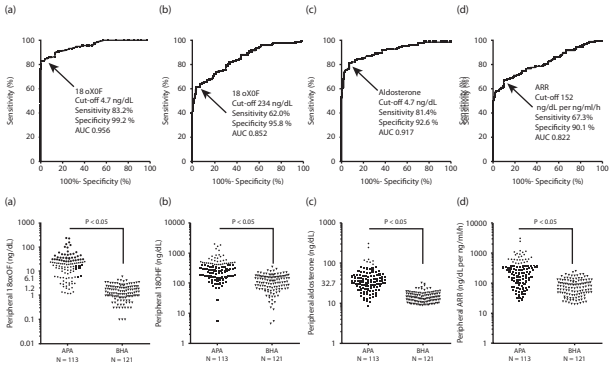
Objective: Definitive diagnosis of primary aldosteronism requires a long process, including adrenal venous sampling, which currently represents the only reliable method to distinguish unilateral from bilateral diseases. In this study, we attempted to determine whether peripheral plasma levels of 18-oxocortisol and 18-hydroxycortisol could contribute to the clinical differentiation between aldosteronoma and bilateral hyperaldosteronism.

Design and method: This study included 234 primary aldosteronism patients including CT-detectable aldosteronoma (APA) (n = 113) and bilateral hyperaldosteronism (BHA) (n = 121), all of whom underwent adrenal venous sampling. All aldosteronomas were surgically resected and their diagnosis was both clinically and histopathologically confirmed. Both 18-oxocortisol and 18-hydroxycortisol were measured using liquid chromatography tandem mass spectrometry.

Results: ROC analysis of 18-oxocortisol discrimination of adenoma from hyperplasia demonstrated sensitivity/specificity of 0.83/0.99 at a cutoff value of 4.7 (ng/dL), compared to that based upon 18-hydroxycortisol (sensitivity/specificity: 0.62/0.96). 18-oxocortisol levels above 6.1 ng/dL and/or of aldosterone above 32.7 ng/dL were found in 95 of 113 aldosteronoma patients (84%) but in none of 121 bilateral hyperaldosteronism, 30 of whom harbored CT-detectable unilateral nonfunctioning nodules in their adrenals. In addition, 18-oxocortisol levels below 1.2 ng/dL, the lowest in aldosteronoma, were found 52 out of the 121 (43%) patients with bilateral hyperaldosteronism. Further analysis of 27 patients with CT-undetectable micro aldosteronomas revealed that eight of these 27 patients had CT-detectable contralateral adrenal nodules, the highest values of peripheral 18-oxocortisol and aldosterone were 4.8 and 24.5 ng/dL, respectively, both below their cutoff levels indicated above.

Conclusions: The peripheral plasma 18-oxocortisol concentrations served not only to differentiate aldosteronoma, but also could serve to avoid unnecessary surgery for nonfunctioning adrenocortical nodules concurrent with hyperplasia or microadenoma.



Receiver operating characteristic (ROC) analysis of patients with APA compared to those with BHA as control and distribution plot analysis. A, B, C and D depict ROC curves to analyze the diagnostic value of respectively peripheral 18-oxocortisol (18oxoF), 18-hydroxycortisol (18OHF), aldosterone and aldosterone-renin activity ratio (ARR), to discriminate APA from BHA. E, F, G and H show respectively the distribution of peripheral 18-oxo-cortisol, 18-hydroxycortisol, aldosterone and aldosterone-renin activity ratio in APA and BHA.

8D.03 EVIDENCE FOR AN ACE-INDEPENDENT TISSUE-SPECIFIC RAS REGULATION AFTER KIDNEY TRANSPLANTATION

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Objective: Angiotensin-converting enzyme inhibitors (ACEis) are beneficial in patients with chronic kidney disease, yet their effects in kidney transplant (TX) recipients remain inconclusive. Allograft quality, transplant vintage and donor-specific antibodies (DSA) might constitute crucial factors, leading to dysregulation of the intrarenal RAS and altered sensitivity to RAS blocking agents such as ACEis. Here, we investigated local angiotensin metabolism in transplant recipients with

varying graft vintage, compared to healthy living donors as controls to assess graft specific and time-dependent changes of RAS effector angiotensin (Ang) II and Ang 1-7 formation rates.

Design and method: In this cross-sectional, single center, exploratory study, 30 kidney biopsies of DSA-positive (BORTEJECT study) and 30 DSA-negative allograft recipients (both groups ACEi treatment vs. no RAS blockade), as well as healthy living kidney donors (n = 5) were used for analyzing intrarenal RAS activity by a highly sensitive mass spectrometry-based assay. Employing selective enzyme inhibitors during ex vivo incubation of biopsy homogenates after Ang I substrate spiking, we investigated ACE and chymase mediated Ang II formation. Respectively, we assessed neprilysin (NEP) and prolyl endopeptidase (PEP)-mediated Ang 1–7 formation from Ang I, as well as ACE2 and prolyl carboxypeptidase (PCP)-mediated Ang 1–7 formation after Ang II spiking. In parallel, we performed immunohistochemical (IHC) renal RAS enzyme stainings. Additionally, we simultaneously quantified multiple systemic angiotensin levels of all patients.

Results: We found increased local Ang II to Ang 1–7 ratios with higher TX vintage in transplant recipients with and without ACEi-treatment. Compared to samples of healthy kidneys, we found a high proportion of ACE-independent Ang II formation rates in biopsies of transplanted patients. Surprisingly, our results revealed that NEP but not ACE2 or PCP is the key Ang 1–7 forming enzyme in transplanted renal tissue independent of TX vintage.

Conclusions: The close association between increased renal Ang II formation rate and the TX vintage, which was independent of ACEi therapy, indicates a profoundly altered local sensitivity to ACEis. Our finding that NEP is the key Ang 1–7-forming enzyme in kidney allografts may have considerable implications for future RAS interfering therapies.

8D.04 CLINICAL BENEFITS OF ADMINISTERING SUPER-SELECTIVE SEGMENTAL ADRENAL VENOUS SAMPLING AND PERFORMING ADRENAL SPARING SURGERY IN THE PATIENTS WITH PRIMARY ALDOSTERONISM

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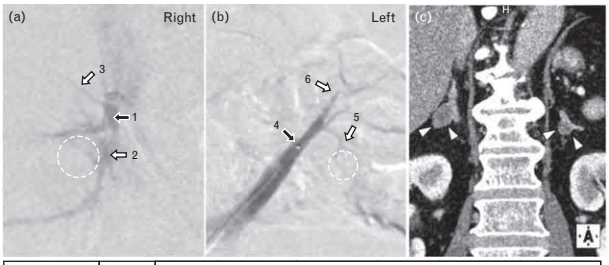
Objective: Adrenal venous sampling (AVS) has been well known to play pivotal roles in clinical differential diagnosis of unilateral aldosterone producing adenoma (APA) from bilateral idiopathic hyperaldosteronism (IHA). However, it is also true that a central vein AVS or c-AVS which collects the blood from right and left central adrenal veins can by no means discriminate bilateral APA from BHA. There have been no published studies reporting the reliable clinical differential diagnosis between bilateral APA and IHA, especially IHA cases with bilateral non-functioning adenomas (NFA), which has been considered practically impossible in clinical differential diagnosis. As an attempt to this clinical dilemma, segmental AVS (S-AVS), which could evaluate segmental effluents from adrenal tributary veins, has been recently developed.

Design and method: We have performed S-AVS in these patients above following C-AVS, via the insertion of a microcatheter in up to three intra-adrenal first-degree tributary veins on bilateral adrenals.

Results: S-AVS did enable us to evaluate the intra-adrenal localization of corticosteroidogenesis. These data did indicate that S-AVS should be performed in the PA patients who had increased aldosterone levels in bilateral central vein and demonstrated space occupying lesions in the bilateral adrenals in order to avoid bilateral adrenalectomy or long lasting medical treatment toward persistent PA. In addition to the situations above, we have administere S-AVS to the following patients; those who had clinically suspected APA but not sufficiently high lateralization indexes according to the results of C-AVS, very young ones with higher clinical probability of recurrence and those who could benefit from partial adrenalectomy by demonstrating the sites of specific steroidogenesis. However, it is also entirely true that S-AVS is more expensive, time-consuming and labor-intensive compared to C-AVS.



	EIV	Right			Left		
		Central vein (1)	APA segment (2)	Non-tumor segment (3)	Central vein (4)	APA segment (5)	Non-tumor segment (6)
Aldosterone (ng/dl)	48.2	22336	38031	722	9459	25800	405
Cortisol (g/dl)	12.7	1106	932	807	947	830	145
A/C ratio (ng/ml/h)	3.80	20.0	40.79	0.89	9.99	31.08	2.80

The angiography during S-AVS (A, B), the coronal CT image (C), and the data in external iliac vein (EIV), each central vein (1, 4) and each tributary vein (2, 3, 5, 6) of 66 year-old male patient with bilateral APAs.

Conclusions: We should carefully select the candidate patients who should undergo S-AVS, which will give a benefit to themselves by demonstrating intra-adrenal steroidogenesis for a safer preserving adrenalectomy.

8D.05 THE ROLE OF NEPRILYSIN IN ANGIOTENSIN 1-7 FORMATION IN THE KIDNEY

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Objective: Cardiovascular and renal pathology is frequently associated with a hyperactivated Renin-Angiotensin-System (RAS) and increased levels of its vasoconstrictive metabolite Angiotensin II. RAS blockade is a widely used therapeutic approach to treat hypertension and prevent hypertonic nephropathy. Due to a well-documented vasodilatory and renoprotective activity of Angiotensin 1–7 and its receptor Mas, the so-called alternative RAS axis reached the focus of therapeutic research. ACE2, a well-described Angiotensin 1–7 producing enzyme, is appreciated as the most important enzyme shifting the RAS towards the alternative RAS-axis. In this study, we aimed to investigate renal angiotensin metabolism and the enzymatic characterization of Angiotensin 1–7 formation pathways in murine and human kidneys.

Design and method: We assayed murine kidney angiotensins in wildtype and ACE2 knockout mice by RAS-Fingerprint analysis. Moreover, we investigated the ex vivo metabolism of spiked Angiotensin I or Angiotensin II in presence and absence of selective inhibitors in kidney extracts by mass spectrometry. MALDI-Imaging was used to investigate renal location of angiotensin metabolism.

Results: Renal Angiotensin 1–7 concentrations were unaffected by ACE2 deficiency, pointing to alternative enzymes contributing to the renal formation of this peptide. Metabolic analysis revealed a major role of Prolyl-Carboxypeptidase (PCP) in Angiotensin 1–7 formation in mice. We identified neprilysin (NEP) depended conversion of Angiotensin I to Angiotensin 1–7 to be the main pathway of Angiotensin 1–7 formation in murine kidneys, which was mainly located in the renal cortex, as confirmed by MALDI-Imaging.
Further testing the potential relevance of these findings for antihypertensive and renoprotective therapy in humans, we analysed angiotensin metabolism in human living donor kidney biopsies. In contrast to mice, the Angiotensin II degrading activity of ACE2 directing the RAS to the alternative Angiotensin 1–7 axis is predominant compared to PCP.

Conclusions: Our data show that in contrast to ACE2, NEP is an important activator of the alternative RAS in the murine and human kidney, which could lead to novel therapeutic strategies in hypertonic nephropathy and could explain molecular mechanisms of action of renoprotective drugs in use.

8D.06 ANGIOTENSIN II TYPE 2 RECEPTOR- AND ACETYLCHOLINE-MEDIATED RELAXATION: THE ESSENTIAL CONTRIBUTION OF FEMALE SEX HORMONES AND CHROMOSOMES

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Objective: Angiotensin II induces vasoconstriction via its type 1 receptors (AT1R), while type 2 (AT2) R are believed to be vasodilator. The latter is not a universal finding and may be limited to women. AT2R-induced vasodilation, if occurring, is mediated via nitric oxide (generated by endothelial NO synthase, eNOS) and/or endothelium-derived hyperpolarizing factors (EDHFs). Studies in eNOS knockout mice suggest that EDHF predominate in women. To distinguish the contribution of female sex hormones and chromosomes to AT2R function and EDHF-mediated vasodilation, we made use of the four core genotype (FCG) model, where the testis-determining Sry gene has been deleted (Y-) from the Y chromosome, allowing XY- mice to develop a female gonadal phenotype. Simultaneously, by incorporating the Sry gene onto an autosome, XY-Sry and XXSry transgenic mice develop into gonadal males.

Design and method: FCG mice underwent a sham or gonadectomy (GDX) operation, and after 8 weeks, animals were sacrificed and iliac arteries were collected to assess vascular function. Vascular function was also studied in C57bl/6 males treated with estrogen after GDX.

Results: XY-Sry males responded more strongly to Ang II than XX females, and the AT2R antagonist PD123319 revealed that this was due to a dilator AT2R-mediated effect occurring exclusively in XX females. The latter could not be demonstrated in XXSry males and XY- females, nor in XX females after GDX, suggesting that it depends on both sex hormones and chromosomes. Indeed, treating C57bl/6 GDX males with estrogen could not restore Ang II-mediated, AT2R-dependent relaxation. To block acetylcholine-induced relaxation of iliac arteries obtained from FCG XX mice, both eNOS - and EDHF inhibition were required, while in FCG XY animals eNOS inhibition alone was sufficient. These findings were independent of gonadal sex, and unaltered after GDX.

Conclusions: AT2 receptor-induced relaxation requires both estrogen and the XX chromosome sex complement, while only the latter is required for EDHF. Estrogen treatment of male mice confirms that this approach is insufficient to re-introduce AT2 receptor-induced relaxation.

8D.07 GENE EXPRESSION ANALYSIS AND BIOINFORMATICS REVEALED POTENTIAL TRANSCRIPTION FACTORS ASSOCIATED WITH RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN ATHEROMA

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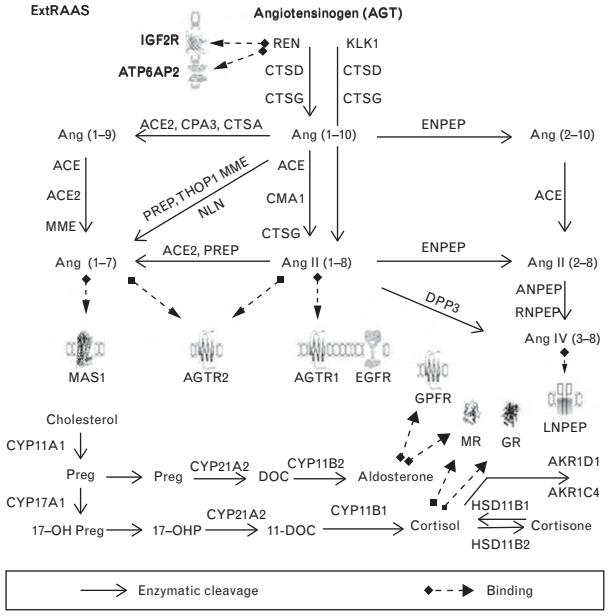
Objective: The implication of the renin-angiotensin-aldosterone system (RAAS) in atheroma development is well described. However, a complete view of the local RAAS in atheroma is still missing. In this study we aimed to reveal the organization of RAAS in atheroma at the transcriptomic level and identify the transcriptional regulators behind it.

Design and method: Extended RAAS (extRAAS) was defined as the set of 37 genes coding for classical and novel RAAS participants (Figure 1). Five microarray datasets containing overall 590 samples representing carotid and peripheral atheroma were downloaded from the GEO database. Correlation-based hierarchical clustering (R software) of extRAAS genes within each dataset allowed the identification of modules of co-expressed genes. Reproducible co-expression modules across datasets were then extracted. Transcription factors (TFs) having common binding sites (TFBSs) in the promoters of coordinated genes were identified using the Genomatix database tools and analyzed for their correlation with extRAAS genes in the microarray datasets.

Results: Expression data revealed the expressed extRAAS components and their relative abundance displaying the favored pathways in atheroma. Three co-expression modules with more than 80% reproducibility across datasets were extracted. Two of them (M1 and M2) contained genes coding for angiotensin metabolizing enzymes involved in different pathways: M1 included ACE, MME, RNPEP, and DPP3, in addition to 7 other genes; and M2 included CMA1, CTSG, and CPA3. The third module (M3) contained genes coding for receptors known to be implicated in atheroma (AGTR1, MR, GR, LNPEP, EGFR and GPER). M1 and M3 were negatively correlated in 3 of 5 datasets. We identified 19 TFs that have enriched TFBSs in the promoters of genes of M1, and two for M3, but none was found for M2. Among the extracted TFs, ELF1, MAX, and IRF5 showed significant positive correlations with peptidase-coding genes from M1 and negative correlations with receptors-coding genes from M3 ($p < 0.05$).

Conclusions: The identified co-expression modules display the transcriptional organization of local extRAAS in human carotid atheroma. The identification of several TFs potentially associated to extRAAS genes may provide a frame for the discovery of atheroma-specific modulators of extRAAS activity.



8D.08 MATRIX METALLOPROTEINASE (MMP) 2 AND MMP9 ACTIVITY IS INCREASED IN CONDITIONS OF ALBUMINURIA ESCAPE UNDER CHRONIC RENIN-ANGIOTENSIN SYSTEM SUPPRESSION

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Objective: Matrix metalloproteinase (MMP) 2 and MMP9 are involved in the pathophysiology of cardiovascular and renal diseases. The aim of this study was to analyze if albuminuria escape that some well-controlled hypertensive patients develop even under chronic renin-angiotensin system (RAS) suppression could be related to an increase in MMPs activity.

Design and method: Concentration of MMP2/9 was analyzed by ELISA, and its activity by gelatin zymography in plasma samples from normoalbuminuric ($n = 17$) and albuminuric patients (moderate $n = 14$ or severe $n = 8$ albuminuria). The interaction between MMPs and its tissue inhibitor (TIMP) was analyzed by a novel assay developed in our laboratory using AlphaLISATM technology. The study of MMPs activity in the kidney as one of the target organs of this pathology was performed in Munich Wistar Frömter (MWF) rats, an experimental model of spontaneous albuminuria. Due to albuminuria is associated with a locus placed on chromosome 8, consomic MWF-8SHR rats, in which chromosome 8 from MWF rats was replaced by the respective one from spontaneously hypertensive rats (SHR), were also studied in order to analyzed whether MMP pattern is differentially associated with albuminuria development or conversely depends on a hypertensive.

Results: Plasma MMPs concentrations were no different while their activities were increased in albuminuric patients as well as collagen type IV, one of their targets molecules. This increase in their activity is due to a significant decrease in MMP2/TIMP2 and MMP9/TIMP1 interaction in albuminuric patients. MMP2/9 activity was also increased in albuminuric MWF rats, and a positive correlation

in MMP9 activity between plasma and kidney samples was observed. Consomic MWF-8SHR rats, showed a decrease in systemic and renal MMP9 activity compared with albuminuric MWF rats.

Conclusions: i) The exclusive determination of circulatory MMP concentration could be underestimating its real activity in the clinical practice; ii) MMPs are multiorganic targets specifically involved in albuminuria escape that present well-controlled hypertensive patients even under chronic RAS blockade.

8D.09 NIGHTTIME HYPOTENSIVE EFFECTS OF CENTRAL ANGIOTENSIN II TYPE 2 RECEPTOR STIMULATION THROUGH IMPROVED SPONTANEOUS BAROREFLEX SENSITIVITY: MORE IN SHR THAN IN WKY

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Objective: The angiotensin II type 2 receptor (AT2R) has been suggested to counterbalance the angiotensin II type 1 receptor (AT1R) in the central regulation of blood pressure and sympathetic tone. We previously reported the decrease in mean arterial pressure (MAP) to selective stimulation of central AT2R with Compound 21 (C21) in conscious spontaneous hypertensive rats (SHR) and normotensive Wistar Kyoto rats (WKY). Here we show the differences in day- and nighttime pressure. We also assess the impact on spontaneous baroreflex sensitivity (SBRS), norepinephrine (NE) plasma levels and autonomic function.

Design and method: Animals were implanted with a radio-telemetry device and an intracerebroventricular cannula connected to a miniosmotic pump delivering saline vehicle, AT2R-agonist C21 alone or in combination with AT2R-antagonist PD123319. MAP was assessed for 14–21 days: 7 days baseline (saline), 7–14 days treatment (e.g. C21) (n = 6–8/group).

Results: During daytime, 7-day C21-infusion decreased MAP similarly in the two strains (WKY -5.5 ± 0.6 mmHg, SHR -5.4 ± 1.5 mmHg). During nighttime, C21 reduced MAP significantly more in SHR (-12.6 ± 1.9 mmHg) than in WKY (-8.2 ± 0.8 mmHg;$p < 0.01$). In SHR, the nighttime hypotensive response was significantly greater than during daytime both after 7 ($p < 0.05$) and 14 ($p < 0.001$) days; a similar trend was seen in WKY. SBRS, on day 2 and day 7 of baseline period, was significantly impaired in SHR compared to WKY (SBRS (ms/mmHg): WKY D2 2.6 ± 0.3, D7 2.5 ± 0.4; SHR D2 2.0 ± 0.1, D7 1.8 ± 0.2;both $p < 0.05$). C21-infusion immediately increased SBRS significantly in both strains; this effect was maintained throughout the infusion period (SBRS(ms/mmHg): WKY D9 3.6 ± 0.3, D14 3.7 ± 0.4;both $p < 0.01$ vs baseline; SHR D9 3.2 ± 0.2, D14 3.4 ± 0.2, D21 3.7 ± 0.1;all $p < 0.01$ vs baseline). The improvement in SBRS on D14 was more pronounced in SHR than in WKY (84 vs 46%;$p < 0.001$). Co-infusion of PD123319 abolished these effects. C21 significantly decreased NE plasma levels and attenuated the bradycardic response to ip bolus propranolol.

Conclusions: Chronic stimulation of central AT2R with C21 lowers MAP through sympatho-inhibition in WKY and SHR. The improvement in SBRS and the hypotensive effect during nighttime is more pronounced in SHR than in WKY. Central AT2R-stimulation could open new therapeutic opportunities in hypertension or diseases characterized by sympatho-excitation.

ORAL SESSION

ORAL SESSION 9A
INFLAMMATION AND IMMUNITY

9A.01 HYPERURICEMIA IS AN INDEPENDENT DETERMINANT OF ARTERIAL STIFFNESS

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Objective: The aim of the study was to identify determinants of arterial stiffness in patients with increased uric acid levels.

Design and method: 280 consecutive subjects (51.4% male) aged 52.98 ± 22.9 years were included in the study. Subjects were never treated before for hypertension or uric acid. A physician measured office BP three times in each subject using a mercury sphygmomanometer. All subjects underwent 24h-ABPM on a usual working day. Pulse wave velocity (PWV) was measured after 15 min of rest in the supine position. The subject was not speaking or sleeping in a quiet, semi-darkened, temperature-controlled laboratory. Participants had been advised to refrain from eating, smoking and drinking caffeine beverages and alcohol before measurement. PWV was calculated as the transit time of the arterial pulse along the carotid-femoral distance divided with the distance measured directly.

Results: Carotid-femoral PWV was independently associated (ANCOVA analysis) with age (B = 0.13, P < 0.001), 24 h average SBP (B = 0.07, P < 0.05) and uric acid (B = 0.72, P < 0.001), but not with office BP values, e-GFR, lipid levels, gender and BMI. Carotid-femoral PWV was found 8.215 ± 0.41 m/sec (SE) in patients with normal uric acid values and 10.252 ± 0.91 m/sec (SE) in patients with hyperuricemia after adjustment for age, gender, office BP, 24 h SBP, 24 h pulse pressure, e-GFR, fasting serum cholesterol, triglycerides and BMI. The difference in carotid-femoral PWV between normal uric acid subjects and hyperuricemic patients was 2.037 ± 1.008 m/sec (SE). This difference was statistically significant at the 0.05 level after Bonferroni's adjustment for multiple comparisons.

Conclusions: Arterial stiffness was found increased in patients with hyperuricemia suggesting a role for increased uric acid in the pathophysiology of large arteries arteriosclerosis independent of age, gender, obesity, blood pressure levels and kidney function.

9A.02 SODIUM SENSITIVE HYPERTENSION: CAN IT BE ASSESSED BY MEASURING URIC ACID LEVELS?

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Objective: It was already documented, by many investigators, that hyperuricemia presents an important factor in the development of essential arterial hypertension. The goal of this study was to examine correlation between serum uric acid levels in patients with essential arterial hypertension and index of sodium sensitivity, as the main parameter of salt-sensitive hypertension.

Design and method: The investigation included 236 participants of both sexes. Clinical group included 178 of participants, mean age 59 ± 18.2 years, with at least 5 years of hypertension history and preserved kidney function. They were divided into 2 subgroups according to the serum uric acid levels. Control group involved 58 healthy volunteers, who were age and sex matched with the clinic group. The levels of serum uric acid were measured spectrophotometrically. Sodium sensitivity index was assessed as the main parameter of salt sensitive hypertension. It was calculated as the difference in 24 hours sodium excretion between period of sodium rich diet (250 mmol/24 hours) and sodium lean diet (50 mmol/24 hours), divided by mean arterial pressure, measured twice respectively.

Results: First clinical subgroup had 95 patients, with normal uric acid serum values (256 ± 35 μmol/l), and the second subgroup had 83 patients, with significant increase of uric acid serum values (572 ± 49 μmol/l; p < 0.01). Sodium sensitivity index in the first subgroup had normal values (0.026 ± 0.005), and in a second subgroup was significantly higher (0.078 ± 0.02; p < 0.01). We found a high positive correlation (r = 0.721, p < 0.01) between an increase in serum uric acid level and salt-sensitivity index in patients.

Conclusions: Hyperuricemia and salt-sensitivity index correlate highly, therefore serum uric acid levels may be used as diagnostic parameters of salt-sensitive arterial hypertension in the population of patients with essential hypertension.

9A.03 OSTEOPONTIN AND OSTEOPROTEGERIN ACTIVATE MONOCYTES INTO ANTI-INFLAMMATORY PROPERTIES IN THE PATIENTS WITH HYPERTENSION-RELATED VASCULAR CALCIFICATION

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Objective: Monocytes/macrophages are believed to play roles in vascular calcification(VC). Here, we analyzed whether osteopontin(OPN) and osteoprotegerin(OPG) might exert effects by promoting macrophage polarization into an anti-inflammatory phenotype in the patients with hypertension(HT)-related VC.

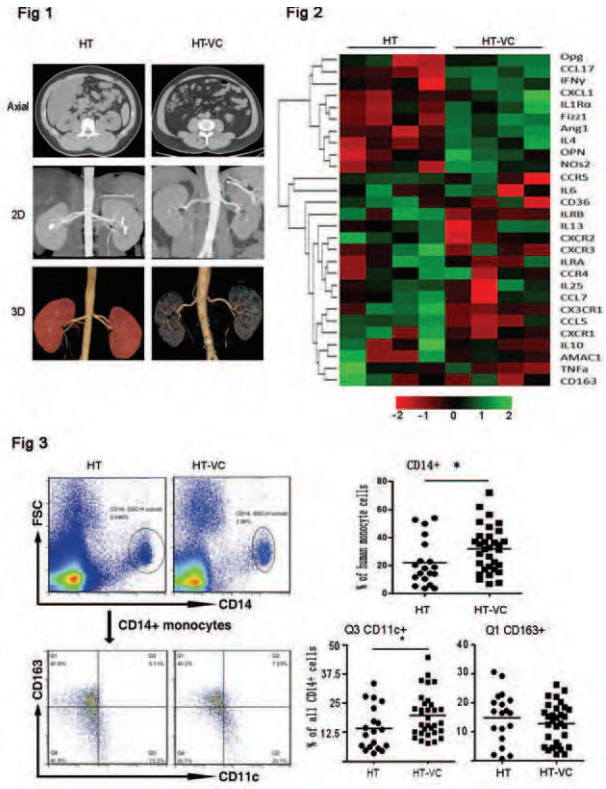

Fig 1. Hypertenison patients with Vascular calcification(HT-VC)or without vascular calcificaiton(HT) was identified by using artery electronic calculators tomography.
Fig 2. M1 and M2 macrophage cytokines qPCR-array.
Fig 3. Human peripheral blood CD14+ cells including M1~like CD11c+ and M2~like were analysised by flow cytometer. CD14+ cells %of human monocyte and CD11c+ cells% of CD14+ cells was significantly increasesd in HT-VC *P<0.05.

Design and method: In this study, 412 HT patients with or without VC were identified by using artery electronic calculators tomography(fig 1). Histological analysis was performed in the samples of aortic blood vessel from calcified vessels. Human peripheral blood CD14+ monocytes including M1~like CD11c+ and M2~like CD163+ cells were analysised by flow cytometery. The effects on M1 and M2 macrophages corrlated with cytokines and chemokines were assessed by qPCR.

Results: We show that in HT patients,VC was correlated with higher systolic pressure,the higher incidence and more intima-media thickness of the plaque of carotid artery and was associated with arterial stiffness(including higher carotid-femoral pulse wave velocity, aortic systolic pressure, augment pressure, augment index($P < 0.05$)). Furthermore, The phenotype of M1∼like monocyte/ macrophages was significantly increasesd in HT patients with VC ($P < 0.05$)(Fig 3). Although both Serum OPN and OPG levels increased in HT patients with VC, they significantly upregulated anti-inflammatory M2 macrophages marks ($P < 0.05$) and only OPN downregulated pro-inflammatory M1 macrophages marks.

Conclusions: The phenotype of M1 macrophages and M2 macrophages is promoted by VC(fig 2). The ability of OPN and OPG to promote differentiation of macrophages into an alternative, anti-inflammatory phenotype may explain their protective effects in VC of HT patients. These data provide novel insight into the link between inflammtion and VC diseases.

9A.04 CARDIOVASCULAR RISK FACTOR PROFILE IN AN ITALIAN COHORT OF PATIENTS WITH RHEUMATOID ARTHRITIS: RESULTS OF A THREE YEARS FOLLOW-UP

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Objective: Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by an elevated cardiovascular morbidity and mortality, but detailed informations on the risk score profile using different approaches, as well as on the major determinant(s) of the cardiovascular risk of these patients are scanty.

Design and method: The present study reports data collected in a cohort of RA patients with CV risk score calculators Framingham and SCORE uncorrected or corrected according to European League against Rheumatism (EULAR) recommendations. Cardiovascular events were recorded during the 3 yrs follow-up, to determine the burden of CV morbidity and the relative impact of traditional CV risk factors and disease activity/severity.
We enrolled in the study 198 pts, 77% females, age 65.0 ± 11.6 yrs (means $\pm$ SD), disease duration 13 ± 9 yrs. 76% of pts were RF +, 68% ACPA+ and 46% with erosive disease. 3% were smokers and 32% ex smokers. Mean BMI (24.6 ± 4.4), plasma levels of cholesterol (total,HDL,LDL), triglycerides and glucose and prevalence of smokers were comparable with those detected in the local general population, while the prevalence of hypertension and diabetes were significantly higher in both males and females.

Results: Risk scores with Framingham were lower than in general population and comparable using SCORE, but the application of 1.5x correction factor for RA, as recommended by EULAR, modified these figures. The number of hypertensive and diabetic pts increased significantly ($P<.0001$/ $.019$) during the follow-up as well as the mean values of Framingham and SCORE ($p < .015$/$.011$). The MI and stroke prevalence were 5% and 2% respectively: the incidence rate/1000 person/year were 8.8 and 3.7 versus 2.7 and 2.6 in the general population. No relation was detectable between disease activity indices and CV events or risk scores.

Conclusions: The present study provides evidence that 1) RA is associated with an increased CV morbidity even in the medium follow-up period, 2) risk score needs to be adjusted as by EULAR indications to obtain sensitive assessment of risk and 3) that hypertension represents a major CV risk factor in this population.

9A.05 SYMPATHETIC NERVOUS SYSTEM DRIVES RENAL INFLAMMATION BY ALPHA(2A)-ADRENOCEPTORS

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Objective: Inflammatory processes play a pivotal role in pathogenesis of chronic kidney disease (CKD). alpha2A-adrenoceptors (alpha2A-AR) in adrenergic neurons are known for regulating sympathetic tone by controlling norepinephrine (NE) release from sympathetic nerve endings by a negative feedback mechanism. Increased sympathetic tone leads to hypertension and the progression of CKD. In addition, there is some evidence that alpha2A-ARs on non-adrenergic cells have modulating effects on the inflammatory response. Here, we tested our hypothesis that deletion of alpha2A-AR exaggerates renal fibrosis.

Design and method: Unilateral ureteral obstruction (UUO), a model of renal fibrosis, was performed in FVB mice lacking the alpha2A-AR (KO) and compared to its wild-type (WT). Renal NE tissue content was measured by HPLC. Immunohistochemistry and gene expression analysis were performed 7 days after UUO. Murine macrophages were isolated from the peritoneal cavity, subsequently cultured and stimulated.

Results: Renal sympathetic neurotransmission and NE tissue content was significantly exaggerated in KO compared to WT. Despite an increased sympathetic activity, renal fibrosis, assessed by sirius red/ fast green collagen staining ($p = 0.0428$) and renal collagen-1 expression ($p = 0.001$), was significantly attenuated in KO compared to WT 7 days after UUO. Moreover, the expression of the pro-inflammatory and pro-fibrotic cytokines TNF-alpha ($p < 0.05$) and TGF-beta ($p < 0.05$), as well as the chemokines CCL2 ($p < 0.05$) and CCL5 ($p < 0.05$) were significantly reduced in mice lacking the alpha2A-AR compared to WT indicating a pro-inflammatory role of alpha2A-AR on immune cells in the progression of renal fibrosis. In addition, F4/80-staining confirmed the reduced renal infiltration of macrophages in KO. Stimulation of isolated murine peritoneal macrophages from WT mice with the alpha2-AR-agonist UK14.304 (0.1 μM) induced a 2-fold expression of TNF-alpha ($p < 0.05$).

Conclusions: Alpha2A-ARs appear not only to be a key player in regulating sympathetic tone, but also promote inflammation and the progression of renal fibrosis in response to kidney injury. To dissect the cell type and whether adrenergic or non-adrenergic alpha2A-ARs are responsible for these effects further experiments are necessary. Experiments with a transgenic mouse re-expressing the adrenergic alpha2A-ARs are planned. First results give an idea that non-adrenergic alpha2A-ARs could responsible for the observed effects.

9A.06 IMPACT OF METABOLIC, HEMODYNAMIC AND INFLAMMATORY FACTORS ON TARGET ORGAN DAMAGE IN HEALTHY SUBJECTS

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Objective: We wanted to test the impact of metabolic, hemodynamic and inflammatory factors on target organ damage (TOD) defined as cardiac hypertrophy, atherosclerosis, arterioclerosis and microvascular damage.

Design and method: In a population based cohort study of 2115 healthy subjects (1049 male 1066 female) with a mean age of 53.1 ± 10.5 without known diabetes or cardiovascular disease we measured fasting plasma glucose (FPG), serum insulin, lipid profile, soluble urokinase receptor (suPAR), c-reactive protein (CRP), urine albumin/creatinine ratio (UACR), 24-hour ambulatory systolic (24hSBP) and diastolic blood pressure (24hDBP), left ventricular mass index (LVMI) by M-mode echocardiography, carotid plaques (CP) by carotid ultra sound and carotid-femoral pulse wave velocity (PWV). To establish best model for association of LVMI, CP, PWV and UACR we used multiple linear regression analysis starting with inclusion of all variables without co-linearity taking away one by one non-significant variables.

Results: Cardiac hypertrophy assessed by LVMI was primarily associated with gender ($\beta = 0.37$), 24hSBP ($\beta = 0.26$) and HR ($\beta = -0.15$). Insulin resistance (IR) and inflammation only had minor albeit significant impact on LVMI assessed by HOMA ($\beta = 0.09$) and CRP ($\beta = 0.05$). Atherosclerosis assessed by CP was primarily associated to age ($\beta = 0.31$), 24hSBP ($\beta = 0.13$) and smoking ($\beta = 0.13$). Arteriosclerosis indicated by PWV was primarily associated to age ($\beta = 0.39$), 24hSBP (β=0.31), gender ($\beta = 0.14$) and HR ($\beta = 0.15$). Additionally, FPG ($\beta = 0.04$), total cholesterol/high density lipoprotein ratio (TC/HDL) ($\beta = 0.04$) and CRP ($\beta = 0.03$) had positive independent impact on PWV. Microvascular damage assessed by UACR was primarily associated to gender ($\beta = -0.16$), 24hSBP ($\beta = 0.09$) suPAR ($\beta = 0.09$), smoking ($\beta = 0.05$) and age (β=0.05).

Conclusions: We conclude that 24hSBP were independently associated to cardiac hypertrophy, arteriosclerosis, atherosclerosis as well as microvascular damage, whereas IR and inflammation were only weakly, independently associated to hypertrophy, arteriosclerosis and microvascular damage in healthy subjects.

9A.07 CARDIOVASCULAR TARGET ORGAN DAMAGE IN PREMENOPAUSAL SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS AND IN CONTROLS. ARE THERE ANY DIFFERENCES?

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Objective: In patients with systemic lupus erythematosus (SLE) a greater prevalence of structural and functional cardiovascular (CV) alterations has been described, possibly explaining the higher incidence of CV events, as compared to subjects matched for age and sex.
Aim of this study was to analyze the presence of target organ damage in premenopausal women with SLE and in controls matched not only for demographic characteristics but also for other cardiovascular risk factors.

Design and method: 34 patients with SLE clinically stable (SLEDAI Score 2.5 +/- 1.5) (mean age 32 ± 7 years, range 19–44) and 34 controls matched for sex, age, body mass index (BMI), clinic blood pressure (BP) and antihypertensive treatment (if present), underwent: 24 hours BP monitoring, echocardiography with tissue Doppler analysis (TDI) for the evaluation of left ventricular (LV) structure and of systolic and diastolic function, carotid ultrasound for intima-media thickness (IMT) and carotid distensibility measurement, and pulse wave velocity measurement for aortic stiffness (PWV).

Results: By definition no difference was observed for age, sex, BMI and clinic BP values and a similar Framingham risk score was observed between SLE and controls (1.3 ± 2.7 vs 1.5 ± 2.3%, p = ns). No significant differences were observed for all echocardiographic parameters except LV longitudinal systolic function (Sm), an early index of LV systolic dysfunction (see Table). Carotid IMT and distensibility, as well as PWV and the prevalence of an abnormal aortic stiffness were both similar in the two groups. At the logistic analysis, PWV was independently associated with LV mass in controls and with the steroid weekly dose in SLE patients.

	Controls	SLE	*p*
24 hours Systolic BP (mmHg)	117±9	115±10	ns
24 hours Diastolic BP (mmHg)	74±7	73±10	ns
24 hours Heart Rate (bpm)	75±9	81±9	0.005
LV mass index ($g/h^{2.7}$)	27±6	28±6	ns
Relative Wall Thickness	0.29±0.4	0.28±0.5	ns
Sm cm /sec	9.6±1.4	9.0±1.3	0.038
PWV (m/s)	6.98±0.73	6.77±0.80	ns
IMT (mm)	0.44±0.07	0.44±0.07	ns
Distensibility ($kPa^{-1}\ 10^{-3}$)	19.4±6.4	22.2±10.0	ns

Conclusions: In patients with SLE and low activity index of the disease we did not observe significant vascular alterations as compared to controls with similar cardiovascular risk. The early LV systolic impairment observed in this group of patients needs confirmation in larger cohorts.

9A.08 INTERLEUKINS 33 AND 1B SERUM LEVELS ARE CONNECTED TO COMMON CAROTID ARTERIES REMODELING IN HYPERTENSIVE PATIENTS WITH OBESITY

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Objective: To investigate interrelations between interleukin 33 (IL-33) and 1B (IL-1B) serum levels and common carotid arteries (CCA) remodeling in hypertensive patients with obesity.

Design and method: 80 hypertensive patients (51 obese) have been observed. An ultrasound examination of CCA with estimation of its geometrical type was performed (cut-off value for vascular wall hypertrophy was vascular segment mass >0,275 g/cm, concentric remodeling was diagnosed with relative wall thickness of CCA >0,2). IL-33 and IL-1B serum levels were estimated using ELISA.

Results: IL-33 and IL-1B levels were higher in hypertensive patients (p < 0,001), independently of BMI. Cluster analysis was made to reveal both cytokines' levels impact on CCA geometry. IL-33>73 pg/ml, IL-1B>25 pg/ml was associated with 80,0% prevalence of normal CCA geometry and 20,0% of its concentric hypertrophy. IL-1B>20 pg/ml with IL-33 < 71 pg/ml was characterized by 80,0% prevalence of normal geometry, 10,0% of non-hypertensive concentric remodeling of CCA, 5,0% of concnetric and 5,0% of eccentric hypertrophy. IL-33>71 pg/ml with IL-1B<25 pg/ml was associated with decrease of normal CCA geometry prevalence to 50,0% with increase of concentric hypertrophy rate to 41,7%; other 8,3% patients had eccentric hypertrophy of CCA. IL-33<71 pg/ml, IL-1B<20 pg/ml (p>0,05 vs control group) had 57,9% of normal geometry, 15,8% of concentric remodeling, 15,8% of concnetric hypertrophy and 10,5% of eccentric hypertrophy of CCA.

Conclusions: IL-33 and IL-1B serum levels were elevated in hypertensive patients independently of presence of obesity. A pronounced isolated increase in IL-33 level was associated with abrupt increase of CCA hypertrophy prevalence, especially its concentric variant. Accompanying increase in IL-1B level reduced this effect.

9A.09 PROTECTION AGAINST COMPLEMENT ACTIVITY IS REDUCED IN ARTERIAL HYPERTENSION

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Objective: Different elements contribute to arterial hypertension (HTN) etiology. Among these, endothelial dysfunction and vascular inflammation are now considered important co-factors. We hypothesized that distinctive molecular pathways of endothelial activation are present in HTN patients.

Design and method: 6 HTN patients, free of any other condition that may have affected the vascular endothelium, (mean[SD] age 40[11], 67% female) and 13 healthy controls (age 39[10], 37% female) participated. Endothelial cells (ECs) were harvested from a superficial forearm vein through 20-gauge angiocatheter by inserting 3 endovascular wires sequentially under sterile conditions. ECs were washed from wires and fixed on slides. Each harvesting yielded 2000–5000 ECs. Purified ECs were stained for immunofluorescence.

Results: We identified reduced expression of CD59, a plasma membrane-bound protein that prevents the final assembly of the terminal complement complex (TCC), in HTN patients compared to controls (0.2551 vs 0.5790, p = 0.05). In vitro experiments confirmed an increased complement deposition/activity in CD59-knockout endothelial cells vs controls. (C5b-9 positivity[SD] 23.3[4.8]% vs 8.3[2.8]%, p < 0.05)

Conclusions: Protein expression is similar among arterial and venous endothelial cells, but venous ECs are not subject to the direct effect of elevated blood pressure, since they are located in low-pressure districts barely influenced by arterial blood pressure. Therefore, an increased arterial blood pressure cannot be the cause of this protein dysregulation. On the contrary, we suggest that the presence of reduced CD59 expression may be a co-factor in the development of arterial hypertension and the increase in vascular risk.

ORAL SESSION

ORAL SESSION 9B
ENDOCRINE HYPERTENSION

9B.01 CLINICAL SIGNIFICANCE OF CONTRALATERAL ADRENAL SUPPRESSION DURING ADRENAL VEIN SAMPLING IN PRIMARY ALDOSTERONISM

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Objective: Adrenal vein sampling (AVS) is recognized by Endocrine Society guidelines as the only reliable mean to distinguish between aldosterone producing adenomas and bilateral adrenal hyperplasia, the two most common subtypes of primary aldosteronism (PA). However, despite being the gold-standard procedure, AVS protocols are not standardized and vary widely between centers. The objective of the present study was to assess whether the presence or absence of contralateral adrenal (CL) suppression has an impact on the postoperative clinical and biochemical parameters in patients who underwent unilateral adrenalectomy for PA.

Design and method: The study was retrospectively carried out in eight referral hypertension centers in Italy, Germany and Japan. Case detection and subtype differentiation were performed according to the Japan Endocrine Society and The Endocrine Society guidelines and a total of 234 AVS procedures were included in the study. CL suppression was defined as aldosterone/cortisol non dominant adrenal vein/aldosterone/cortisol peripheral vein less than 1.

Results: Overall, 82% of patients displayed CL suppression at AVS, with no statistically significant differences among centers. This percentage was significantly higher in ACTH-stimulated compared with basal procedures (90% vs 77%). The contralateral ratio was inversely correlated with the aldosterone level at diagnosis and, among AVS parameters, with the lateralization index ($P < 0.02$ and $P < 0.01$, respectively). To investigate whether the presence of CL suppression was correlated with response to adrenalectomy, we analyzed the CL suppression status with regard to the patient's clinical and biochemical postoperative parameters. No differences were observed between the two groups for the main clinical and biochemical parameters (systolic and diastolic blood pressure, aldosterone, PRA, PRC, K+, number of drugs, reduction of blood pressure levels, and the number of classes of drugs assumed), but patients with CL suppression underwent a significantly larger reduction in aldosterone levels after adrenalectomy.

Conclusions: For patients with lateralization indices of greater than 4 (which comprised the great majority of subjects in this study), contralateral suppression should not be required to refer patients to adrenalectomy because it is not associated with a larger blood pressure reduction and might exclude patients from curative surgery.

9B.02 SOMATIC MUTATIONS IN THE PROMOTER REGION OF THE TWIK-RELATED ACID-SENSITIVE K+ CHANNEL 2 (TASK-2) GENE IN ALDOSTERONE PRODUCING ADENOMAS

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Objective: We previously showed that a blunted expression of the Twik-related Acid-Sensitive K+ channel 2 (TASK-2) is a common feature of Aldosterone Producing Adenoma (APA). Thus, we aimed at investigating the presence of mutations in the promoter region of the TASK-2 gene (KCNK5) in APA.

Design and method: We sequenced the entire TASK-2 promoter region of 88 APA and 98 primary hypertensive patients (controls). We next tested the in vitro effects of the most frequently detected mutation by fusing the mutated and wild type TASK-2 promoter region to the luciferase coding sequence and transfecting the reporter vectors in H295R cells.

Results: We detected only one mutation (C999T) in one of 98 primary hypertensive patients. Seven novel mutations were found in 16% of APA: the C999T variant was found in 6% of APA, the G595A in 3.5% of APA, the G36A in 2% of APAs, while the Gins466, G263C, C1247T and G1140T mutations in 1% of APA. None was germline. By site-direct mutagenesis we demonstrated that the C999T mutation significantly decreased the TASK-2 transcription activity and luciferase signal of the reporter vector in transfected H295R cells (fold change of normalized luciferase signal: 0.55 ± 0.22, $p < 0.01$) as compared to the wild type promoter sequence.

Conclusions: Thus, we demonstrated that 16% of APA have seven recurrent mutations in the promoter region of TASK-2 gene. One of these TASK-2 genetic variants blunts the transcription of the TASK-2 in human adrenal cells, thus suggesting a possible molecular mechanism contributing to the autonomous aldosterone secretion typical of APA.

9B.03 A NOVEL INSERTIONAL SOMATIC KCNJ5 MUTATION IN AN AUSTRALIAN PATIENT WITH AN ALDOSTERONE PRODUCING ADENOMA

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Objective: Primary aldosteronism (PA), in which there is excessive and autonomous adrenal production of aldosterone, accounts for around 5–10% of hypertension. PA may be unilateral (usually aldosterone-producing adenoma [APA]) or bilateral (usually adrenal hyperplasia). Recently, somatic mutations in KCNJ5 (encoding a potassium channel) have been detected in about 40% of surgically removed APAs. The aim of this study was to screen for additional somatic mutations in KCNJ5 in a cohort of APAs removed from 87 Australian patients.

Design and method: The full-length coding sequence and flanking regions of KCNJ5 in APA and adjacent cortex was resequenced. Functional changes caused by a novel mutation were studied by expressing wild-type (WT) or the mutant KCNJ5 channel in Xenopus oocytes (to examine electrophysiological effects) and transfecting empty GFP vector or the GFP-tagged mutant channel in human adrenocortical carcinoma (H295R) cells (to assess aldosterone release).

Results: KCNJ5 mutations were detected in 37 APAs, and included the previously reported E145Q (n = 3), G151R (n = 20) and L168R (n = 13) mutations plus a novel 12-bp mutation, c.414–425dupCGCTTTCCTGTT (A139_F142dup) that duplicates the AFLP sequence just upstream of the selectivity filter. No mutations were found in adjacent cortices. On expression in Xenopus oocytes, the A139_F142dup mutation reduced the resting membrane potential and channel selectivity for potassium (K/Na permeability ratio 31 in WT KCNJ5 channels vs 7 in the A139_F142dup mutant). When transfected into H295R cells, A139_F142dup increased basal aldosterone release 2.3-fold over WT. This was not increased further by incubation with ATII. Clinically, the 54-year-old male from whom the mutation-bearing APA was removed had relatively severe PA with resistant hypertension, markedly elevated aldosterone/renin ratio (aldosterone 490 pmol/L, renin 2 mU/L, ratio 296) and an 11 mm left adrenal tumour on CT with lateralization to that side on adrenal venous sampling.

Conclusions: Resequencing of a large Australian cohort of patients with APA further confirmed the major role of KCNJ5 somatic mutations in APA. The novel duplication mutation we report here has similar functional effects to the other mutations affecting the selectivity filter of the KCNJ5 channel with reduced membrane polarization, reduced selectivity to K and increased aldosterone release.

9B.04 DOES CONTRALATERAL SUPPRESSION AT ADRENAL VENOUS SAMPLING PREDICT OUTCOME FOLLOWING UNILATERAL ADRENALECTOMY FOR PRIMARY ALDOSTERONISM? A RETROSPECTIVE STUDY

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Objective: In primary aldosteronism (PA), adrenal vein sampling (AVS) distinguishes unilateral and bilateral disease. In AVS aldosterone/cortisol ratios (A/F) correct aldosterone concentration for dilution from non-adrenal blood. Comparisons are then made between left, right and peripheral A/F ratios. Criteria for interpretation however vary widely. Most units use the lateralisation index (LI); A/F dominant: A/F non-dominant with a cut-off value varying from 2–4 for unilateral disease. We use the criteria of 'contralateral suppression' (CS) defined as: A/F (adrenal) < = A/F (peripheral) on the unaffected side, combined with a ratio >=2 times peripheral on the affected side. Patients with one side clearly dominant but without CS are however sometimes offered surgery. The importance of CS in AVS interpretation is unclear, and we therefore performed a retrospective study to determine if CS in unilateral PA was associated with blood pressure (BP) and biochemical outcomes.

Design and method: All patients who underwent unilateral adrenalectomy for PA at the Princess Alexandra Hospital between 2000 and 2014 were included if AVS was successful (cortisol (adrenal): cortisol (peripheral) >=3 bilaterally), if the LI was >=2 and if they had >=6 months of post-operative follow up. Cases were reviewed for BP and biochemical outcomes with respect to the presence and degree of CS.

Results: 80 patients were suitable for review, and 66 had CS. Baseline characteristics were similar. At post-operative follow up, those with CS had a lower systolic BP (SBP; 128mmHg vs. 144mmHg p=0.001), a greater proportion with cure or improvement of hypertension (96% vs 64%, p = 0.0034), a greater proportion with biochemical cure of PA on fludrocortisone suppresion testing (43/49 (88%) vs 4/9 (44%), p = 0.002) and were on a lower number of antihypertensive medications (0 vs 1.5, p = 0.0032). In a multivariate model, the degree of CS and pre-operative SBP were independently associated with post-operative SBP, but LI, gender and age were not.

Conclusions: In this study the presence of CS correlated with good BP and biochemical outcomes from surgery. This suggests that CS should be a factor in deciding whether to offer surgery for treatment of PA.

9B.05 ASSOCIATION OF PLASMA PARATHYROID HORMONE WITH NIGHTTIME BLOOD PRESSURE IN PRIMARY HYPERPARATHYROIDISM. THE "EPLERENONE IN PRIMARY HYPERPARATHYROIDISM" TRIAL

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Objective: High parathyroid hormone (PTH) is a cardiovascular risk factor. Elevated plasma PTH levels are independently linked with high nighttime blood pressure (BP) in hypertensive patients. We therefore investigated the association between PTH and nighttime BP in patients with primary hyperparathyroidism (pHPT).

Design and method: We analyzed patients with pHPT who participated in the "Eplerenone in Primary Hyperparathyroidism" (EPATH) Trial. Blood sampling was performed after an overnight fast and all laboratory parameters were determined immediately after blood sampling. 24-hour ambulatory BP monitoring was performed using a certified device (Mobil-O-Graph, I.E.M., Stolberg, Germany). Patients with regular use of the PTH modifying drug cinacalcet or with a reduced left ventricular ejection fraction <= 45% were excluded.

Results: We enrolled 120 patients (mean age: 66 +/- 10 years, 98 were females [82%]). Median PTH (IQR) was 94 pg/mL (79 – 113), mean systolic and diastolic nighttime BP were 117 +/- 17 mmHg and 68 +/- 10 mmHg, respectively. PTH was directly correlated with mean systolic and mean diastolic nighttime BP (Spearman rho = 0.246, p = 0.007; rho = 0.214, p = 0.019, respectively). In multivariate linear regression analyses adjusted for age, sex, cholesterol, HbA1c, intake of antihypertensive drugs, 25-hydroxy vitamin D and glomerular filtration rate (CKDEPI), PTH remained significantly related to mean systolic nighttime BP (adjusted beta-coefficient = 0.194, p = 0.047), while the relationship with mean diastolic nighttime BP was not significant (beta = 0.260, p = 0.109).

Conclusions: Plasma PTH was associated with mean systolic nighttime BP in patients with pHPT, independently of potential confounders. These novel data from the EPATH Trial further support the notion that PTH directly interferes with nighttime BP regulation. Whether lowering circulating PTH concentrations reduces the burden of high BP remains to be shown in future studies.

9B.06 COMPARISON BETWEEN ALDOSTERONE AND RENIN MEASUREMENT BY CHEMILUMINESCENT IMMUNOASSAY AND RADIOIMMUNOASSAY FOR THE DIAGNOSIS OF PRIMARY ALDOSTERONISM

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Objective: Primary aldosteronism (PA) is the most frequent cause of secondary hypertension responsible for an increased rate of cardiovascular events. According to the Endocrine Society Guidelines, up to 50% of hypertensive patients should be screened for PA, using the aldosterone to renin (or plasma renin activity, PRA) ratio (AARR and ARR, respectively). The automated Diasorin LIAISON® chemiluminescent immunoassay for renin and aldosterone measurement became available and in many laboratories is currently used instead of the classical radioimmunometric PRA and aldosterone assay. Aim of the study was to prospectively compare the diagnostic accuracy of AARR and ARR as screening test for PA and the two aldosterone assays also during confirmatory test in patients with a positive screening test.

Design and method: One hundred patients were screened for PA and 44 patients underwent confirmatory test (either by intravenous saline load or by captopril challenge test). We considered as cut off for the AARR 2.7 (ng/dL/mU/L) and for the ARR 30 (ng/dL/ng/mL/h). All patients positive to one of the two screening test underwent confirmatory test; patients with positive confirmatory test underwent subtype diagnosis by CT scanning and adrenal vein sampling.

Results: Seventy three patients were diagnosed as essential hypertensives, 22 had bilateral adrenal hyperplasia and 5 had an aldosterone producing adenomas (APA). The AARR displayed a sensitivity of 78% and a specificity of 100%, whereas the ARR had a sensitivity of 96% and a specificity of 90%. Of the 6/27 PA patients missed by AARR, none resulted to be affected by APA. All PA patients were correctly diagnosed by chemiluminescence at confirmatory test. In the overall sample of 181 measurements available both the correlation for the PRA with renin and for aldosterone in chemiluminescence and radioimmunoassay were highly significant (Rho = 0.66, p < 0.0001 and Rho = 0.80, p < 0.0001, respectively). On ROC curves, the AUC for AARR was 0.905 (95% CI 0.821-0.988) and for ARR 0.947 (95% CI 0.903–0.991) and they were not significantly different.

Conclusions: The automated aldosterone and renin chemiluminescent assay is a reliable alternative to the well-established radioimmunometric method, especially for the detection of APA.

9B.07 EFFECT OF POSTURAL CHANGES ON ALDOSTERONE TO PLASMA RENIN RATIO IN PATIENTS WITH SUSPECTED SECONDARY HYPERTENSION

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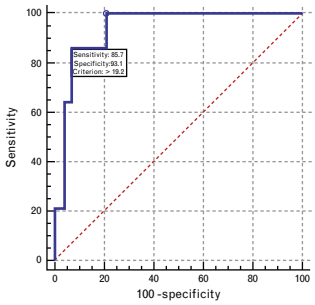
Objective: The aldosterone to renin ratio(ARR)is currently the most reliable available means of screening for Primary aldosteronism. It could be measured in the supine, seating or upright positions. The Endocrine Society and recent French guidelines recommended screening primary aldosteronism by the measurement of ARR in the seating position.
The aim of this work is to study the influence of postural changes on ARR in patients with suspected secondary hypertension & to evaluate sensitivity and specificity of seated ARR compared to supine and upright ARR.



ARR seated	True negatives	False negatives	True positives	False positives	Sensitivity	Specificity	PVV	NPV
Cut-off 23 pg/ UI	28	7	7	1	50%	96.5%	87.5%	80%
Cut-off 19 pg/ UI	26	2	12	3	85.7%	89.6%	80%	92.8%

Design and method: 43 patients were prospectively hospitalized for secondary hypertension exploration (age 51 ± 16,5; SBP/DBP:139 ± 12/85 ± 9mmHg, number of antihypertensive drugs:2 ± 1).After a conventional washout of drugs interfering with renin angiotensin aldosterone system, plasma aldosterone concentration was measured by RIA method(Normal values: 40–175ng/l)and direct renin concentration(DRC)with CLIA method (Normal values: 4,2–59.7 μUI/l).Aldosterone and renin samples were collected in the morning, at bed after an overnight supine position, then out of bed after 1 hour of upright position and finally 2 hours later after 15 minutes in seating position. When DRC was <5 μUI/l it was counted 5 μUI/l as recommended.

Results: Referring to ARR cut-off value of 23pg/μUI, the sensitivity of seated ARR was 50% with a specificity of 96.5%. The negative predictive value was 80% and the positive predictive value was 87.5%.Compared to these results, a cut-off value of 19pg/μUI improved sensitivity to 85.7% with a specificity of 89.6%.Negative predictive value and positive predictive value were 92.8%and80% respectively.
Seated ARR mean value(17 ± 15pg/μUI/l) was lower than supine and upright ARR, respectively measured at 23 ± 20pg/μUI and 24 ± 20pg/μUI. This could be explained by an overall increase in DRC at seating compared to the supine position with a mean increase by factor 2.2 (53 μUI/l vs 24 μUI/l), whereas at the same time, aldosterone just slightly increased by a factor 1.05(235ng/l vs 223ng/l).Seated ARR correlated to supine and upright ARR with correlation coefficients (r)of 0.89 and 0.93 respectively (p < 0,0001).

Conclusions: Current recommended measurement of ARR in the seating position is fairly correlated to ARR in supine and upright positions. However, even if the recommended cut-off value of 23pg/μUI offers a good specificity, a suggested cut-off value of 19pg/μUI increases the discriminating power of this test.

9B.08 CARDIAC AND VASCULAR DAMAGE IN PATIENTS WITH PRIMARY ALDOSTERONISM AND ESSENTIAL HYPERTENSION

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Objective: Primary aldosteronism is a relatively common condition in hypertensive patients. Only few studies, in small groups of patients, have evaluated large arteries alterations. In some, but not in all studies, positive relationship with vascular damage was observed.
Aim of the study: To compare the prevalence of cardiac and large arteries vascular organ damage in patients with essential hypertension (EH) or primary aldosteronism (PA).

Design and method: In 243 consecutive patients with no interfering therapy (147 M, mean age 48 ± 11 years) a routine blood sample, including measurement of aldosterone/renin ratio (ARR) and saline load if ARR>30, was obtained. Echocardiography, carotid ultrasound and measurement of pulse wave velocity (PWV) were performed. We considered 3 groups: 48 patients with EH (ARR < 30); 122 patients with positive ARR screening but negative saline load (indeterminate aldosteronism, IA); 73 patients with PA (positive ARR and post saline aldosterone >100ng/ml)(51 % with adrenal adenoma).

Results: No differences between groups were observed in age, gender, BMI, BP values (clinic and 24 hours), glucose, lipids and renal function. LVMI was greater in PA vs both IA and EH (PA 45 ± 18, IA 39 ± 12, EH 39 ± 10 gr/m2.7, p < 0,05). Left atrial volume/BSA was significantly greater in PA vs EH (PA 27 ± 10, IA 24 ± 8, EH 23 ± 6 ml/m2, p < 0,05 for PA vs EH). A positive correlation was observed between ARR and LVMI (r = 0,20 p = 0,002), left atrium volume (r = 0,201,p < 0,001) and relative wall thickness (r = 0,394, p < 0,005). Indices of vascular damage did not differ between groups (see table). Aldosterone levels and ARR were not significantly correlated with indices of vascular damage.

	PA (n=48)	IA (n=122)	EH (n=73)	p
Meanmax IMT (mm)	1,06±0,7	0,97±0,25	0,91±0,21	n.s.
CBMMax IMT (mm)	1,14±1,1	1,01±0,23	0,97±0,23	n.s.
PWV (m/sec)	9,0±1,6	8,9±1,5	8,9±1,3	n.s.

Conclusions: A greater prevalence of cardiac, but not of large arteries damage is observed in PA as compared to EH when a simultaneous assessment of cardiac and vascular OD is performed.

9B.09 IDENTIFICATION OF MARKERS PREDICTIVE FOR MALIGNANT BEHAVIOR OF PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS

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Objective: Pheochromocytomas and paragangliomas (PPGL) are relatively rare and mostly benign tumours. Approximately 10% of PPGL are malignant, as defined by the presence of metastases, i.e chromaffin tissue at a location that usually does not contain chromaffin cells. However, up to 35% of tumours in patients carrying an SDHB mutation appears to be malignant. Nowadays, no reliable marker allows to predict whether a PPGL is, or will become malignant. In addition, there are no curative treatments if metastases occur. The aim of the present study was to dentify genetic markers allowing to distinguish benign from malignant tumours.

Design and method: An mRNA expression array was performed on benign and malignant PPGL. The genes showing a different expression between the benign and malignant tumours were selected to be confirmed and validated by qRT-PCR. Finally, the remaining genes were stained by immunohistochemistry on Tissue MicroArray including a large series of PPGL.

Results: Forty benign and 12 malignant PPGL were investigated for differences in mRNA expression with Affymetrix arrays. Expression data were normalized according to Affymetrix recommendations. Then, using Pomelo II (http://pomelo2.bioinfo.cnio.es/), a Limma t-test was performed, to assess which genes were differentially expressed between benign and malignant PPGL. First, a non-clustered analysis was performed and 10 genes with a False Discovery Rate (FDR) below 0.05 and a relative overexpression ratio of at least 4 were found, including Interleukin 13 Receptor alpha 2 (IL13RA2) and Monooxygenase DBH-like 1 (MOXD1). Secondly, a supervised cluster analysis was performed (based on HIF target genes), resulting in 2 groups, which were both investigated for differences in mRNA expression between benign and malignant tumours. Five genes showed an FDR below 0.01 and were overexpressed in malignant tumours with a ratio higher than 4, including Contactin 4 (CNTN4), Iroquois Homeobox 3 (IRX3), and Sulfatase 2 (SULF2). These genes were further investigated using qRT-PCR, and immunohistochemistry on Tissue Micro Array including 91 benign and 12 malignant PPGL.

Conclusions: Significant overexpression of Contactin 4 was shown in malignant compared to benign tumours, and may therefore contribute to distinguish malignant from benign PPGL.

ORAL SESSION

ORAL SESSION 9C
THERAPEUTIC ASPECTS

9C.01 WHICH RISK FACTORS ARE IMPORTANT FOR ENDPOINT CARDIOVASCULAR EVENTS IN THE FEVER STUDY? A PRACTICAL APPLICATION OF ROC CURVES IN CLINICAL TRIALS

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Objective: Many randomized clinical trials, including the Felodipine Event Reduction (FEVER) study, have reported event reduction by BP-lowering treatment. Usually the COX model is used, and the importance of coexisting risk factors can be compared with the same model, but receiver operating characteristic (ROC) curves can also be used for analyzing relations between risk factors and endpoint events. Sensitivities and specificities of event occurrence can be calculated for randomized patients.

Design and method: The FEVER study randomized 9711 Chinese hypertensive patients to more or less intense anti-hypertensive treatment during 40 month follow-up. ROC curves were drawn for FEVER data. Area under the curve (AUC) was used for the comparisons between different factors without any assumption on distributions, the ROC curves being a non-parametric method. Every risk factor of an event corresponds to a ROC curve, and its AUC is related to the risk of a given event. Software SAS9.2 was used.

Results: For total cardiovascular events (TCVE), the risk factors considered were age(a), body mass index(b), screening SBP(c), screening DBP(d), smoking amount(e1) or smoking state, Y/N,(e2), serum cholesterol(f), study-end SBP(g), study-end DBP(h), left ventricular hypertrophy (i), previous diabetes (j), sex(k), previous cardiovascular disease(l).
Using to different models of ROC and AUC, their risk importance sequences for TVCE were:
a>h>k>l>TREAT>j>f>b>e1>i; and a>h>k>l>TREAT>j>f>e2>b>i.
Using LOGISTIC regression, the sequences were:
j>l>k>TREAT>i>a>d>e1>b>f; and j>l>k>e2>TREAT>i>a>d>b>f.
TREAT randomization to either Felodipineor placebo

Conclusions: Age is more important for TCVE than blood pressure; Both dichotomous and continuous variables may appear in the same model and the dichotomous risks are overestimated in LOGISTIC regression. ROC is more suitable than LOGISTIC regression, because ROC is a nonparametric method. A good example is the two types of smoking variables (state and amount): their risk importance is the same by ROC, but different by LOGISTIC analyses.

9C.02 EFFECT OF DIFFERENT ANTIHYPERTENSIVE DRUG CLASSES ON SURVIVAL IN UNILATERAL AND BILATERAL RENAL ARTERY STENOSIS: A RETROSPECTIVE RECORD-LINKAGE STUDY

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Objective: Randomized trials in atherosclerotic renovascular disease (ARVD) have failed to show a survival advantage of renovascular stenting relative to medical management. The comparative survival benefit of widely used antihypertensive drug classes has not been previously studied in this cohort. We aimed to determine this among individuals with unilateral (URAS) and bilateral renal artery stenosis (BRAS).

Design and method: In this retrospective record-linkage study, anonymised data over a 6 year period on approximately 800,000 people across Tayside and Fife, Scotland, was studied. Magnetic resonance and percutaneous angiography reports were used to select controls and subjects with URAS and BRAS. Biochemistry, prescribing and demographic data were accessed via electronic patient records and laboratory reports. ICD10 codes were used to identify cardiovascular events. Survival in each group was determined using Cox proportional hazard analysis and Kaplan-Meier survival curves, adjusted for all relevant covariates. A time-updated analysis was performed to confirm the findings.

Results: The mean follow-up duration was 3.5 years. Mortality rates were 36.0% and 50.8% in URAS and BRAS respectively. Baseline eGFR (URAS (P = 4.07x10-8, HR = 0.966(0.95, 0.97), BRAS (P = 0.001, HR = 0.966(0.94, 0.99)), duration of diabetes (URAS (P = 0.02, HR = 1.04(1, 1.07), BRAS (P = 0.001, HR = 1.08(1.03, 1.13)) and age (URAS (P = 0.001, HR = 1.04(1.01, 1.06), BRAS (P = 0.01, HR = 1.05(1.01, 1.09)) independently predicted survival.
22% of URAS and 42% of BRAS patients underwent revascularization, however stent in-situ at baseline did not significantly improve survival in URAS (P = 0.8) or BRAS (P = 0.8). Baseline use of calcium channel blockers (CCBs) (P = 0.01, HR = 0.67(0.46, 1.00)) and angiotensin converting enzyme inhibitors (ACEIs) (P = 0.008, HR = 0.35(0.16, 0.76)) were independently associated with survival in URAS. In the time-updated analysis, ACEI use did not improve survival in URAS (P = 0.443) or BRAS (P = 0.06). However, use of CCBs was associated with a survival advantage for both populations; URAS P = 1.88x10–5, HR = 0.44(0.30, 0.64), BRAS P = 0.001, HR = 0.38, (0.21, 0.67).

Conclusions: This study is consistent with published data showing no additional benefit of revascularization. CCBs significantly increase survival in both URAS and BRAS. Further prospective studies should identify whether this occurs independently of a reduction in blood pressure.

9C.03 THE BENEFIT FROM HEMODYNAMICALLY GUIDED ANTIHYPERTENSIVE THERAPY DEPENDS ON BASELINE BLOOD PRESSURE

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Objective: Impedance cardiography (ICG) revealed to be useful in tailoring antihypertensive therapy to the patient's individual hemodynamic profile but little is known who benefits more from such therapeutic approach. The aim of this study was to estimate the effectiveness of ICG-guided antihypertensive therapy in 12-weeks observation with respect to baseline blood pressure (BP).

Design and method: This analysis involved 272 patients with untreated AH, recruited in two randomized, prospective and controlled trials (www.nauka-polska.pl: ID227062 and ClinicalTrials.gov: NCT01996085). After baseline evaluation including office blood pressure measurement (OBPM: OSBP, ODBP, OMBP) and ambulatory blood pressure monitoring (ABPM: 24-mean_SBP, 24-mean_DBP) the subjects were randomly assigned to groups of: [GE] empiric and [HD] ICG-guided antihypertensive therapy. The effectiveness of ICG-guided therapy was evaluated after 12 weeks in subgroups derived from median of OMBP (110 mmHg) of: higher (n = 120) and lower baseline OMBP (n = 121). The comparative analysis included absolute change of BP (d_OSBP, d_ODBP, d_24-mean_SBP, d_24-mean_DBP) and percentage of patients with change of BP equal or higher than 10 mmHg (d10_OSBP, d10_ODBP, d10_24-mean_SBP, d10_24-mean_DBP).

Results: In the whole study group the BP reduction in HD group was higher than in GE group: d_OSBP (18.3 vs. 14.3 mmHg; p = 0.011), d_ODBP (11.9 vs. 8.5 mmHg; p = 0.011), d_24-mean SBP (15.9 vs. 11.6 mmHg; p = 0.011) and d_24-mean SBP (10.4 vs. 8.9 mmHg; p = 0.147). However, the effect of ICG-guided therapy was significantly more pronounced in subjects with higher baseline OMBP – Table.

	higher baseline BP			lower baseline BP		
	HD	GE	*p*	HD	GE	*p*
d_OSBP (mmHg), mean ± SD	23.3 ± 10.8	18.5 ± 13.9	*0.035*	12.1 ± 10.0	10.8 ± 10.3	*0.485*
d_ODBP (mmHg), mean ± SD	16.0 ± 6.3	11.6 ± 9.6	*0.003*	7.0 ± 8.0	6.0 ± 8.3	*0.512*
d_24-mean_SBP (mmHg), mean ± SD	17.7 ± 10.8	13.1 ± 13.1	*0.035*	13.6 ± 11.1	10.4 ± 11.7	*0.128*
d_24-mean_DB (mmHg), mean ± SD	11.7 ± 7.2	10.3 ± 8.6	*0.312*	8.7 ± 6.8	7.9 ± 7.6	*0.539*
d10_OSBP, %	87.7	69.1	*0.012*	50.9	55.9	*0.589*
d10_ODBP, %	69.2	47.3	*0.015*	26.3	23.5	*0.715*
d10_24-mean_SBP, %	72.3	52.7	*0.018*	54.7	48.5	*0.368*
d10_24-mean_DBP, %	53.8	52.7	*0.841*	39.6	36.8	*0.625*

Conclusions: The ICG-guided therapy effects with increased BP reduction in patients with AH, especially those with higher baseline BP. The patients with advanced AH can benefit more from individual these therapeutic approach.

9C.04 TREATMENT WITH LCZ696 COMPARED TO AT1-RECEPTOR BLOCKADE IS ASSOCIATED WITH NON-SUSTAINED INCREASES OF NATRIURESIS AND DIURESIS IN ASIAN PATIENTS WITH SALT-SENSITIVE HYPERTENSION

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Objective: Patients with salt-sensitive hypertension (SSH) retain sodium in response to salt load and display a relative deficiency of atrial natriuretic peptide (ANP). LCZ696 is an angiotensin receptor neprilysin inhibitor (ARNI) expected to increase ANP levels while simultaneously blocking the AT1-receptor. This study investigated the effects of LCZ696 compared to valsartan on natriuresis and diuresis in Asian patients with SSH.

Design and method: Randomized, double-blind, cross-over study in 72 patients with SSH (10% or higher increase in MAP when switching from 50 mmol/day to 320 mmol/day for 7 days each). Patients received LCZ696 400 mg once daily and valsartan 320 mg once daily for 4 weeks each. Natriuresis and diuresis were assessed for 6 h and 24 h after dosing on Days 1 and 28.

Results: On Day 1, LCZ696 but not valsartan resulted in significant increases from baseline in 6 h natriuresis ($p < 0.001$) and in 24 h natriuresis ($p < 0.001$). LCZ696 compared to valsartan demonstrated a significantly higher Day 1 natriuresis for the 6 h (adjusted treatment difference: 24.5 mmol; $p < 0.001$) and the 24 h intervals (adjusted treatment difference: 50.3 mmol; $p < 0.001$). On Day 28, 6 h and 24 h natriuresis were comparable to baseline and not different between treatment groups. On Day 1, LCZ696 but not valsartan resulted in significant increases from baseline in 6 h diuresis ($p < 0.001$) and in 24 h diuresis ($p < 0.001$). LCZ696 compared to valsartan demonstrated a significantly higher Day 1 diuresis for the 6 h (adjusted treatment difference: 291.2 mL; $p < 0.001$) and the 24 h intervals (adjusted treatment difference: 356.4 mL; $p = 0.003$). On Day 28, 6 h and 24 h diuresis were comparable to baseline and not different between treatment groups.
Plasma sodium and potassium levels were not different between treatment groups.

Conclusions: Treatment with LCZ696 400 mg compared to valsartan 320 mg once daily for 4 weeks was associated with non-sustained increases in natriuresis and diuresis. This differentiates LCZ696 from diuretics and ARBs and may suggest an added long-term benefit with respect to improved sodium balance in patients with SSH.

9C.05 META-ANALYSIS OF AMLODIPINE VERSUS ANGIOTENSIN RECEPTOR BLOCKERS ON BLOOD PRESSURE, SOME ECHOCARDIOGRAPHIC INDICATORS OF LEFT VENTRICULAR DAMAGE AND ADVERSE EVENTS IN PATIENTS WITH HYPERTENSION

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Objective: The aim of this meta-analysis is to evaluate two echocardiographic indicators of left ventricular damage, amlodipine and angiotensin receptor blockers, and associated adverse events in patients with hypertension.

Design and method: A meta-analysis was conducted using PubMed, Cochrane Library and EMBASE to investigate and analyze the effects of amlodipine versus angiotensin receptor blockers for blood pressure, associated adverse events, and cardiac structure and function. Data was collected from database inception through October 2014.

Results: Nineteen randomized-control clinical trials were included in the meta-analysis. 4,248 subjects from the collected trials were given either amlodipine or angiotensin receptor blockers (ARBs) for management of hypertension. The results showed no significant differences between amlodipine and ARBs in ability to lower blood pressure. However, when measuring the decrease of left ventricular mass index (LVMI), amlodipine was shown to be inferior to both irbesartan (weighted mean difference= -15.1, 95% confidence intervals: -22.97 to -7.23, $P < 0.001$) and valsartan (weighted mean difference = -17.77, 95% confidence intervals:-31.28 to -4.27, $P = 0.01$). Amlodipine showed decreased performance compared to losartan in early diastolic mitral annular velocity (E´), the ratio of left ventricular early diastolic filling velocity to early diastolic mitral annular velocity (E/E´) and an increased number of adverse events[(E´:weighted mean difference= -0.09, 95%CI -1.76 to -0.04, $P = 0.04$), (E/E´:weighted mean difference = 3.00,95%CI 1.22 to 4.78, $P = 0.001$), (adverse events: OR = 3.78, 95%CI 1.29 to 11.06, $P = 0.02$)]. Additionally, amlodipine led to more adverse events when compared with valsartan (OR = 1.80, 95% confidence intervals:1.17 to 2.78, $P = 0.008$).

Conclusions: Amlodipine is comparable to several ARBs in its potential to lower blood pressure. However, it is less effective in prevention of left ventricular hypertrophy and exhibits a higher incidence of clinically adverse events, such as dizziness, fatigue, headache, peripheral edema, and erectile dysfunction.

9C.06 COMPARISON BETWEEN CARDIOLOGY AND ENDOCRINOLOGY PHYSICIANS IN THEIR MANAGEMENT OF HYPERTENSION AND DIABETES MELLITUS: A CHINA REGISTRY

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Objective: To investigate the comorbidity rate of diabetes or hypertension in cardiology outpatients with hypertension or endocrinology outpatients with diabetes.

Design and method: A multi-center, cross-sectional, non-interventional disease registry study has been conducted in a sample of 2,510 outpatients enrolled from 20 cardiology and 20 endocrinology departments, respectively. The demographic data, medical history and physical examination results were recorded and questionnaire on illness perception were conducted. Diagnosis of hypertension and diabetes were determined by measured blood pressure and HbA1c (or FBG). Obesity, metabolism syndrome (MS), and consumption of tobacco and alcohol were used to estimate CVD risk. The tests of microalbuminuria and ECG were performed by central lab, and the treatment pattern was evaluated by patient's chart or self-reporting.

Results: The proportion of hypertension in 1180 diabetic patients was 59.0% (95% CI, 56.1%-61.8%); meanwhile the proportion of diabetes in 1330 hypertensive patients was 32.6% (95% CI, 30.1%–35.2%). The proportions of patients with MS, tobacco and alcohol consumption were higher in endocrinology than cardiology group (61.7%, 17.8% and 16.9% vs. 55.6%, 17.0% and 16.8% respectively), while for patients with obesity was opposite (48.6% vs. 52.0%). The prevalence of albuminuria (15.4% vs. 21.3%; $P = 0.39$) and ECG-left ventricular hypertrophy (8.0% vs. 7.9%; $P = 0.99$) between the two groups was similar. In previously diagnosed hypertensive patients in cardiology ($n = 1330$) and endocrinology department ($n = 607$), in spite of similar antihypertensive treatment rate (87.7% vs. 88.1%; $P = 0.82$), the proportion of antihypertensive monotherapy was lower (37.1% vs. 56.7%; $P < 0.0001$) and combination therapy was higher (50.6% vs. 31.5%; $P < 0.0001$) in cardiology department than endocrinology department.

Conclusions: In spite of similar treatment pattern, the intensity of treatment differed substantially between cardiologists and endocrinologists. In addition, the real-life medications may be different from guideline recommendations, which indicate an important need to further bridge the gap.

9C.07 MULTICENTRE RANDOMISED, DOUBLE BLIND, EVALUATION OF NEBIVOLOL PLUS HCTZ AND IRBESARTAN PLUS HCTZ IN THE TREATMENT OF ISOLATED SYSTOLIC HYPERTENSION IN THE ELDERLY: THE NEHIS STUDY

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Objective: According to the 2013 ESH/ESC guidelines combination drug treatment is recommended in the treatment of isolated systolic hypertension (ISH) to improve blood pressure (BP) control. The present study was aimed at comparing the antihypertensive effects, tolerability and side effects profile of nebivolol/hydrochlorothiazide vs irbesartan/hydrochlorothiazide combination in elderly patients with ISH.

Design and method: 124 ISH patients aged 69.1 ± 3.1 (mean ± SEM) followed by 13 general practictioners in Netherlands and Belgium were enrolled and randomized in a double blind fashion to Nebivolol 5 mg/Hydrochlorothiazide 12.5 mg (NH, $n = 62$) or Irbesartan 150 mg/Hydrochlorothaizide 12.5 (IH,$N = 62$) once daily for a 12 week period on sitting office BP, ambulatory BP, 24 hour BP variability, pulse pressure, tolerability and safety profile.

Results: 9 pts were withdrawn after randomization. After 12 weeks NH caused a significant greater reduction than IH in sitting SBP (-25.8 ± 1.6 vs -20.6 ± 1.7 mmHg, P < 0.03) and heart rate (HR, -7.0 ± 1.0 vs 2.5 ± 1 b/min, P < 0.01), while the decrease in diastolic and pulse BP showed a non significant tendency to be greater in NH than in IH (-7.4 ± 1.0 and -18.3 ± 1.5 vs -5.0 ± 0.09 and -15.7 ± 1.7 mmHg, P = NS for both). The magnitude of the 24-h, day-time and night-time SBP reduction was almost superimposable in the 2 groups, while HR reduction induced by NH was significantly (P < 0.001) greater during the 24-h, the daytime as well as the nighttime period than that induced by IH. NH caused a significantly greater reduction than IH in 24-h SBP variability, both when expressed as standard deviation (-4.4 ± 2.7 ± vs -2.2 ± 5.1 mmHg, P < 0.02) or as coefficient of variation (-2.0 ± 2.6 vs -0.3 ± 3.4, P < 0.01). This was the case also for pulse pressure and mean BP. Both the 2 drug combinations were well tolerated.

Conclusions: These data provide evidence that NH induces an office BP reduction greater than IN but similar effects throughout the 24 hours. NH, however, reduces, at variance from IH, 24-h systolic, mean and pulse BP variability, suggesting a greater protection against a variable known to adversely affect morbidity and mortality in hypertensive patients.

9C.08 HEART RATE AS A PREDICTOR OF CARDIOVASCULAR OUTCOMES: NEW EVIDENCE FROM THE ACTION TRIAL DATABASE

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Objective: Received wisdom suggests that treatments which reduce heart rate (HR), or avoid cardio-acceleration, are associated with improved cardiovascular (CV) outcomes. However, in the SIGNIFY trial in 12,049 patients with symptomatic angina, a sub-group analysis demonstrated a small but significant increase in the combined risk of CV death or non-fatal MI with the new anti-anginal agent, ivabradine, which is designed to reduce heart rate. The safety and efficacy of the long-acting calcium channel blocker, Nifedipine GITS (an established anti-anginal agent) has been confirmed via the positive results in the placebo-controlled ACTION trial in patients with stable symptomatic coronary artery disease (CAD). This further, retrospective analysis of the ACTION database has evaluated the inter-relationships between baseline HR, and its on-treatment changes, on subsequent cardiovascular outcomes.

Design and method: The retrospective analyses of the ACTION trial were performed for quintiles of HR, using the multivariate Cox proportional hazard model, for baseline HR and the achieved HR after 6 weeks of the trial (by which time titration of both placebo and nifedipine GITS was complete).

Results: For baseline HR, the risk in the lowest (<56 bpm) was significantly reduced when compared to the highest quintile (HR > 72BPM) for the primary trial endpoint (HR = 0.81 CI 0.70, 0.94); any cardiovascular (CV) event (HR = 0.82 CI 0.70, 0.96); and new onset heart failure (HR = 0.48 CI 0.31, 0.74). No significant differences were apparent for myocardial infarction (MI) or debilitating stroke. In contrast, there was no evidence that on-treatment HR was predictive of outcome: for example, for the primary efficacy endpoint (any CV event, HF, MI and debilitating stroke) the event rates were similar across the quintiles of HR. Correspondingly, there was no significant HR-related treatment effect (comparing nifedipine GITS and placebo).

Conclusions: Whilst retrospective analyses must always be interpreted with caution, these results suggest that with "best practice therapy", CV risk is lowest at baseline in those patients with the lowest HR. However, when compared to placebo, the addition of nifedipine GITS improved overall outcomes and had no deleterious effects across the quintiles of achieved HR.

9C.09 TREATMENT WITH CANDESARTAN UNMASKS HIGHER URINARY NOREPINEPHRINE EXCRETION IN WHITE COAT HYPERTENSIVE PATIENTS COMPARED TO HEALTHY NORMOTENSIVE PARTICIPANTS

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Objective: White coat hypertensive is a pre-hypertensive state that has been associated with increased sympathetic drive. The objective of the study was to compare the exposure of the kidney to sympathetic nerve activity using urinary normetanephrine (UNMN) as a marker of renal sympathetic exposure in white coat hypertensive (WCH) and healthy normotensive (HN) participants.

Design and method: This was a double-blind randomized placebo-controlled crossover study.WCH were included if office blood pressure was >140/80 mmHg and ambulatory blood pressure <135/85 mmHg and HN if OBP was <140/90 mmHg and ABP <135/85 mmHg Participants were randomized to receive either 16 mg of candesartan or a matched placebo for one week before study day. On the study day systemic and renal hemodynamics as well as plasma norepinephrine and urinary excretion of normetanephrine (measured by LC/MS-MS were measured after one hour of baseline, one hour of lower body negative pressure and one hour of recovery period. Excretion of UNMN was expressed as the total of UNMN excreted during these three hours (cumUNMN). Paired or unpaired t-test were used for comparison.

Results: 25 HN and 12 WCH participants were included in the study. Mean age (±standard deviation), BMI were respectively 31.0±10.5 years and 22.0 ± 2.2 Kg/m2 in HN and 40.7±17.8 years and 26.7 ± 6.3 Kg/m2 in WCH.

Table 1 Baseline mean blood pressure, plasma noradrenaline and cumulated UNMN during placebo and candesartan

Variable	Group	Placebo	Candesartan 16 mg
MBP(mmHg)	WCH	96.8±11.5¶	91.8±10.3¶
	HN	79.5±7.6	77.0±6.9
pNE(nM)	WCH	1.71±1.31	1.94±0.91
	HN	1.30±0.69	1.54±0.73
cumUNMN	WCH	178±34	246±32*¶
	HN	135±9	170±12*

*P<0.05 vs placebo, ¶ P<0.05 WCH vs HN, MBP: mean blood pressure, pNE: plasma norepinephrine, cumUNMN: cumulated urinary normetanephrine; WCH: white coat hypertension, HN:healthy normotensive

Mean blood pressure was higher during placebo and candesartan in WCH compared to HN. Cumulated UNMN was higher in both groups after candesartan treatment. Cumulated UNMN was higher in WCH than in HN only after candesartan treatment.

Conclusions: Urinary excretion of normetanephrine is increased in WCH compared to HN when treated with candesartan. The increased excretion of uNMN when the renin angiotensin system is blocked might reflect an increased sensitivity of WCH to stress conditions such as orthostatic stress.

ORAL SESSION

LATE-BREAKERS SESSION 3

LB03.01 MORNING HYPERTENSION IS AN IMPORTANT RISK FOR STROKE IN ASIAN POPULATION. FROM J-HOP STUDY

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Objective: Blood pressure (BP) self-measured at home is a more accurate prognosticator than conventionally measured BP. Home blood pressure (BP), which is mainly measured in morning and evening, is prognositically superior to office BP. Although morning BP, per se, is an important prognostic factor, much less information about this association is available in ambulatory patients.

Design and method: In the Japan Morning Surge Home Blood Pressure (J-HOP) study, 4310 Japanese patients (mean age, 64.8 [SD, 10.9] years; 47% men) who had one or more than risk factor were recruited and followed up by their physicians, and measured home BP in the morning and evening on 14 consecutive days at baseline. Cardiovascular events were the combination of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, aortic dissection, and hospitalization for heart failure or angina performed with coronary angioplasty or coronary artery bypass graft surgery.

Results: At the end of follow-up, clinical status was known for 99.4% of patients. During 3.9 years of follow-up (median), at least 1 cardiovascular events had occurred in 192 (incidence, 11.7/1000 patient-years), and 75 stroke events (4.3/1000 patient-years) and 122 cardiac and other vascular events (7.2/1000 patient-years) occurred. When we divided morning systolic BP (MSBP) into four groups (<135mmHg [n = 1948], 135–145mmHg [n = 1037], 145–155mmHg [n = 684], >155mmHg [n = 586]), the risk of cardiovascular events was increased in >155mmHg of MSBP compared with < 135mmHg (1.82; 95%CI [1.19–2.80]) after adjusted by covariates, and MSBP was not risk for cardiac and other vascular events. The risk for stroke events was higher in the group with 135–145mmHg (relative risk [RR], 2.48; 95% confidence interval [CI], 1.19–5.15), 145–155mmHg (2.71; 95%CI [1.25–5.85]), >155mmHg (4.13; 95%CI [1.92–8.90]) than those with <135mmHg. This association was similar after adjusting evening systolic BP.

Conclusions: Uncontrolled morning BP assessed by home BP is associated with stroke in Japanese ambulatory patients.

LB03.02 ASSOCIATION BETWEEN PATERNAL CARDIOVASCULAR STATUS AND OFFSPRING ADOLESCENT BLOOD PRESSURE TRAJECTORIES

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Objective: To investigate the association between paternal circulatory health in middle age and offspring blood pressure across childhood and adolescence in order to examine the importance of inter-generational influences on blood pressure trajectories and the potential development of hypertension in later adult life.

Design and method: We used data from 1,969 paternal-offspring pairs recruited as part of the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. Paternal pressures and arterial stiffness (systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse wave velocity (PWV) and augmentation index (AI)) were measured at the Focus on Fathers clinic between 2011 to 2013. This was linked to 6 prior measures of offspring SBP and DBP taken at research clinics when the ALSPAC participants were approximately 7, 9, 10, 11, 15 and 17 years old. We used both multivariable linear regression and 2 level linear-spline models to model the associations between a one standard deviation increase (z-score) in paternal circulatory measures and offspring SBP and DBP at each time point as well as the intercept (BP at age 7) and rate of blood pressure change from linear slopes between ages 7–11, 11–15 and 15–17 from our multi-level model.

Results: A positive association was found between paternal SBP and male offspring systolic and diastolic blood pressures in simple and adiposity adjusted analyses (SBP +1.48 mmHg; CI 0.82 - 2.14 mmHg, p < 0.0001 at age 7 for 1 z-score increase in paternal SBP). These associations remained similar throughout adolescence. No associations were seen with paternal PWV or AI and male offspring pressures. Far weaker or null associations were seen for female blood pressures (p-value for gender interaction=0.01 at 7 years).

Conclusions: This study demonstrates sexual dimorphism for associations between paternal and offspring blood pressures which require replication from other studies. The associations were strongest in the pre-pubertal period and, if anything, weakened with adolescence suggesting other environmental factors may be more important in determining age-related increases in blood pressure. Future follow-up is required to test whether associations reappear in later life.

LB03.03 ANTI-INFLAMMATORY EFFECTS OF ANTI-PLATELET DRUGS: IMPLICATION FOR ATHEROSCLEROSIS

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Objective: Cardiovascular disease due to atherosclerosis is the leading cause of death worldwide. There is a strong association between pro-inflammatory CD14++CD16+ monocyte levels and the presence of atherosclerosis. Our previous work showed that platelet activation is a main determinant in the acquisition of a CD16+ phenotype by circulating monocytes. Using the influenza immunisation, a validated model of acute inflammation, we assessed whether anti-platelet therapy could modify the circulating monocyte profile under pro-inflammatory conditions.

Design and method: 75 healthy subjects were studied before and 48 hours after receiving the influenza immunisation, with or without concomitant treatment with anti-platelet agents, namely aspirin, clopidogrel, or ticagrelor. Blood samples were collected prior to the immunisation and again 48 hours later. Whole blood was immunostained for human anti-CD14 and anti-CD16. Flow cytometry was performed to assess monocyte populations. Serum was tested for high-sensitivity C-reactive protein (hsCRP) and pro-inflammatory cytokine levels.

Results: hsCRP rose from 1.422 (± 0.2919) mg/l at baseline to 1.945 (± 0.3289) mg/l post-immunisation, (p < 0.0001), confirming the induction of inflammation. The monocyte phenotype in the untreated group showed significant changes post-immunisation, with the proportion of pro-inflammatory CD14++CD16+ monocytes rising from 6.32% ± 0.79 to 12.37% ± 1.30 (p = 0.0008) while the classical CD14++CD16- monocytes fell from 87.14% ± 1.30 to 81.54% ± 1.54 (p = 0.0099). All anti-platelet agents attenuated this response.

Conclusions: These data support the concept that platelet activation is a principal factor in the development of a CD14++CD16+ monocyte phenotype whilst platelet inhibition modifies the circulating monocyte profile under pro-inflammatory conditions. Our preliminary results indicate that anti-platelet agents can reduce a key biomarker associated with cardiovascular risk.

LB03.04 SPHYGMOMANOMETER CUFF CONSTRUCTION AND MATERIALS AFFECT TRANSMISSION OF PRESSURE FROM CUFF TO ARTERIAL WALL. FINITE ELEMENT ANALYSIS OF HUMAN PRESSURE MEASUREMENTS AND DICOM DATA

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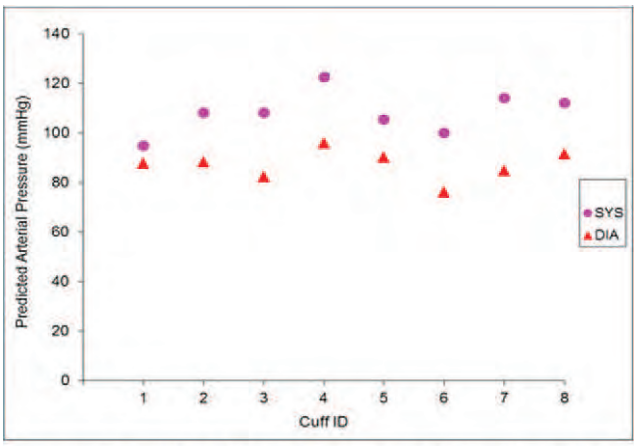
Objective: Sphygmomanometer cuff pressure during deflation is assumed to equal systolic arterial pressure at the point of resumption of flow. Previous studies demonstrated that pressure decreases with increasing depth of soft tissues whilst visco-elastic characteristics of the arm tissue cause spatial and temporal variation in pressure magnitude. These generally used non-anatomical axisymmetrical arm simulations without incorporating arterial pressure variation. We used data from a volunteer's Magnetic Resonance (MR) arm scan and investigated the effect of variations in cuff materials and construction on the simulated transmission of pressure from under the cuff to the arterial wall under sinusoidal flow conditions.

Design and method: Pressure was measured under 8 different cuffs using Oxford Pressure Monitor Sensors placed at 90 degrees around the mid upper arm of a healthy male. Each cuff was inflated 3 times to 155 mmHg and then deflated to zero with 90 seconds between inflations. Young's modulus, flexural rigidity and thickness of each cuff was measured.
Using DICOM data from the MR scan of the arm, a 3D model was derived using ScanIP and imported into Abaqus for Finite Element Analysis (FEA). Published mechanical properties of arm tissues and geometric non-linearity were assumed. The measured sub-cuff pressures were applied to the simulated arm and pressure was calculated around the brachial arterial wall. which was loaded with a sinusoidal pressure of 125/85 mmHg.

Results: FEA estimates of pressure around the brachial artery cuffs varied by up to 27 mmHg SBP and 17 mmHg DBP with different cuffs. Pressures within the cuffs varied up to 27 mmHg. Pressure transmission from the cuff to the arterial surface achieved a 95% transmission ratio with one rubber-bladdered cuff but varied between 76 and 88% for the others. Non-uniform pressure distribution around the arterial wall was strongly related to cuff fabric elastic modulus. Identical size cuffs with a separate rubber bladder produced peri-arterial pressure 14 mmHg higher than with a fabric bladder.



Predicted "systolic" and "diastolic" pressures at the brachial arterial wall using 8 different cuffs loaded with a sinusoidal pressure of 125/85 mmHg

Conclusions: Wide variations of pressure within and under cuffs and at the artery wall interface, dependent on differing cuff materials and construction, may critically affect blood pressure measurement.

LB03.05 THE ANTI-CONTRACTILE EFFECTS OF PVAT ARE MODULATED BY AGE. THE ROLE OF NITRIC OXIDE

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Objective: Ageing is the biggest independent risk factor for cardiovascular disease; the leading cause of death worldwide. Recent studies demonstrate that age-related endothelial dysfunction, a major risk factor for cardiovascular disease, may be due to decreased bioavailability of the endogenous vasodilator nitric oxide (NO), synthesised in the vascular endothelium by endothelial nitric oxide synthase (eNOS); which is phosphorylated and thus activated by AMP-activated protein kinase (AMPK). Vascular reactivity is further regulated via the perivascular adipose tissue (PVAT), which has a net anti-contractile effect. PVAT is known to be a source of additional NO, as well as secreting factors that augment local endothelial NO production, potentially through AMPK activation. Whilst this anti-contractile effect of PVAT is well characterised in young animals, it is unknown what effects ageing has on this relationship.Our hypothesis is that PVAT dysfunction may occur with ageing.

Design and method: Small diameter mesenteric arteries were taken from male Wistar rats aged 3 months old (m.o.), 12m.o., 18m.o. and 24m.o. and contractility to U46619 (10nM-3 μM) and phenylephrine (1nM-30 μM) assessed via wire-myography in the presence and absence of PVAT and the NO-synthesis inhibitor L-NNA (50 μM). Western blotting for AMPK, p-AMPK, eNOS and p-eNOS was performed on mesenteric artery samples from rats aged 3m.o. and 24m.o.

Results: Results showed that PVAT was anti-contractile in 3m.o. and 12m.o. old rats but that this effect was lost by 18m.o., remaining absent at 24m.o.. Incubation with L-NNA reversed the anti-contractile effect of PVAT at 3m.o., but not 24m.o. Expression of total AMPK was reduced in arteries from 24m.o. compared to 3m.o. whereas the ratio of p-AMPK/total AMPK remained unchanged. Expression of eNOS remained unchanged at 24m.o., whereas p-eNOS/total eNOS ratio was significantly decreased.

Conclusions: The anti-contractile effect of PVAT is lost with age in rats, due at least in part to reduced NO bioavailability. This reduced bioavailability may be the result of reduced eNOS phosphorylation downstream of reduced AMPK expression.

LB03.06 AUTOMATED INTERPRETATION OF HOME BLOOD PRESSURE ASSESSMENT (HY-RESULT® SOFTWARE) VERSUS PHYSICIAN'S ASSESSMENT. A VALIDATION STUDY

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Objective: Hy-Result® software is designed to help patients to comply with the home blood pressure measurement (HBPM) protocol and self-interpret their results. We compare in a daily routine care setting, the classification generated by Hy-Result® with the physician's clinical evaluation.

Design and method: The algorithm combines BP readings with patient's characteristics. According to the ESH guidelines, BP readings and automatically generated text messages are made available to the patient in a report. The primary assessment criterion was whether classification of the BP status generated by the software concurred with the physician's classification (blinded to the software's results) following a consultation (n = 195 patients) (gold standard).

Results: In the 58 untreated patients, the agreement between classification of the BP status generated by the software and the physician's classification was 87.9%. In the 137 treated patients, the agreement was 91.9%. The kappa test applied for all the patients was 0.81 [95%CI: 0.73–0.89]. After correction of errors identified in the algorithm during the study, agreement increased to 95.4% (kappa 0.9[95% CI: 0.84–0.97]). For 100% of the patients with comorbidities (n = 46), specific text messages were generated indicating that a physician might recommend a target BP lower than 135/85 mmHg. Specific text messages were also generated for 100% of the patients for whom global cardiovascular risks greatly exceeded norms relating to BMI, tobacco and/or alcohol consumption. Remaining discrepancies were more attributable to human error (physician), than software. The limitation is that the algorithm remains dependent on patient's capacity to complete their profile.

Conclusions: Classification by Hy-Result® is at least as accurate as that of a specialist in current practice. Hy-Result® is the first validated free use software for self-interpretation of HBPM results, taking into account both the recommended thresholds for normal values and patient characteristics (www.hy-result.com). Hy-Result® will soon be available as a Smartphone application (Health Mate), accessible in an entirely automated format in conjunction with a validated wireless BP monitor (Withings BP-800).

LB03.07 ANTIHYPERTENSIVE THERAPY AND RISK OF ADMISSIONS FOR MOOD DISORDERS

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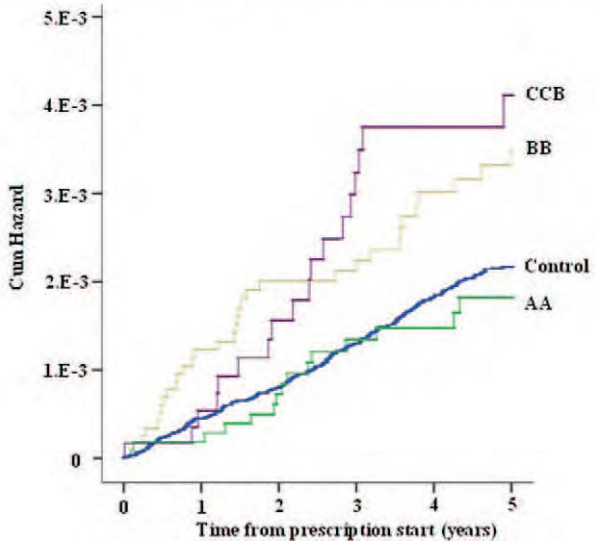
Objective: To explore if calcium channel blocker (CCB) treatment is associated with a different or lower risk of mood affective disorder hospital admissions compared to other antihypertensive drugs.

Design and method: Two cohorts were studied: the Glasgow Blood Pressure Clinic (GBPC) and a hospital cohort of admissions from two Glasgow hospitals from 1980 to March 2013. These cohorts included 17,610 and 525,046 patients respectively. Prescription refill data from 2004–2013 was used to create monotherapy groups for ACE inhibitors /angiotensin-receptor blockers (AA), beta blockers (BB) and CCB with duration >90 days and a control of no antihypertensive exposure in the hospital cohort. Only prescriptions started after the 1st of April 2004 were included to exclude prevalent use. In the GBPC and hospital cohort, patients were >18 years of age and 40–80 years respectively. Admissions were classified as ICD-10 F30–39 or ICD-9 295–7.

Results: There were 1,927 eligible patients with 31 incident admissions for mood disorders in the GBPC over 10 years and 144,087 with 302 admissions over 5 years in the hospital cohort. Mean ages were 58 and 56 respectively. After adjustment for age at prescription and sex in both cohorts and additional baseline demographics of blood pressure, height, weight, BMI, smoking and alcohol consumption, eGFR and cardiovascular disease in the GBPC, BB showed a higher risk of admission (HR: 3.2, [95% CI: 1.2–8.6], P = 0.017) compared to AA in the GBPC. In the hospital cohort compared to controls of no antihypertensive exposure BB (1.6[1.1–2.4], P = 0.009) and CCB (1.8[1.1–3.0], P = 0.014) showed higher risks (Figure 1).

Figure 1: Kaplan Meier plot of mood disorder admissions in the hospital cohort



Conclusions: Calcium antagonists may exert similar effects on mood symptoms compared to beta blockers. This association has not been previously recognised.

LB03.08 HYPERTENSION RELATED VARIANT OF SOLUTE CARRIER FAMILY 39 MEMBER 8 GENE INFLUENCES CADMIUM UPTAKE AND CELL TOXICITY

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Objective: hSLC39A8 (human solute carrier family 39 member 8) encodes a transmembrane protein that co-transports divalent heavy metal cations, such as Cd2+, with elusive physiological role. Recent genome-wide association studies have identified a non-synonymous single nucleotide polymorphism rs13107325 to be associated with hypertension. To investigate the functional impact of rs13107325 resulting in an amino acid substitution from Ala to Thr (A391T) in SLC39A8 on Cd2+ transport and the downstream signalling pathways.

Design and method: Intracellular Cd2+ uptake was measured in HEK293 cells overexpressing SLC39A8 (Measure-iTTM Pb and Cd assay kit), and in human umbilical vascular endothelial cells (HUVECs) of different genotypes. Cd2+- and genotype-dependence of ERK1/2 and NF-kB pathway's activation were investigated by immunoblotting and dual-luciferase reporter assay. Cytotoxicity was measured by the lactate dehydrogenase assay and MTS assay.Molecular dynamics simulations were performed to predict in silico the effect of A391T on the structure and dynamics of SLC39A8 by using Robetta, TMHMM and etc.

Results: Overexpression of Ala variant in HEK293 resulted in higher Cd2+ uptake and higher cytotoxicity as compared with the Thr variant. This is associated with increased phosphorylation of ERK1 and NF-kB activation. Similar trends were observed in HUVECs with endogenous SLC39A8. Bioinformatics tools also suggested a conformational change of the α-helical structural transition (residual 390–392) in the Thr mutant, which potentially attenuates the protein function.

Conclusions: Increased Cd2+ uptake by SLC39A8 Ala variant (blood pressure raising allele) is associated with higher cell death in human kidney and endothelial cells. Therefore its altered function due to rs13107325 may indicate a potential therapeutic target in hypertension.

LB03.09 THERAPEUTIC INERTIA IS A MAJOR DETERMINANT OF BP CONTROL RATES IN CHINA. A HYPERTENSION ATTITUDE PERSPECTIVES AND NEEDS (HAPPEN) STUDY REPORT

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Objective: Rates of blood pressure (BP) control are poor in China, even among patients receiving treatment. A real-world survey – Hypertension Attitude PersPEctives and Needs (HAPPEN) – was conducted to examine the role of physician and patient attitudes in BP control.

Design and method: Tier 3 hospitals (Beijing [n = 34], Shanghai [n = 18] and Guangzhou [n = 25]) were randomly selected for surveying. Cardiologists, nephrologists and patients with hypertension at these hospitals were randomly screened to participate. Physician inclusion criteria included practising for> = 5 years and seeing >=100 patients with hypertension every month. Eligible patients were visiting a cardiologist or nephrologist, had a diagnosis of hypertension for >=1 year and were receiving prescription treatment for >=6 months. Questionnaires were conducted by trained interviewers following the ESOMAR Code of Conduct. The survey was completed by 100 cardiologists, 30 nephrologists and 400 patients (primary hypertension [n = 160], hypertension with chronic kidney disease [n = 100], diabetes [n = 58], coronary artery disease [n = 51], stroke [n = 15] or others [16]).

Results: Although physicians claimed to inform 90% of patients of their BP target, only 67% (n = 263) of patients knew their target. Of these patients, 31% (n = 81) were achieving their BP target according to measurements recorded in the previous 2 weeks. This agrees with previously reported BP control rates of 31.6% among treated patients with hypertension in tier 3 hospitals. In contrast, perceived levels of BP control were high; 85% (n = 223) of patients aware of their BP target claimed to reach it all/most of the time. Similarly, physicians claimed 70% of their patients achieve target BP and 62% were completely or somewhat satisfied with the proportion of their patients that reach target. Only 14% of patients reported they were concerned if they did not achieve BP control, and 88% were satisfied with their current treatment.

Conclusions: In this study, physicians and patients in China overestimated BP control rates. The large gap between perceived and actual BP control rates may contribute to therapeutic inertia and poor BP control among treated patients with hypertension.