THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Cardio-Pulmonary-Renal Interactions

A Multidisciplinary Approach

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ABSTRACT

Over the past decade, science has greatly advanced our understanding of interdependent feedback mechanisms involving the heart, lung, and kidney. Organ injury is the consequence of maladaptive neurohormonal activation, oxidative stress, abnormal immune cell signaling, and a host of other mechanisms that precipitate adverse functional and structural changes. The presentation of interorgan crosstalk may include an acute, chronic, or acute on chronic timeframe. We review the current, state-of-the-art understanding of cardio-pulmonary-renal interactions and their related pathophysiology, perpetuating nature, and cycles of increased susceptibility and reciprocal progression. To this end, we present a multidisciplinary approach to frame the diverse spectrum of published observations on the topic. Assessment of organ functional reserve and use of biomarkers are valuable clinical strategies to screen and detect disease, assist in diagnosis, assess prognosis, and predict recovery or progression to chronic disease. (J Am Coll Cardiol 2015;65:2433-48) © 2015 by the American College of Cardiology Foundation.

he concept of organ crosstalk refers to the complex biological communication and feedback between different organs, mediated via mechanical, soluble, and cellular mechanisms. Although crosstalk is essential to maintain body homeostasis, pathological states in 1 or more organs can lead to functional and structural dysfunction in other organs. The classification of cardiorenal syndromes has been expanded into 5 subtypes. Types 1 and 2 involve acute and chronic cardiovascular disease scenarios leading to acute kidney injury (AKI) or accelerated chronic kidney disease (CKD). Types 3 and 4 describe AKI and CKD, respectively, leading primarily to heart failure (HF), although it is possible that acute coronary syndromes, stroke, and arrhythmias could be

cardiovascular disease outcomes in these forms of CRS. Finally, CRS type 5 describes a systemic insult to both the heart and the kidneys, such as sepsis, where both organs are injured simultaneously in persons with previously normal heart and kidney function at baseline. Pulmonary-renal syndromes represent heterogeneous clinical entities, described by a combination of diffuse alveolar hemorrhage on the basis of pulmonary capillaritis in conjunction with glomerulonephritis as well as acute respiratory distress syndrome (ARDS) associated with AKI in the absence of hematuria. Hepatorenal syndrome can involve the development of functional cardiopulmonary changes and AKI in patients with advanced liver failure (acute or chronic) and is beyond the scope of this review.

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ABBREVIATIONS AND ACRONYMS

AKI = acute kidney injury

ARDS = acute respiratory distress syndrome

BNP = B-type natriuretic peptide

CKD = chronic kidney disease

CPRI = cardio-pulmonary-renal interactions

FGF = fibroblast growth factor

GFR = glomerular filtration rate

HF = heart failure

LV = left ventricular

PH = pulmonary hypertension

CARDIO-PULMONARY-RENAL INTERACTIONS: NEED FOR DEFINITION OF A SYNDROME?

With growing knowledge of interdependent feedback mechanisms involved in the heart, lung, and kidney crosstalk, the descriptive classification of a syndrome can represent a framework for exploring epidemiology, pathophysiology, detection, and management. Because of the complicated courses of hospitalization and the high mortality of patients with involvement of all 3 organs, an integrative approach is needed. The sequence of organ involvement can vary depending on the acuity and nature of the underlying disorder. Many patients with

disorders of 1 organ (e.g., CKD) die of complications of the other (e.g., HF) before the first organ's failure reaches its fullest extent, or the dysfunction of every organ may develop slowly until a "collapse" is reached and full-blown decompensation occurs. That is, each dysfunctional organ has the ability to initiate and perpetuate mutual injury through hemodynamic, neurohormonal, and cell signaling feedback mechanisms, while multiple episodes of acute (on chronic) decompensation may lead to reciprocal end-organ disease progression (Central Illustration). Given the multitude of contributing factors and the time sequence of events in cardio-pulmonary-renal interactions (CPRI), it is challenging to identify the underlying pathophysiological mechanisms and develop a strategy for diagnostic and therapeutic intervention. This review summarizes recent advances in our understanding of CPRI.

LUNG IN ORGAN CROSSTALK: THE PULMONOLOGIST'S VIEW

Open to environmental influence, the lung is a highly immunologic organ, representing a gateway to the environment. The lung has critical pathophysiological connections to the failing heart and kidney (Figure 1A).

LUNG INJURY, ABNORMAL CELL SIGNALING, AND OXIDATIVE STRESS. The lung conducts gas exchange via 3 mechanisms: ventilation, diffusion, and perfusion. Any imbalance can cause respiratory disturbance, which can be compensated to a certain degree by hyperventilation, greater oxygen extraction from blood by the tissues, and increased cardiac output, depending on the organ's functional reserve. In both noncardiogenic and cardiogenic pulmonary edema, fluid accumulation in the fissure and alveolar spaces can be seen as a result of increased pulmonary capillary permeability, elevated intravascular hydrostatic pressure, low colloid osmotic pressure, and insufficient lymphatic drainage (1). Changes to the alveolar-capillary barrier can induce an inflammatory cascade and oxidative stress of the pulmonary microcirculation, which results in cycles of alveolar wall injury predisposing and/or aggravating lung injury (Figure 1B) (2). Invasive and noninvasive measurements include analysis of pulmonary edema fluid, exhaled breath condensate (pH, arachidonic acid derivatives), proinflammatory cytokines (interleukin [IL]-1 β , -2, -6, -8, -12, and -17; interferon gamma; and tumor necrosis factor [TNF]- α), antiinflammatory cytokines (IL-4, -5, -10, and -13 and TGF- β), and chemokines (IL-8, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1 β), reactive oxygen and nitrogen species, and exhaled nitric oxide (3,4). The concept of subclinical lung injury (e.g., due to previous smoking) takes into account that even asymptomatic events can lead to increased future susceptibility to respiratory failure events, and new diagnostic techniques may provide early detection (5,6).

Circulating factors have been implicated in the pathogenesis of pulmonary inflammation following renal and hepatic ischemia/reperfusion injury in animal models and humans (7-9). In ischemic AKI, experimental studies demonstrate increased pulmonary vascular permeability, cellular apoptosis, alveolar hemorrhage, and leukocyte trafficking due to the production and/or decreased clearance of mediators of lung injury (2). Intraluminal neutrophils contribute through phagocytosis and release of mediators, including reactive oxygen species and proteases, and activation of dendritic cells, augmenting the immune response. Pro-inflammatory cytokines produced by renal tubular cells as well as white blood cells include TNF- α and IL-1 β and -6. Conversely, there are counterbalancing cell signaling peptides, including the anti-inflammatory IL-10, which has been shown to reduce lung injury in experimental models (2). Delayed recovery of kidney function may impair resolution of lung inflammation post-AKI (10). The altered mechanisms for water transport in pulmonary edema are described in detail in the "Uremic Lung" section.

MECHANICAL VENTILATION AND ARDS. Mechanical ventilation increases intrathoracic pressure and produces adverse hemodynamic effects that are opposite to normal spontaneous ventilation. Mechanical ventilation compresses pulmonary vasculature, which may result in increased right ventricular afterload and diminished cardiac output, leading to hypotension



and fluid-responsive shock; this scenario is commonly seen in the initial post-intubated period when ventilation is initiated. Similarly, decreased venous return and/or diminished diaphragmatic and abdominal wall compliance can compromise renal blood flow (11). Importantly, increased intra-abdominal pressure may contribute to reduced ventilatory volumes, impaired throughput of blood through the kidneys, and impaired venous return to the right heart, resulting in CPRI.

The severest form of lung injury is ARDS. Its definition includes the onset of lung failure within 1 week of the onset of illness, and it is characterized by hypoxemia in the presence of bilateral infiltrates on the chest x-ray that cannot be explained by HF or fluid overload. Whereas resolution of cardiogenic



and heart injury, reserve capacity and chronic organ failure, and its clinical features. **(B)** The cellular pattern of lung injury, repair, and fibrosis. Klotho may be an intermediate mediator that attenuates acute and chronic injury in all 3 organs. AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; CKD = chronic kidney disease; ECM = extracellular matrix; ESRD = end stage renal disease; HF = heart failure; IL = interleukin; LV = left ventricular; PEEP = positive end-expiratory pressure; PH = pulmonary hypertension; RAAS = renin-angiotensin-aldosterone system; RFR = renal functional reserve; ROS = reactive oxygen species; RV = right ventricular; TGF = transforming growth factor; TNF = tumor necrosis factor.

pulmonary edema can be rapid, the rate of edema resolution in most patients with ARDS is markedly impaired (1). The role of the alveolar-capillary barrier is very important in ARDS and governs both the rapidity of onset and the delayed clearance of alveolar fluid. ARDS is a major cause of mortality associated with appreciable morbidity, and AKI as an additional risk factor often develops as a component of a multiorgan system dysfunction. Even though ARDS mortality is currently declining (25% to 40%), AKI combined with ARDS increases mortality to 50% to 80% and negatively affects clinical outcomes, rising with AKI severity (12). ARDS is a breakdown of normal lung architecture, loss of functioning lung units, and development of a high-permeability pulmonary edema, all of which result in clinically-stiff, noncompliant, and heterogeneous lungs. Often requiring mechanical ventilation, it can itself induce and/or exacerbate lung injury contributing to distant organ effects and deleterious outcomes (2). Mechanistically speaking, pathophysiological changes occur from the direct effect of high pressure on the lung: barotrauma, from the damage caused by lung overdistension; volutrauma, from the shear stress of repetitive opening and closing of alveoli; and atelectotrauma, from the generation of cytokines and an inflammatory cascade, resulting in biotrauma. Here, lung-protective ventilation strategies not only improve mortality from ARDS, but also lead to improved distant organ function, suggesting the presence of iatrogenic trauma as a result of high volume ventilation that can further trigger hemodynamic, neurohormonal, and cell signaling pathophysiological mechanisms (including right ventricular stress with progressive pulmonary hypertension [PH]) (10,13). In addition, fluid overload and venous congestion is an independent predictor of increased mortality in AKI that is thought to further contribute to respiratory complications (14). Here, the goal of optimal fluid management for recovery of both organs is an area of active study (10). Furthermore, the role of inhaled nitric oxide for alleviation of ARDS and altering renal function has to be defined, including its anti-inflammatory properties (15). Several favorable effects are known, although trials and meta-analyses have failed to demonstrate its beneficial use in ARDS (16). Inhaled nitric oxide causes selective vasodilation of pulmonary vessels in ventilated areas without affecting systemic blood pressure and cardiac output, improves ventilationperfusion mismatch, and is a valuable option to reduce PH in susceptible patients (17). In addition, nitric oxide exerts positive effects in acute hyperoxic lung injury models by diminishing inflammation and by protecting both endothelium and alveolar epithelium from oxidative injury (18).

Outside of the setting of ARDS, there is convincing evidence that pro-inflammatory effects of mechanical ventilation can be a source of AKI. In lung-injurious ventilator strategies, animal models demonstrate the production of a variety of inflammatory cytokines (e.g., IL-8 and monocyte chemotactic protein-1), expression of nitric oxide synthase (shown to exert cytotoxic effects), induction of renal epithelial cell apoptosis, and dysregulation of renal vascular response (19). Injurious mechanical ventilation induces myocardial inflammation, including the up-regulation of pro-inflammatory myocardial cyclooxygenases and expression of IL-8, whereas lung-protective strategies ameliorate myocardial inflammation (20).

PULMONARY VASCULAR REMODELING AND FIBROSIS. Patients with chronic respiratory disease often have multiple comorbidities such as concomitant cardiovascular disease, hypertension, and a decline in renal function (21). The diseases' natural course and severity, as well as quality of life, are diverse, depending on pathology in the respiratory system and on other organ dysfunction. Comorbidities are frequently the reason for hospitalization and have led to a common view that chronic respiratory disorders contribute to both airway and systemic inflammation affecting distant organs (22). Polypharmacy is frequent in these cohorts, and impaired renal clearance of drugs could increase the risk of adverse reactions. Pulmonary congestion in chronic HF can initiate lung structural remodeling by proliferation of fibroblasts with fibrosis and extracellular matrix deposition, resulting in thickening of the alveolar wall (Figure 1B) (23). Similar mechanisms are assumed in CKD, in addition to uremia-related dysfunction of the pulmonary microcirculation (24). Although the resultant reduction in vascular permeability is initially protective against pulmonary edema and can be seen as a restorative mechanism, the process can cause a restrictive, poorly compliant lung with impaired gas exchange, and reduced exercise capacity. The lung diffusion capacity for carbon monoxide is one of the most clinically-valuable tests to assess the alveolar-capillary membrane. In acute decompensated HF, it can be normal or elevated due to an increased alveolar capillary blood volume, whereas the previously-mentioned mechanisms can lead to its impairment in chronic HF (25). In CKD, a marked decrease in diffusion capacity for carbon monoxide correlates with the severity of renal impairment after correcting the effects of renal anemia (26). The multifunctional protein Klotho regulates phosphate/calcium metabolism and is identified as an important molecule in the aging processes. Its cytoprotective role is currently investigated in CKD and cardiac remodeling, and Klotho appears as 1 of several unifying mechanisms in the CPRI. Animal studies emphasize its antioxidative (27) and antifibrotic (28) capacity by suppressing vascular endothelial growth factor and the pro-fibrotic TGF-β1/ Smad 3 expression in pulmonary epithelia.

Chronic hypoxia and vascular remodeling is assumed to be responsible for resultant secondary and in some cases fixed pre-capillary PH, which is an independent predictor of mortality (29). The transition from a primary vasoconstrictive to a vasoproliferative process is the hallmark of fixed PH. This histopathological pattern is defined by "hypertrophy of the medial layer of the vessel wall, hyperplasia of the intimal layer, proliferation of the adventitial layer, and/or plexiform lesions" (29). The natural course of PH is generally progressive, with osteoblastic transformation of vascular smooth muscle cells and deposition of hydroxyapatite crystals in the interstitium. As a result, pulmonary vascular stiffness markedly increases. In this scenario, a selective pulmonary vasoactive therapy can potentially worsen a patient's condition by causing increased venous engorgement and a shift of the interventricular septum, thus inducing left ventricular (LV) failure with pulmonary

edema (30). PH has been reported in >60% of patients with HF with reduced ejection fraction, >80% of patients with HF with preserved ejection fraction, and in 78% of patients prior to mitral valve surgery (31).

First established in 1998, the clinical classification of PH has become more granular over time, and in 2013, chronic renal failure was added as a risk factor (29). The prevalence of PH and concomitant CKD increases with declining renal function, and in current understanding, kidney function may itself have an effect on pulmonary vascular remodeling in a predisposed patient, analogous to connective tissue disease, human immunodeficiency virus, or portal hypertension (32). Pathophysiological features include endothelial dysfunction, decreased bioavailability of nitric oxide, increased levels of endothelin-1, fluid overload, and shunting via arteriovenous fistulae (32).

BLOOD GAS DISTURBANCES. Maintenance of normal gas exchange is not achieved in patients with chronic underlying pulmonary disease and in severely ill patients; hypoxemia and/or hypercapnia develops with relative degrees of renal acid/base compensation. Reflecting alveolar ventilation in most cases, acute and chronic changes in carbon dioxide tension elicit renal adaptive buffering mechanisms. In pulmonary diseases, vasodilator properties of hypercapnia lead to a decrease in systemic vascular resistance and blood pressure with consequent neurohormonal activation, retention of salt and water, and reduction in renal blood flow and glomerular filtration rate (GFR); cardiac output is not reduced, and renal blood flow and GFR increase when hypercapnia improves (21,33). Supported by recent findings, the relative contribution of blood gas disturbances may be crucial in CPRI and its prognosis. The targeted long-term use of noninvasive ventilation (biphasic positive airway pressure) for reduction of hypercapnia in stable chronic obstructive pulmonary disease patients significantly improves survival (34). Likewise, forms of assistance in ventilation for obstructive and central sleep apnea effect improvements in renal blood flow and glomerular filtration (35). Short-term noninvasive ventilation reduces albuminuria, high-sensitivity Creactive protein levels, and urinary norepinephrine excretion in HF patients (36). On the contrary, permissive hypercapnia in acute respiratory disorders may be beneficial in diminishing lung inflammation and lung/kidney cell apoptosis (37).

HEART IN ORGAN CROSSTALK: THE CARDIOLOGIST'S VIEW

Cardiovascular diseases remain the major cause for hospitalization, disability, and mortality worldwide.

Among those, HF is a pivotal and progressive condition that leads to a cascade sequence of interorgan crosstalk, including lung and kidney (**Figure 2A**). HF comprises different scenarios, depending on acuity and origin (38). Most frequently, acute decompensated HF develops in the presence of an underlying chronic HF, although in 15% to 30% of all causes it may present as new onset HF.

Distant organ damage is often proportional to duration of HF and represents a daily multidisciplinary challenge. Recently, a TNM-like method was proposed for HF staging, which includes the characterization "H" for heart, "L" for lung, and "M" for malfunction of other organs including the kidney (39). Most distant organ malfunctions (e.g., liver, kidney, or bowel) are the result of right-sided HF and acute on chronic venous congestion (40). Additionally, AKI occurs in 25% to 33% of acute decompensated HF, which is an independent risk factor for prolonged hospitalization, need for renal replacement therapies, readmission, increased stroke risk, and mortality (41). In 60% of cases of acutely decompensated HF, AKI can be seen as an exacerbation of previously-diagnosed CKD, whereas in chronic HF, CKD has been reported as a comorbidity in 26% to 63% (42).

CARDIAC INJURY, ABNORMAL CELL SIGNALING, AND OXIDATIVE STRESS. Analogous to the lung, cardiomyocytes show the ability to promote distant organ damage (e.g., AKI), following ischemic and mechanical injury via innate immune system response, neurohormonal signaling, and possibly, by release of metabolic products (e.g., catalytic iron) (41). IL-1 and TNF- α induce expression of ICAM-1, an intercellular adhesion molecule promoting diapedesis of leukocytes into interstitium, thereby depressing LV function by presumably inducing cardiomyocyte hypoxia and apoptosis (Figure 2B) (43). In response to biomechanical strain, ST2 acts as a decoy for IL-33 on its receptors in resident satellite cells and cardiomyocytes. Additionally, in response to stimulation by aldosterone and other factors, macrophages secrete galectin-3, which is a powerful stimulus for fibroblasts to proliferate and produce increased interstitial collagen. In concomitant AKI, renal tubular cells can further contribute to the circulating levels of inflammatory cytokines. The important role of these cells in the handling of inflammatory mediators and resulting efflux into systemic circulation is discussed in the section "Acute Kidney Injury, Abnormal Cell Signaling, and Oxidative Stress" (44). Oxidative stress has been implicated as the final common pathway of injury in various pathological systems that are prevalent in cardiac, pulmonary, and



IGFBP = insulin-like growth factor binding protein; PVR = pulmonary vascular resistance; RVR = renal vascular resistance; other abbreviations as in Figure 1.

renal disorders (1,44). Accumulation of oxidativedamage products and failure to adapt to reactive oxygen species stress may result in an immune system activation and a proinflammatory and/or profibrotic milieu to generate functional and structural abnormalities, and consequently evoke cell death.

RIGHT VENTRICULAR STRESS AND VENOUS CONGESTION. Pulmonary vascular resistance is in constant interplay with right ventricular function. In the normal state, the right ventricle is a thin-walled, compliant, low-pressure chamber that pumps the same stroke volume as the left ventricle, but with $\approx 25\%$ of the stroke work due to the typically low resistance of the pulmonary vasculature (45). In PH, the stressed heart tries to balance pre-load and afterload to accommodate increased pulmonary vascular resistance. Resultant neurohormonal activation (endothelin, arginine vasopressin) leads to water and salt retention, worsening venous congestion, and further reduced cardiac output (46).

In HF, renal failure has traditionally been thought to be caused by renal hypoperfusion due to lowoutput failure. However, most hospitalizations for acute decompensated HF occur because of symptoms of pulmonary and systemic venous congestion rather than poor perfusion (47). As 85% of the total blood volume is located in the venous side of circulation, an expansion in total blood volume may occur without changes in the arterial circulation (46). However, a dysfunctional left ventricle is prone to afterload variations, and therefore, increased systemic blood pressure can cause pulmonary congestion, irrespective of the intravascular volume. As reviewed earlier, the pulmonary sequelae extend beyond simply lung edema and congestive pneumonia. Hydrostatic effects can induce lung injury and barrier dysfunction, initiating a cascade of local and systemic organ injury, whereby pulmonary vascular remodeling results from chronic affection. Recurrent decompensation can account for the vulnerability of HF patients. Additionally, venous congestion may increase gut endotoxin absorption contributing to the harmful environment, although activation of venous endothelium itself is a stimulus for release of inflammatory mediators (48). As with the heart, the surrogate central venous pressure is 1 of the most important hemodynamic determinants for worsening renal function and is independently associated with higher mortality (47). On the basis of animal models, venous congestion is likely to decrease renal perfusion pressure through an increase in back pressure and formation of renal edema, although the renal "intracapsular tamponade" may aggravate back pressure (49). Venous congestion represents a part of a cascade with stepwise development of fluid overload, deteriorating LV dysfunction, pulmonary congestion, secondary fixed pre-capillary PH, right ventricular overload and enlargement with tricuspid incompetence, and interference with LV filling. The additional resultant central venous pressure rise is transmitted to the kidney and leads to a positive feedback loop evolving toward refractory congestive HF. Those patients are at high risk and have a narrow window for fluid management of venous congestion; extremes in either parameter can be associated with worsened renal and right ventricular function.

CARDIAC REMODELING AND FIBROSIS. HF represents a heterogeneous group of syndromes leading to structural (hypertrophy, fibrosis, and/or ventricular dilation) and functional alterations (myocardial stiffness and incomplete relaxation of contractile units) (50). Here, sequence of abnormal gene expression, cell signaling, and oxidative stress due to uncontrolled hypertension, diabetes mellitus, and other factors are a common link that is responsible for exuberant repair (fibrosis) pathways (**Figure 2B**) (41). The transformation predisposes the heart to become more vulnerable to re-entrant arrhythmias and pump failure. Accumulation of cardiac fibrosis may be the mechanism by which age contributes as a determinant of HF in the community (51).

At a cellular level, angiotensin and aldosterone are major stimuli for galectin-3 secretion with activation of oxidant stress signaling pathways that decrease levels of bioavailable nitric oxide, increase inflammation and TGF- β , and promote fibroblast proliferation, migration, extracellular matrix remodeling, and deposition of pro-collagen (52,53). Fibrosis in the myocardium, lung, and kidney strongly suggests that neurohormonal translation to cell signals is part of the pathogenesis and progression of disease. The mammalian fibroblast growth factor (FGF) family plays a crucial role via distinct action mechanisms among cardiomyokines and represents a promising novel endeavor. FGF2 and FGF23 promote cardiac hypertrophy and fibrosis by activating mitogen-activated protein kinases signaling and circulating (α)-Klotho-independent calcineurin/nuclear factor of activated T cells signaling, respectively. FGF2 significantly induces TGF-β1 that acts downstream of angiotensin II and promotes cardiac remodeling (54). The bone-derived hormone FGF23 regulates phosphate in association with parathyroid hormone and vitamin D in coordination with its coreceptor Klotho, whereas CKD progression results in elevated serum levels of FGF23 (55). In contrast, FGF16 and FGF21 seem to prevent cardiac remodeling (54). In vitro, Klotho inhibits TGF- β 1-, angiotensin II-, or high phosphate-induced fibrosis (56) and confers resistance to oxidative stress and endothelial dysfunction (57). In experimental models, intravenous delivery of α -Klotho can ameliorate cardiac hypertrophy, independent of FGF23 and phosphate levels (55). However, the mechanism of α -Klotho-independent FGF23 signaling in the heart remains unclear (54). Whether modulation of this complex system would improve cardiac outcome in such a high-risk population awaits further investigation.

LV remodeling is associated with increased interstitial matrix, decreased capillary density, accelerated apoptosis, chamber dilation, and dyssynchrony, leading to pump failure and sudden death (58). HF with preserved systolic function remains an elusive condition associated with concentric LV hypertrophy and impairment of diastolic LV function. It accounts for more than one-half of hospitalizations for HF and has no agreed-upon definitions for detection or management (59). Activation of the reninangiotensin-aldosterone system is 1 potential unifying element in diastolic HF and CPRI, and the potential efficacy and antifibrotic role of mineralocorticoid receptor antagonists in cardiac, pulmonary, and renal disease merits further investigation in clinical trials (52).

KIDNEY IN ORGAN CROSSTALK: THE NEPHROLOGIST'S VIEW

The kidney is the window to neurohumoral and immunological diseases and plays a key role in clearance, fluid, electrolyte, and acid-base homeostasis in mammalian physiology. AKI remains 1 of the most complex clinical challenges and is associated with excess morbidity and mortality, especially in critically ill patients (44). Regardless of the cause, cardiac and/or pulmonary symptoms are the leading clinical manifestation (Figure 3A). Current definitions of AKI are commonly linked to creatinine rise and urinary output, are insensitive to the severity of renal injury, and can lead to delayed diagnosis and underestimation of the degree of tubular damage. The concept of subclinical AKI emphasizes that even patients who do not fulfill current consensus criteria for AKI are still likely to have acute tubular damage that may expose them to an increased susceptibility to future injury and elevated risk for subsequent CKD development (60), providing a significant impulse for the initiation of organ crosstalk with the heart and lung. The recent KDIGO clinical practice guideline proposed a new conceptual model, called acute kidney disease, to emphasize the need to follow patients who survived AKI episodes. Here, assessment of renal functional reserve seems to be a promising tool to predict kidney recovery versus early function decline (61). Despite medical advances and the widespread availability of renal replacement therapy, the mortality rate of severe AKI has not declined in recent decades, reaching 50%, and therapy is limited (62). Early and increased renal replacement therapy does not appear to improve outcome. Much of the mortality risk is thought to be the consequence of complex interactions between the actual insult, activation of inflammation, and distant organ effects. To reduce the systemic inflammatory response, especially in combination with AKI, recent efforts are being made to use renal replacement therapy as a means to reduce cytokines.

AKI, ABNORMAL CELL SIGNALING, AND OXIDATIVE STRESS. The renal tubular epithelium is fundamental in the regulation of inflammatory processes and is immunologically active (44,62). During AKI, it represents a major site of cell injury and death, catalyzing circulating mediators in local and systemic inflammation/oxidative stress by different mechanisms including epigenetic processes (Figure 3B). In animal models, the kidney responds with an expression of IL-1 β , vascular cell adhesion molecule-1, and TGF- β consistent with renal cell infiltrates and, in advanced stages, perivascular, periglomerular, and peritubular fibrosis with increased markers of collagen formation (63). Here, innate and adaptive, cellular, and humoral immune systems contribute to AKI, which are presumably involved in repair process as well (62). However, a detailed discussion of immunomodulation is beyond the scope of this review. Recently, many efforts have been made to dissect the mechanisms of ischemic preconditioning as a powerful intervention to protect the heart, lung, and kidney from injury (64,65). Endothelial cells, cardiomyocytes, and vascular smooth muscle cells have all been shown to alter cellular processes as a result of repeated episodes of nonlethal hypoxia. Thus, these changes may someday be mimicked by drugs or other interventions to improve cell survival during ischemic episodes. AKI can clearly lead to CKD. The incidence of tubulointerstitial fibrosis has the best correlation with CKD development (66). Interestingly, Klotho is mainly expressed in renal distal convoluted tubules (56). Thus, renal tubular cells and renal fibroblasts may be the primary cell types in the progressive development of CKD contributing to the progressive nature of cardiovascular and pulmonary diseases.

UREMIC LUNG. Chronic uremia affects the lungs and results in the characteristic central butterfly appearance that contrasts with the translucent periphery in anteroposterior x-rays of the lung. In 1951, Bass et al. (67) reported its association with cardiac hypertrophy and LV failure in advanced kidney failure. Uremia results in a decrease in diffusion capacity for carbon monoxide (26), small airway dysfunction (68), and impaired peak oxygen consumption (69). The uremic milieu presumably contributes to the development of lung injury and dysfunction, which can be reversed by renal transplantation (9,70). With the introduction of dialysis, the classic presentation of uremic lung in the absence of volume overload has become less common. Still, its pathophysiologic principles are operative in CPRI.

At a cellular level, mechanisms for impaired resolution of pulmonary edema in acute lung injury (1), in cardiogenic pulmonary edema (71), and in response to AKI (9) have been identified demonstrating reduced expression of epithelial sodium channel, sodium-potassium ATPase, and aquaporin 5. Epithelial sodium channel-inhibition (e.g., with amiloride) can alter alveolar fluid clearance, promoting reversed



(A) The vicious circle of heart and lung injury, reserve capacity, and chronic organ failure, and its clinical features. (B) The cellular pattern of renal injury, repair, and fibrosis. Activation of RAAS may contribute to renal fibrosis by diminishing the cytoprotective effects of Klotho. HF = heart failure; LV = left ventricular; RV = right ventricular; VCAM = vascular cell adhesion molecule; other abbreviations as in Figure 1.

transepithelial ion transport with active augmentation of pulmonary edema. In animal model, inhibition of either the apical cystic fibrosis transmembrane conductance regulator or sodium-potassium-chloride cotransporter 1 (e.g., with furosemide) can prevent active alveolar fluid secretion (71).

UREMIC CARDIOMYOPATHY. CKD accelerates coronary artery atherosclerosis by several mechanisms, notably hypertension, dyslipidemia, and abnormal calcium/phosphorus metabolism, associated with vascular remodeling and development of noncompliant vessels. Still, these mechanisms cannot account for cardiovascular risk, as reflected in high rates of sudden cardiac death, HF, sustained arrhythmias, and myocardial infarction (72). Uremic cardiomyopathy defines the structural and electrophysiological remodeling of the heart, characterized by biventricular hypertrophy, systolic and diastolic dysfunction, capillary rarefication, cardiac fibrosis, and an enhanced susceptibility to further injury (73). Involvement of the fibrotic pericardium is classically manifested as acute on chronic uremic pericarditis with sterile effusion, and is a less common complication since the introduction of dialysis. Contrarily, reversal of renal dysfunction (e.g., after renal transplantation) can improve cardiac function (74). Uremic cardiomyopathy may represent the advanced alteration of cardiac remodeling described earlier and FGF23 excess/Klotho deficiency might make a considerable contribution in CKD patients (56).

In type 3 cardiorenal syndrome, AKI can lead to cardiac dysfunction by fluid overload, electrolyte and acid-base shift, and renin-angiotensin-aldosterone system or central nervous system activation. Analogous to the lung, AKI induces endothelial cell activation, leukocyte trafficking, and myocardial infiltration (the role of ICAM-1 was reviewed earlier), and pro-apoptotic cascades, resulting in myocardial damage and long-term dysfunction (44). Following cardiac ischemia, ventricular fibrillation appears much more frequent in the setting of AKI (75). Impaired cardiac function alters the interdependency of the cardiopulmonary circuit. Pulmonary congestion, in combination with AKI-induced compromise of tubular epithelial ion pumps, may act synergistically to further compromise cardiopulmonary function.

CKD AND FIBROSIS. The high prevalence and burden of CKD is well established and can represent the origin and/or continuum of chronic cardiopulmonary disorders. The concept of subclinical AKI was discussed, and early pathological changes can occur without apparent clinical presentation due to the high renal adaptability, but they still depict a slowly progressing degenerative process that is both local and systemic. Once the adaptive threshold is reached, the progression to CKD is fast. It is generally accepted that all primary causes of CKD share a common pathogenic pathway of progressive renal injury due to the destructive consequences of fibrosis. As fibrosis increases, the nephron that normally has a potent regenerative capacity loses this ability, leading to apoptosis. Proteinuria is a surrogate marker of CKD progression and reflects endothelial dysfunction. Even a modest increase in albuminuria is associated with chronic pulmonary disorders (76), right ventricular/LV remodeling, and adverse cardiovascular outcomes (77), although by the time proteinuria manifests, renal structural damage has already occurred. Here, clinical and emerging biomarkers (e.g., galectin-3) have been identified (78). Still, it is important to underscore that most CKD patients will never reach the point of needing renal replacement therapy. They are more likely to die prematurely due to accelerated cardiovascular diseases.

ORGAN FUNCTIONAL RESERVE

Given the multitude of contributing factors and the time sequence of events in CPRI, it is challenging to predict early functional and/or structural changes. The normal heart, lung, and kidney permit a degree of physiological reserve that can maintain normal organ function for any given insult. The functional reserve of an organ can be defined as the difference between the minimum baseline function and the maximum attainable function in response to a physiological or pathological stimulus. Yet, the mutual dependence of the organs is not defined. In daily routine, assessment of cardiac and pulmonary functional reserve is a valuable parameter to define status, recovery, and prognosis toward the organ's response to an acute event or chronic disease. Care and attention is needed in chronic disorders, because these patients are more prone to develop injury, decreasing the remaining functional mass. Thus, patients with "acute on chronic" organ injury are at the highest risk. Genetic disposition and environment influence the individual course, while the organ functional reserve declines with age as a consequence of physiological aging. Frequent physical activity can develop and maintain cardiopulmonary reserve best reflected by peak oxygen consumption, but no factors have been identified that can lead to increased renal functional reserve.

CARDIAC FUNCTIONAL RESERVE. Cardiac functional reserve is the ability of the myocardium to augment its cardiac output and tissue delivery of oxygen during stress. The spectrum of myocardial dysfunction may range from diastolic dysfunction in the early stage to overt systolic dysfunction. Both limit exercise tolerance before resulting in symptoms at rest, normally manifested by exertional dyspnea and impaired oxygen kinetic during exercise. LV diastolic reserve is the ability of the LV filling pressures to remain normal during stress, whereas in systolic dysfunction, stress can reveal both LV and right ventricular impaired contractile reserve (e.g., to unmask subclinical ischemia or PH) (79,80). However, the presence and extent of coronary artery disease, ischemic burden, old myocardial infarction, and medication (e.g., diminished chronotropic reserve with beta-blockers) are all factors determining assessment (79). Probably the best measure of cardiac functional reserve is the peak oxygen consumption measured during maximal exercise and expressed as ml/kg/min. This variable has been shown to be predictive of survival in the general population and in

those with myocardial infarction, HF, and virtually all other chronic conditions.

PULMONARY FUNCTIONAL RESERVE. Pulmonary functional reserve is the ability of the lung to augment its respiratory minute volume during stress. Its measurement is complex and includes several variables for determination whether exercise capacity is reduced (mostly the case) or a reduced ventilatory capacity limits exercise. The breathing reserve, expressed as the difference between the maximal voluntary ventilation and the maximum exercise ventilation, and respiratory frequency represent valuable criteria for maximal pulmonary exertion (81). As with cardiac functional reserve, the peak oxygen consumption can be thought of as an objective surrogate of cardiorespiratory endurance and aerobic fitness, because it reflects both pulmonary capabilities for ventilation and gas exchange as well as cardiac output and tissue perfusion (82).

RENAL FUNCTIONAL RESERVE. The concept of renal functional reserve represents the capacity of intact nephron mass to increase GFR in response to stress and stands for the difference between peak "stress" GFR induced by protein load (oral or intravenous) and the baseline GFR (61). In physiological (e.g., pregnancy or solitary kidney) or pathological hyperfiltration (e.g., diabetes mellitus or nephrotic syndrome), renal functional reserve allows for an increase in GFR by recruitment of dormant nephrons, replacing the lost function and maintaining the whole organ GFR. Renal functional reserve may represent a future tool to exploit renal filtration capacity, even when subclinical damage is present and creatinine is still normal, whereas a reduction of renal functional reserve may represent the equivalent of renal frailty or susceptibility to insults.

BIOMARKERS

Inflammation is classically defined by 4 elements: immune cells (typically granulocytes), antibodies, cell signals (cytokines, interleukins, and so on), and complement. In the absence of infection, acute organ injury in the lungs, heart, and kidneys has very little involvement by granulocytes, antibodies, or complement. Thus, inflammation, despite its popularity as a term, may not be optimal to describe the primary role of abnormal cell signaling in the pathogenesis of CPRI. Novel biomarkers extend the spectrum to prevention, early diagnostic evaluation, treatment, and course of the disorder (Central Illustration). However, the relative paucity of biomarkers that link a cardiopulmonary-renal interaction should be emphasized as an area that needs further study. In the following text, we review a select group of currentlyestablished and promising future biomarkers in CPRI.

HIGH-SENSITIVITY CARDIAC TROPONIN. High-sensitivity troponin I and T have been introduced as biomarkers of myocardial injury detectable at a much earlier stage compared with prior troponin assays. In stable PH, chronic obstructive pulmonary disease, and CKD, elevated levels may indicate subclinical myocardial injury that subsequently contributes to HF (83,84). Knowledge of its determinants in CPRI may guide further research and help to stratify patients at early cardiovascular risk.

B-TYPE NATRIURETIC PEPTIDE AND N-TERMINAL **PRO-B-TYPE NATRIURETIC PEPTIDE.** B-type natriuretic peptide (BNP) and its inactive cleavage protein N-terminal pro-B-type natriuretic peptide (NTproBNP) are markers of cardiac stretch from increased wall tension, and are established diagnostic, prognostic, and management tools for acutely decompensated HF, chronic HF, and acute coronary syndromes (85). BNP is also prognostic for PH, probably due to increased right ventricular wall tension and up-regulation of the pre-proBNP gene (86). Elevations in BNP in the setting of acutely decompensated HF and acute coronary syndromes is associated with an increased risk of AKI (38,85). Patients with CKD have higher levels of BNP than ageand sex-matched patients with normal renal function, and this probably represents both increased cardiac production of BNP due to subclinical pressure overload, volume overload, and cardiomyopathy as well as decreased renal clearance, more notably with NT-proBNP than BNP (38).

SOLUBLE SUPPRESSOR OF TUMORIGENICITY 2. Soluble suppressor of tumorigenicity 2 (ST2) is a circulating inhibitor of the IL-33 receptor and counteracts the antifibrotic effects of IL-33 (87). Soluble ST2 has received major attention as it may have an important role in the development of fibrosis and/or as a biomarker of disease severity, although it lacks organ specificity. Higher concentrations are associated with worse outcome in ARDS and PH (88,89). Soluble ST2 has prognostic value in risk stratification for HF, and presumably CKD, and is not adversely influenced by age and impaired renal function (90).

GALECTIN-3. Galectin-3 is a β -galactoside-binding lectin with putative roles in immunomodulation, transformation, and aldosterone-induced fibro-genesis. In the heart, galectin-3 is implicated in the pathogenesis of fibrosis but is also increased with normal aging and renal impairment (53). Galectin-3 levels have prognostic value in patients with HF, independent of etiology and HF typology, and provide

an additive value to natriuretic peptide measurements. Galectin-3 has been shown to promote TGF- β mediated activation of fibroblasts in the lung (91) and kidney (78). Complementary prospective studies are needed to assess whether galectin-3 may be used to predict which patient with cardiac, pulmonary, and renal involvement may benefit from antifibrotic agents.

RENAL CELL CYCLE ARREST MARKERS. In the setting of cellular injury, 1 of the earliest processes to be affected is the cell cycle, which is down-regulated to preserve cellular energetics and metabolic functions in the setting of hypoxia or other insults. Both the proximal and distal renal tubular cells release tissue inhibitor of metalloproteinase (TIMP)-2 and insulin-like growth factor binding protein (IGFBP)-7, which are measured in the urine and appear to predict a reduction in renal filtration function at ≥ 12 h after serious illness (92). The multiplication of the 2 concentrations yields a renal risk score, with a score >0.3 U having a high negative predictive value and a score >1.2 a strong positive predictive value in AKI. The relationship of these cell-cycle arrest makers in the urine, which have been recently become available as a commercialized, in-vitro diagnostic test, and other manifestations of CPRI have not been explored.

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN. Neutrophil gelatinase associated lipocalin (NGAL) is expressed in the distal tubules and collecting duct, seems to be 1 of the earliest renal markers of ischemic or nephrotoxic injury, and is detected in blood and urine soon after AKI (93). Moreover, NGAL has been implicated in the induction of cardiomyocytes apoptosis and is highly expressed in failing myocardium (65). Plasma NGAL has been associated with adverse cardiovascular outcomes or death and is a strong predictor of all-cause mortality in acute decompensated HF, suggesting that renal damage has a role in determining the prognosis of HF patients. However, peak 24-h urinary NGAL seems to predict best the 30-day mortality and dialysis in intensive care patients, compared with plasma NGAL and cystatin C (93). In small studies, plasma and urinary levels of NGAL do not correlate with PH (94). Yet, its role in acute decompensated right ventricular failure is not defined. Plasma, but not urinary NGAL, increases markedly with GFR reduction and can possibly generate a high number of false positive diagnoses of AKI in stable CKD patients. Both plasma and urine NGAL are commercially available assays for AKI.

L-TYPE FATTY ACID BINDING PROTEIN. In the setting of AKI, renal tubular cells release L-type fatty

acid binding protein (L-FABP) into the urine. L-FABP is a housekeeping protein that moves rapidly out of the cytosol through the apical membrane of tubular epithelial cells and has been shown to be an early marker of AKI (95). It can be readily measured and is a commercialized urine test for AKI. Its relationships to other manifestations of CPRI have not been determined.

KIDNEY INJURY MOLECULE-1. Kidney injury molecule (KIM)-1 is a transmembrane tubular protein solely expressed in response to ischemic or nephrotoxic insults to proximal renal tubular cells, and has been proposed as an early marker of AKI as well as important in the transition from AKI to CKD (96). KIM-1 is measurable in blood and urine and is predictive of AKI in patients undergoing coronary angiography and in HF (95). Conversely, higher levels are associated with incident HF risk (97). There are no data describing the use of KIM-1 in pulmonary disorders.

USE OF BIOMARKERS IN COMBINATION. The Acute Dialysis Quality Initiative panel has recommended the use of both functional (creatinine, cystatin C) filtration markers as well as renal tubular injury markers (TIMP-2, IGFBP-7, NGAL, L-FABP, KIM-1, IL-18, and so on) to both screen and detect AKI as well as to aid in the prognosis for important outcomes, including the need for dialysis and mortality (98). This has been well supported by recent published data in several settings including patients undergoing cardiac surgery (99).

CONCLUSIONS

We have summarized current concepts in the pathogenesis of CPRI including abnormalities, cardiopulmonary and systemic hemodynamics, neurohormonal activation, abnormal cell signaling, and tissue fibrosis. A sustained injury to the alveolar-capillary barrier can initiate lung structural and vascular remodeling, leading to chronic lung disease and pulmonary hypertension. Cardiac injury represents the origin of cascading deleterious events that may lead to myocardial remodeling with fibrosis and heart failure. Acute kidney injury might occur as a result of abnormal immune cell signaling of the injured tubular epithelial cells, whereas recurrent AKI leads to an elevated risk for subsequent CKD development. Much is yet to be learned about the time sequence of organ injury and damage and what, if any, are the key modifiable mediators in the propagation of organ dysfunction. Multiple disciplines working together hold the hope of future interventions that can lead to improved survival in the critically ill patient with evidence of cardiac, pulmonary, and renal failure.

ACKNOWLEDGMENTS The authors thank Drs. Fernando E. Núñez Gomez, Daniel Murillo Brambila, Aashish Sharma, Renhua Lu, and Carla Estremadoyro for their devoted help in the development of the manuscript.

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KEY WORDS acute kidney injury, acute respiratory distress syndrome, cardiorenal syndromes, chronic kidney disease, heart failure, pulmonary hypertension