Heart failure is a global problem with an estimated prevalence of 38 million patients worldwide, a number that is increasing with the ageing of the population. It is the most common diagnosis in patients aged 65 years or older admitted to hospital and in high-income nations. Despite some progress, the prognosis of heart failure is worse than that of most cancers. Because of the seriousness of the condition, a declaration of war on five fronts has been proposed for heart failure. Efforts are underway to treat heart failure by enhancing myofilament sensitivity to Ca²⁺; transfer of the gene for SERCA2a, the protein that pumps calcium into the sarcoplasmic reticulum of the cardiomyocyte, seems promising in a phase 2 trial. Several other abnormal calcium-handling proteins in the failing heart are candidates for gene therapy; many short, non-coding RNAs—ie, microRNAs (miRNAs)—block gene expression and protein translation. These molecules are crucial to calcium cycling and ventricular hypertrophy. The actions of miRNAs can be blocked by a new class of drugs, antagomirs, some of which have been shown to improve cardiac function in animal models of heart failure; cell therapy, with autologous bone marrow derived mononuclear cells, or autogenous mesenchymal cells, which can be administered as cryopreserved off the shelf products, seem to be promising in both preclinical and early clinical heart failure trials; and long-term ventricular assistance devices are now used increasingly as a destination therapy in patients with advanced heart failure. In selected patients, left ventricular assistance can lead to myocardial recovery and explantation of the device. The approaches to the treatment of heart failure described, when used alone or in combination, could become important weapons in the war against heart failure.

Introduction

Spectacular advances have occurred in the past three decades in cardiovascular medicine and surgery. In high-income countries, early mortality rates associated with acute coronary syndromes (figure 1), valvular and congenital heart disease, hypertension, and many arrhythmias have decreased substantially. However, in many patients with these disorders some myocardial damage has occurred, and although their lives have been prolonged, their heart disease has not been cured; an increasing number become at risk of subsequently developing heart failure, which might be regarded as the price of success, and for many patients this price is steep.

Heart failure is a global problem,⁴ ⁵ with an estimated 38 million patients with this diagnosis worldwide. The Global Burden of Disease 2010 study⁶ reported that from 1990 to 2010, ischaemic heart disease was the most common cause of death worldwide. Although the age-standardised incidence of acute myocardial infarction has decreased worldwide, the prevalence of ischaemic heart failure, the most common type of heart failure, has increased.⁸ Heart failure is now becoming more common in low-income and middle-income countries, where an increasing proportion of the population have a high-income-country lifestyle that leads to obesity, hypertension, and diabetes,⁷ all risk factors for the development of heart failure.

Heart failure is the most common diagnosis for hospital admission in patients aged 65 years and older in high-income countries. Since heart failure occurs most commonly in elderly people, the demographic imperative is immense. Every year, about 1 million hospital admissions occur for heart failure in the USA (figure 1) and a similar number occur in Europe. With the surge in the elderly population that is expected in both industrially developed and developing nations, a 50% increase in the number of new patients with heart failure every year is estimated in 15 years, unless there is real progress in prevention or treatment, or both.⁹,¹⁰

The results of the management of heart failure, as described in practice guidelines, are mixed.⁸,¹¹ In patients with chronic heart failure with reduced ejection fraction, both the survival¹² and quality of life have improved with the use of β-adrenoreceptor blockers, with drugs that block the renin-angiotensin-aldosterone system,¹³ and, according to a recent report,¹⁴ with an angiotensin receptor-neprilysin inhibitor and with devices, including pacemakers, which enhance cardiac synchronisation and implanted cardiac defibrillators.¹⁵

However, we are unable to do much more than reduce congestion with diuretics in patients with chronic heart failure with preserved ejection fraction, which occurs in almost half of the population with heart failure.⁷ ⁹ ¹¹ ¹² The outlook for patients with acute decompensated heart failure, irrespective of ejection fraction, is also grave.¹⁶ In patients older than 65 years in the USA, the 30-day hospital mortality rate for patients admitted to the hospital with heart failure is fairly constant at about 11%, and the 30-day hospital readmission rate is around 30%.¹⁷ Similar outcomes have been reported in England and Wales, in the USA, and in Europe.¹⁸ The 5-year survival rate for heart failure is worse than it is for most cancers and the annual cost of care for heart failure in the USA has been estimated to exceed US$30 billion, most of it spent on hospital care.⁷ Although the increased application of clinical practice guidelines in high-income countries,¹⁹ ²⁰ especially in patients with heart failure with reduced ejection fraction, has resulted in some improvement in outcome,²¹ many patients now experience a more prolonged course, resulting in increases in the prevalence of the disorder,³ and in the economic

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Calcium cycling

Calcium cycling in the cardiomyocyte is crucial to both cardiac contraction and relaxation. Normally, depolarisation of the cell membrane and of its invaginations, the transverse tubules, triggers the entry of small quantities of calcium into the cardiomyocyte, through L-type ion-specific channels located in the cardiomyocyte sarcoplasmic reticulum membrane. This influx of calcium opens the nearby calcium release channels, also known as the type 2 ryanodine receptors (RyR2), large tetrameric protein complexes (figure 2). The release of much larger quantities of calcium from the sarcoplasmic reticulum through the RyR2 results in a large increase in intracytoplasmic calcium, which acts on troponin C to activate cross bridges between actin and myosin filaments in the sarcomeres, causing cardiac contraction.

The sarcoplasmic-endoplasmic reticulum ATPase (SERCA2a) pumps calcium ions from the cytoplasm back into the sarcoplasm reticulum, shutting off contraction and initiating cardiomyocyte relaxation. Phospholamban is a 52 aminoacid peptide that is in close proximity to and regulates SERCA2a activity (figure 2). In the dephosphorylated state, phospholamban inhibits SERCA2a; when phospholamban is phosphorylated by calcium-dependent and calmodulin-dependent protein kinase (CaMKII), this inhibition is lost, SERCA2a is activated, the cytoplasmic calcium decreases, and relaxation occurs.

Several components in the calcium cycling process can be disturbed and cause heart failure. Hyper-phosphorylation of RyR2 by CAMKII or protein kinase A might cause a diastolic leak of calcium, lowering the calcium content of the sarcoplasmic reticulum, thereby reducing the quantity of calcium released during the subsequent activation. This weakens systolic contraction, and by raising cytoplasmic calcium during diastole interferes with myocardial relaxation. Sedej and colleagues described abnormal leaks of sarcoplasmic reticulum calcium through RyR2 in dogs with pacing-induced heart failure. Stabilisation of RyR2 by derivatives of 1,4 benzothiazepine have been reported, and other RyR2 stabilisers are under investigation.

Impairment of SERCA2a activity can result from reduced ATP generation, as occurs in ischaemia and has been reported in both animal models and patients with heart failure. This impairment diminishes the calcium pumped back into the sacroplasm reticulum during diastole, interfering with both contraction and relaxation. In human heart failure, diastolic calcium might be increased, at least partly, by reduced SERCA2a activity but also by increased activity of phospholamban.

Several classes of calcium-binding proteins regulate calcium within the cardiomyocyte. These include S100A, CaMKII, and PKA. S100A1 has a high affinity for calcium and can modify RyR2 function and sarcoplasmic reticulum calcium content. Stimulation of β-adrenergic receptors enhances calcium cycling, improving the rates of both contraction and relaxation. The neurohormonal hyperactivity that is characteristic of chronic heart failure might cause the expression of heart failure.27 This impairment diminishes the calcium content of the sarcoplasmic reticulum, thereby reducing the quantity of calcium released during the subsequent activation.21 This weakens systolic contraction, and by raising cytoplasmic calcium during diastole interferes with myocardial relaxation. Sedej and colleagues described abnormal leaks of sarcoplasmic reticulum calcium through RyR2 in dogs with pacing-induced heart failure. Stabilisation of RyR2 by derivatives of 1,4 benzothiazepine have been reported, and other RyR2 stabilisers are under investigation.

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CaMKII, which can activate L-type calcium channels, inhibit phospholamban, and increase myocardial contractility. However, hyperphosphorylation of CaMKII can activate RyR2, contributing to intracellular calcium overload, cardiomyocyte apoptosis, heart failure, and lethal tachyarrhythmias. Respress and associates have shown that cardiac muscle obtained from patients with dilated cardiomyopathy exhibits increased CaMKII activity, leading to malfunction of the RyR2. They reported that the left ventricular hypertrophy that occurs subsequent to transverse aortic constriction in mice can be largely blocked by preventing diastolic calcium leak through the RyR2 caused by overactivity of CaMKII and protein kinase A.

Substantial efforts are underway to modify the actions of calcium. One approach is directed to the enhancement of the sensitivity of cardiac myosin to calcium to improve cardiac function in patients with heart failure with a reduced ejection fraction. An interesting small molecule, omecamtiv mecarbil, activates cardiac myosin and thereby increases the number and duration of active cross bridges between actin and myosin. Because this drug increases stroke volume by prolonging the duration, but not the velocity, of myocyte contraction, it does not seem to increase the heart’s requirements for oxygen or to increase intracellular calcium as phosphodiesterase-3 inhibitors, such as milrinone, do. In a phase 2 clinical trial on patients with heart failure with reduced ejection fraction, Cleland and colleagues reported that this drug increased the duration of the systolic ejection period and the stroke volume, while reducing both the left ventricular end systolic and end diastolic volumes. Clinical trials of the treatment of chronic heart failure with omecamtiv mecarbil are ongoing.

**Gene therapy**

The idea of replacing a faulty gene with a normal one has been a dream of biologists and clinical investigators for decades. The goal is to correct molecular defects using the affected cell’s own genetic machinery. After a slow start followed by several technical and safety concerns, notable progress in this area has been made. In 2012, the European Medical Agency approved the first gene-based treatment.

![Gene transfer](image)

**Figure 3: Gene transfer**

At the top left in 1, the new gene attaches to the viral DNA (the vector), which enters the target cell, traverses the cytoplasm, penetrates the nucleus, and is incorporated into the target cell’s DNA. Substantial effort has been devoted to identification of the optimal vector(s) to carry genes into cardiomyocytes. Recombinant adenoassociated viruses are appropriate for treatment of a chronic condition such as heart failure. This DNA virus is cardiotropic, is expressed for long periods, and evokes only a mild immune response. However, circulating neutralising antibodies in about half of the population might exclude many patients from receiving gene therapy using this vector.

The gene-carrying vector might be delivered by infusion into a coronary artery, by catheter-directed subendocardial injection or by intracardiac injection, percutaneously or at operation.

To build on the evidence that the activity of SERCA2a is reduced in many forms of heart failure, del Monte and associates have introduced the SERCA2a gene into...
isolated cardiomyocytes obtained from patients with heart failure with a reduced ejection fraction, into aortic banded rat, pig, and sheep models of heart failure. An improvement in myocardial contractility was reported in all of these studies. A phase 1 human trial showed the safety of this approach. CUPID was a phase 2, dose-ranging trial in patients with advanced heart failure with a reduced ejection fraction by intracoronary infusion of recombinant adeno-associated virus serotype 1, carrying the gene for SERCA2a. An improvement in symptoms, functional status, and biomarkers was noted; after 3 years, expression of the transgene and clinical improvement persisted. This treatment seemed to be safe and well tolerated. A phase 2b trial in 200 patients in ten countries is nearing completion (NCT01643330).

Other molecular targets for gene therapy that are associated with abnormal calcium cycling include the silencing of phospholamban with adenosinal gene transfer of antisense phospholamban into isolated failing human cardiomyocytes, and in a sheep model. The upregulation of S100A1 has been shown to improve cardiac performance by enhancement of the activities of both RYR2 and SERCA2a in failing isolated human cardiomyocytes, and in a porcine post myocardial infarction model of heart failure.

Additional targets of gene therapy for heart failure include β-adrenergic receptors, which are downregulated in many patients with heart failure. Uptregulation of β-adrenergic receptors improved left ventricular function in both rat and rabbit models. The delivery of the gene encoding adenylyl cyclase 6 (AC6) increases the formation of cyclic adenosmonophosphate (cAMP) and improves cardiac function in pacing-induced heart failure. A human phase 1/2 trial (NCT00787059) has begun. G-protein-coupled receptor kinase 2 (GRK2) is overexpressed in heart failure, causing desensitisation of β-adrenergic receptors. A cDNA of a terminus of GRK2 has been shown to enhance the responsiveness of β-adrenergic receptors and prolong the survival of mice with heart failure. β-adrenergic receptor kinase gene therapy has been reported to improve cardiac performance in a porcine model. It too is being prepared for a clinical trial.

Further clinical trials of gene therapy for heart failure are expected to commence shortly. Although questions surrounding the selection of the appropriate vector(s) must still be addressed, gene therapy now seems likely to become a clinically significant tool in the future management of selected patients with heart failure.

**MicroRNAs (miRNAs)**

In 1993, two papers published back to back in *Cell* described short, non-coding RNAs (miRNAs), which are present in almost all higher eukaryocytes. miRNAs are gene products processed first in the nucleus and then in the cytoplasm; they silence mRNA by pairing with its messenger sites, thereby preventing protein translation and gene expression. The association between these two forms of RNA is complex; each miRNA might attach to several mRNAs, while each of the miRNAs can bind several microRNAs. Almost 2000 miRNAs have been isolated in human beings and more are being discovered almost weekly. Their roles in various diseases, including cancers and cardiovascular disorders, especially heart failure, are currently under intense investigation.

Preclinical research into miRNAs has shown the important role of these molecules in the control of calcium cycling and in the development of ventricular hypertrophy and heart failure. In some studies, genetic knockouts of specific miRNAs identified their function. For example, the knockout of miRNA22 reduces the activity of the SERCA2a pump, causing heart failure. miRNA208 stimulates ventricular hypertrophy in mice secondary to transverse aortic constriction, whereas its knockout prevents hypertrophy. A second approach is by using chemically engineered oligonucleotide antagonists of miRNAs. These single-stranded RNA analogues named antagomirs are complementary to and silence miRNAs and represent an interesting approach to therapeutics.

Several miRNAs (miRNAs 23a, 208, and 499) are promoters and others (miRNAs 1, 9, 98, 133, and 378) are inhibitors of hypertrophy. miRNAs are potentially important targets of therapy. For example, overexpression of miRNA133 blocked the adverse effects of β-adrenergic stimulation in transverse aortic constriction mice, reducing CAMP formation and inhibiting apoptosis, suggesting that overexpression of this miRNA might enhance the effects of β blockers in heart failure. The antagomir to miR208a (miRNA208a precursor) prevented cardiac remodelling and improved survival in a hypertensive rat model. Both myocardial infarction and transverse aortic constriction in mice cause impaired cardiac function, pathologic remodelling, and upregulation of miRNA34; the antagomir to miR34 improved cardiac function. miRNA-25 is also upregulated in mice with heart failure secondary to transverse aortic constriction in which it interferes with cardiomycyte calcium cycling by blocking the SERCA2a pump. Figure 4 shows the improvement of the left ventricular ejection fraction and of survival when the antagomir to miR25 was administered in these mice. miRNA25 is also increased in the hearts of patients with heart failure and their response to this antagomir would be interesting and potentially very important to study. If beneficial, it could herald a novel approach to the treatment of clinical heart failure.

miRNAs within the myocardium might also be altered with therapy of heart failure. Matkovich and collaborators reported that the miRNA499 levels of patients with heart failure were greatly increased and almost completely normalised after they had been placed on left ventricular support. The safety of administration of antagonirs to patients has been shown in current trials of treatment of hepatitis C. Several miRNAs (21, 24, 299, 30c, 101a or b, and 214) are regulators of fibrosis. 

Review

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miRNA21 is expressed in cardiac fibroblasts and is important to the development of the cardiac fibrosis after transverse aortic constriction; when blocked by its antagonir, fibrosis is suppressed. By contrast, miRNA29 seems to exert an antifibrotic effect.

Mitchell and colleagues reported that miRNAs might enter the bloodstream where they could become useful biomarkers. The concentration of circulating miR4235p is greatly increased in patients with heart failure and increased concentrations of three miRNAs (34, 192, and 194) are predictive of the development of heart failure in patients after acute myocardial infarction. Vogel and colleagues described a multimarker signature of eight miRNAs, which predicted the development of heart failure in patients with non-ischaemic heart failure with a reduced ejection fraction. Whether the information derived from circulating miRNAs is independent of the phenotypic biomarkers, such as natriuretic peptides that are now used in the assessment of patients with heart failure, and whether it provides information useful in understanding the pathobiology of heart failure or its management, remains to be determined.

Cell therapy

Early studies

The potential value of cell therapy was suggested almost a century ago, when Jacobson and colleagues showed the importance of cells in the spleen and bone marrow in protecting mice from otherwise lethal irradiation. In the 1970s, autologous bone marrow transplantation was introduced and this treatment has become routine in the treatment of haematological malignancies. The implantation of stem or progenitor cells into the failing or damaged heart with the hope that they will cause regeneration of heart muscle and thereby improve cardiac function is an interesting and challenging front in the war against heart failure.

In 1991, Eghbali and colleagues showed that rabbit cardiac fibroblasts cultured with transforming growth factor β developed a cardiomyocyte-like phenotype. In 1999, Tomita and colleagues reported that when autologous bone marrow cells were transplanted into ventricular scar tissue of rats, cardiomyocytes were formed and myocardial function improved. In 2001, Orlic and colleagues infused autologous bone marrow into mice with experimentally induced myocardial infarction and induced what was interpreted as myocardial regeneration. Since then, various cell types have been investigated. Autologous skeletal myoblasts were an early choice because they can be obtained by simple muscle biopsy; when injected into damaged, scarred myocardium in animal models, they seemed to improve cardiac performance. However, in a controlled clinical trial, they did not improve ventricular function and were associated with malignant tachyarrhythmias. Clinical trials with skeletal myoblasts have not been resumed.

Stem cells

Allogeneic embryonic stem cells, obtained from the inner layer of the developing blastocyst, can differentiate into any cell type, including cardiomyocytes, and were shown to improve the function of the infarcted rat heart. Cryopreserved human embryonic stem cell-derived cardiomyocytes have been shown to remuscularise infarcted non-human primate hearts. However, they need immune suppression to avoid rejection, they increase the risk of teratoma formation, and their use poses serious ethical considerations. Despite these limitations, two clinical trials (NCT01345006 and NCT0134493) are studying the transplantation of human embryogenic stem cells in the treatment of macular degeneration and spinal cord injury.

Induced pluripotent stem cells can be generated from adult somatic cells using specific transcription factors, and similarly to embryogenic stem cells they are capable of renewal and differentiation into cardiomyocytes. Human induced pluripotent stem cells have been shown to reduce infarct size, enhance revascularisation, and increase contractile function in a porcine ischaemia-reperfusion model. Unlike embryonic stem cells, induced pluripotent
stem cells, being autologous, do not need immune suppression, and the ethical issues are avoided. However, the concern about teratoma formation persists and efforts to eliminate this risk continue.\textsuperscript{90,91} Although no clinical trials with induced pluripotent stem cell cardiomyocytes have been reported thus far, they remain candidates for future trials in the treatment of heart failure. Also, efforts are directed to the reprogramming of cardiac fibroblasts directly into cardiomyocytes with one transcription factor.\textsuperscript{103}

**Bone marrow cells**

Since the bone marrow contains a variety of stem cells, and is relatively easy to obtain, unFractionated autologous bone marrow-derived mononuclear cells (BMMNCs) have been widely used in clinical trials in heart failure and post-acute myocardial infarction. Rather than transdifferentiating into cardiomyocytes, as first suggested, paracrine activity seems to cause their efficacy;\textsuperscript{92,104} this activity involves secretion of growth factors, cytokines, chemokines, and the induction of new capillaries.\textsuperscript{105}

Many clinical trials have been done using BMMNCs, including various patient populations, methods of cell preparation, cell dose, and, in patients with post-acute myocardial infarction, timing of cell administration. Most trials have been small and the results quite variable. In most trials, changes in the left ventricular ejection fraction have been the surrogate endpoint used because they were underpowered to assess clinical outcomes. However, in one of the larger of these early trials, the REPAIR-AMI trial, in which autologous BMMNCs were infused into the reperfused coronary arteries of 204 patients with acute myocardial infarction, the 5-year outcome showed strong trends of improvement in survival.\textsuperscript{106} In a meta-analysis of 50 trials of 2625 patients with ischaemic heart disease, patients who received BMMNCs had a statistically significant higher left ventricular ejection fraction, with an average increase of 3.69%, than those who did not. Although no one trial showed a reduction of mortality, it was significantly reduced in the meta-analysis. In a Cochrane review conducted on 33 randomised controlled trials of patients with post-acute myocardial infarction (some of which overlapped with Jeevanantham and colleagues\textsuperscript{107} meta-analysis), a similar increase in left ventricular ejection fraction in treated patients and a trend towards a reduction of mortality was noted.\textsuperscript{108} However, in assessing the results of clinical trials of autologous BMMNCs, the fact that four trials did not show evidence of improved left ventricular function is concerning.\textsuperscript{109}

Thus, although some encouraging signs of benefit have been reported, the jury is still out about the clinical efficacy of autologous BMMNCs. It is possible that the regenerative capacity of the BMMNCs in patients of an older age and frequent comorbidities is reduced. The BMMNCs, first phase 3 trial of cell therapy in acute myocardial infarction (NCT01569178) is enrolling an expected 3000 patients in ten European countries.

**Mesenchymal cells and adipose-derived stem cells**

UnFractionated BMMNCs contain not only haemopoietic stem cells, but also mesenchymal stem cells,\textsuperscript{90,93,94} which expand rapidly in vitro, and seem to differentiate into cardiomyocytes in the mouse\textsuperscript{95} and in the pig.\textsuperscript{96} Their substantial paracrine effects include the release of antifibrotic matrix metalloproteinases, which might reduce myocardial fibrosis.\textsuperscript{97} Mesenchymal stem cells have been reported to be efficacious in animal models of heart failure and acute myocardial infarction.\textsuperscript{98} Heldman and colleagues\textsuperscript{99} compared the transendocardial injection of autologous mesenchymal stem cells, BMMNCs, and placebo in patients with ischaemic cardiomyopathy. The procedure was safe, with trends of improvement in secondary endpoints.

Precursors of mesenchymal stem cells carry stromal antigens and when enriched with these antigens, mesenchymal stem cells seem to have greater regenerative and engraftment capacities. In the C-CURE trial, patients with heart failure due to ischaemic cardiomyopathy were randomised to either usual care or autologous mesenchymal stem cells treated with a mixture of growth factors delivered by endocardial injection, directed by endocardial mapping, into dysfunctional but viable myocardium (figure 5). Left ventricular ejection fraction and the 6 min walk test improved significantly in the cell-treated patients.\textsuperscript{100} Further clinical trials of enriched mesenchymal stem cells are ongoing (NCT00555828, NCT01768702, and NCT01781390).

Mesenchymal stem cells seem to be hypo-immunogenic, allowing use of both autologous and allogeneic cells;\textsuperscript{101} allogeneic cells have the practical advantage of not requiring immunosuppression.\textsuperscript{102} Allogeneic mesenchymal stem cells have been used as an adjunctive therapy in patients with advanced heart failure who were recipients of left ventricular assist devices.\textsuperscript{103} The direct injection of these cells into the left ventricle at the time of device implantation was safe and there was a potential signal of efficacy. The goal of mesenchymal stem cells administered in this manner is to enhance the likelihood of a bridge to recovery.

Like mesenchymal stem cells, adipose tissue-derived stem cells also seem to have the ability to differentiate into cardiomyocytes,\textsuperscript{104} and might be obtained by liposuction, a procedure that is less invasive than bone marrow aspiration. Their superior efficacy to BMMNCs in rodent and porcine models of myocardial infarction and heart failure has been reported\textsuperscript{105} and a preliminary clinical report is encouraging;\textsuperscript{106} two clinical trials of a stromal vascular fraction of adipose tissue-derived stem cells are underway (NCT00442806 and NCT01216995).

**Cardiac stem cells**

In 1996, Li and colleagues\textsuperscript{107} transplanted cultured fetal rat cardiomyocytes into cryoinjured rat hearts and reported that these cells had formed contractile cardiac tissue. In
immunosuppression. ALLSTAR (NCT01458405) is a cardio spheres might be hypoimmunogenic, permitting the
There is evidence that similarly to mesenchymal stem cells, cardiac spheres obtained by percutaneous endomyocardial
biopsy from patients, were then shown to improve ventricular function in mice and pigs with myocardial infarction. CADUCEUS (NCT00893360) was a phase 1/2 randomised trial of an intracoronary infusion of autologous
cardiospheres in post myocardial infarction patients with a reduced left ventricular ejection fraction. When compared with controls, a reduction of the myocardial scar, and increases in viable heart mass and regional contractility were reported. These changes persisted beyond 1 year. There is evidence that similarly to mesenchymal stem cells, cardiospheres might be hypoinnogenic, permitting the use of allogeneic cells without the need for immunosuppression. ALLSTAR (NCT01458405) is a placebo-controlled trial of the safety and efficacy of allogeneic cardiosphere-derived cells in patients post myocardial infarction with left ventricular dysfunction.

Several important questions regarding cell therapy of heart failure remain to be answered. These include determination of the optimal cell type(s), method(s) of processing of the cells, and the optimum dose, timing, and administration of the cells. At present, mesenchymal stem cells and cardiac stem cells seem to be most promising. The possibility of using allogeneic cells and engineering them in some manner to enhance their regenerative potential seems attractive. Gene transfer into transplanted cells might be useful.

**Left ventricular assistance devices (LVADs)**

Since the development of the cardiopulmonary bypass in the 1950s, the treatment of advanced heart failure by replacing a failing heart with an implanted artificial heart has been an important goal for the treatment of heart failure. After many setbacks in animal experiments, and some widely publicised failures in a few patients, this goal was adjusted to develop devices that would provide left ventricular assistance (LVA) instead of total heart replacement. At first, the assistance was temporary; the extracorporeal LVADs were applied to patients with cardiogenic shock secondary to acute myocardial infarction, cardiotomy, or acute myocarditis.

As the devices improved and could be placed within the chest, albeit with an external power source, the indications for prolonged LVA were broadened to include patients with advanced chronic heart failure who were critically ill, inotrope dependent, and listed for cardiac transplantation. In these patients, LVA served as a bridge to cardiac transplantation until a donor heart became available. In view of the strict eligibility criteria for transplantation, the restricted pool of donor hearts, and the large and growing number of patients with advanced heart failure, consideration was given to use of LVADs for indeterminate durations. The REMATCH trial, using an implanted, pulsatile LVAD for long-term support, showed that survival was improved in patients with near-terminal heart failure who were ineligible for transplantation, thereby opening the door to using LVA as a destination therapy.

When the output of LVADs was changed from pulsatile to continuous flow, when their size was reduced, and their durability lengthened, their use increased greatly. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) in the USA reported that by June, 2013, more than 12 000 patients in the USA had been placed on long-term LVADs, and the number (>2000 per year) had grown to approach those with a cardiac transplantation. At present, the three most common indications for prolonged LVA are a bridge to cardiac transplantation in patients with end stage heart failure.

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**Figure 5: Design of the cardiopoietic stem cell therapy in heart failure (C-CURE) trial**

After bone marrow harvest of the cells (step 1) and isolation or expansion (steps 2A and 2B), patient-derived mesenchymal stem cells were exposed to a cardiogenic growth factor cocktail (step 3A) followed by culture expansion (step 3B). Derived cardiopoietic stem cells were injected into the endocardium (step 4), with clinical follow-up (step 5).
failure; destination therapy in patients with advanced heart failure who are critically ill but are ineligible for transplantation mostly because of age or comorbidity; or a bridge to decision in critically ill patients whom a decision regarding candidacy for transplantation has been deferred. The percentage of patients receiving destination therapy has been growing steadily, to 40% at present (figure 6). The 2-year survival rate in patients with advanced heart failure treated with LVADs is now about 75%; results are superior in high volume centres. LVA devices are constantly undergoing improvement; they are getting smaller and some can be implanted directly into the left ventricle; however, prolonged use is not without risk. Patients with right ventricular failure need biventricular devices, which are associated with a higher mortality.

Permanent anticoagulation with its propensity for bleeding is needed and other complications, including infection, stroke, and device thrombosis, have been reported. Despite these problems, long-term LVA is a substantial victory in the war against heart failure, and further victories on this front seem probable.

Failing hearts that had been on prolonged LVA and were then examined at the time of transplantation showed reverse remodelling with reductions of both preload and afterload. When compared with the cardiac tissue obtained at device implantation, following several months of LVA the supported ventricles exhibited regression of cardiomyocyte hypertrophy, an increase in the density of β-adrenergic receptors, improvement of calcium cycling, with more rapid calcium entry into the cardiomyocytes, enhanced RYR2 function, and SERCA2a activity. The gene expression of components of the nuclear envelope, lamins A and C, were increased as were some of the genes for sarcomeric proteins. Prolonged LVA also reversed the inflammatory responses of heart failure, with reductions of interleukins 6 and 8 and tumour necrosis factor α. Other features of heart failure, the depressed respiratory control index of myocyte mitochondria, and the supranormal production of reactive oxygen species, were also improved. Reductions of circulating neurohormones, including renin, angiotensin II, catecholamines, and vasopressin, occurred. These salutary alterations resulting from prolonged LVA have raised the prospect of myocardial recovery. The treatment of heart failure by resting the failing heart was suggested by Burch and colleagues in the 1960s. They proposed prolonged bed rest and pharmacological reduction of heart rate and arterial pressure in patients with dilated cardiomyopathy with severe heart failure. Some patients treated in this manner apparently improved clinically, but unfortunately, there was no control group.

It is important to distinguish between ventricular reverse remodelling, characterised by normalisation of cardiac chamber size and regression of myocyte hypertrophy, and myocardial recovery, in which the previously failing heart regains sufficient function to be able to support the circulation. Although some degree of ventricular remodelling occurs regularly with prolonged LVA, myocardial recovery is far less common. However, in the late 1990s, reports of successful weaning from prolonged LVA, leading to successful explantation of the device began to appear, thus showing that prolonged LVA can be used as a bridge to recovery, the fourth and perhaps the most intriguing objective of LVAD. In 2001, Yacoub described the addition of intensive pharmacological therapy to LVA to enhance myocardial recovery. He also studied the effects of temporarily shutting off the device on cardiac function, determined echocardiographically, to identify patients with myocardial recovery.

Birks and Yacoub and their collaborators at Harefield Hospital near London have recommended a combination of high doses of an angiotensin-converting enzyme inhibitor, an angiotensin-receptor blocker, an aldosterone receptor blocker, a β blocker, and digoxin, is initiated shortly after LVA is begun. Clenbuterol, a synthetic β-adrenergic receptor agonist that causes physiological hypertrophy of cardiac muscle, is begun after reverse remodelling has occurred to prevent the disuse cardiac atrophy that accompanies prolonged LVA. Birks and colleagues then reported on 19 patients with dilated cardiomyopathy on long-term LVA; 12 of these were successfully weaned and underwent explantation and ten of these 12 patients survived 3 years without recurrence of heart failure. Similar long-term survival of patients on prolonged LVA who underwent cardiac transplantation (bridge to transplantation) and those who were deemed appropriate for device explantation (bridge to recovery) has been reported.

In an attempt to identify patients who are candidates for device explantation, regular and systematic testing of
cardiac function when the flow through the device is reduced or stopped temporarily should be carried out, and a determination made whether myocardial recovery is sufficient to permit explantation. Dandel and colleagues\textsuperscript{114} have reported that in such an assessment, during temporary cessation of pump flow, the combination of a left ventricular ejection fraction of more than or equal to 45% and a stable pre-explant diastolic diameter of less than or equal to 55 mm are predictive of cardiac stability post explantation.\textsuperscript{117} These authors also reported on 53 patients with advanced heart failure secondary to non-ischaemic cardiomyopathy placed on prolonged LVA.\textsuperscript{114} The device was explanted in 36 and, of these, 22 (61%) exhibited cardiac stability for a minimum of 5 years, whereas the other patients had recurrence of heart failure. From a clinical perspective, the ideal patient for recovery is younger than 50 years, with less than one heart failure in 1 year caused by idiopathic dilated cardiomyopathy or myocarditis.

The observation of myocardial recovery in selected patients might herald a change in the current paradigm, in which severe heart failure is thought to be a largely irreversible, progressive condition, the treatment of which is designed to slow the progression of the disease. LVA combined with aggressive pharmacotherapy might improve the underlying condition. As already indicated, patients with advanced heart failure who have achieved myocardial recovery have usually had dilated cardiomyopathy or myocarditis, but not ischaemic cardiomyopathy, the most common cause of advanced heart failure in industrialised countries. However, evidence suggests that myocardial recovery can occur in such patients.\textsuperscript{114}

Although still speculative, the following scenario seems possible and warrants testing. In patients early in the course of heart failure caused by ischaemic cardiomyopathy, before advanced heart failure with irreversible changes has occurred, the combination of complete revascularisation and ventricular unloading with LVA might be instituted. The goal would be to minimise residual ischaemia, which, together with pharmacotherapy and LVA, would enhance the recovery of myocardium, so as to permit successful explantation, thereby interrupting the natural history of this condition. Lenneman and Birs\textsuperscript{115} have suggested that cell-based therapies might be combined with LVA to enhance myocardial recovery, and Ascheim and colleagues\textsuperscript{115} have shown that this is feasible using allogeneic mesenchymal stem cells.

**Conclusion**

As stated, the pandemic of heart failure represents a major global health problem, and one that is likely to grow, especially in the low-income and medium-income countries. A concerted series of actions are needed to deal with this problem, hence the war against heart failure. A combination of two broad approaches will be needed. The first is the prevention of heart failure,\textsuperscript{159} which in turn will need prevention of the development of heart disease.\textsuperscript{159} This is a great goal, but some progress has been made with the primary and secondary prevention of ischaemic heart disease, and the vigorous treatment of hypertension, a frequent antecedent of heart failure. However, prevention of heart failure will take the cooperation of individuals, institutions, organisations, and governments and will need huge educational programmes and changes in lifestyle. This can and should be brought about by large public educational programmes and perhaps by public–private partnerships between governmental health agencies and funders of research, working with medical and cardiological societies and community groups.

A second complementary approach is to improve the treatment of heart failure. This Review describes five areas that show promise. They are certainly not the only such areas, but they seem to be ripe for attack within the next 5–10 years. For optimal results, a combination of these approaches might be needed. Similarly to how patients with heart failure with reduced ejection fraction are now treated simultaneously with diet and several drugs and devices, the pathobiology of individual patients with heart failure will be better defined by the specific miRNAs that are expressed, and this will lead to more personalised therapy, with new drugs, including antagonists, gene or cell therapy. As suggested, the dysfunctional but not yet seriously failing heart can be rested with left ventricular assistance, in combination with off-the-shelf hypo-immunogenic stem cells.\textsuperscript{115} These new therapies will be expensive when they first become available, but this is a problem that the passage of time might solve. Not too long ago blockers of the renin-angiotensin-alderosterone system, β blockers, and statins were prohibitively expensive and not suitable for widespread use on a worldwide scale. As these drugs have become generic, fortunately this is no longer the case.

Several ethical, regulatory, legal, and financial issues will have to be addressed as biological therapies (gene therapy and cell therapy) progress to clinical application. For example, if the bar for approval of these therapies is set in the manner traditionally used for drugs, their use in practice might be delayed for years. Perhaps event-based analyses or the outcomes in several domains, as was done in the CUPID trial,\textsuperscript{9} could be considered. Financial barriers will also have to be overcome. The major costs of these therapies will relate to the know-how necessary for product preparation. Issues of intellectual property will need careful scrutiny. However, once safety and net clinical benefit have been established, none of these barriers will be insuperable.

We are at a crucial juncture in the war against heart failure, a time analogous to 1942, midway through World War 2, when after several major defeats the Allied forces won an important battle. The indomitable Winston Churchill could have been speaking about the war against heart failure, when he declared: “Now, this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.”
Declaration of interests

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References


9 McMurray JJV, Adamopoulos S, Anker SD, et al. The ESC Committee for Practice Guidelines ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33: 1787–847.


