



REVIEW

The cardiac enigma: current conundrums in heart failure research [version 1; referees: 3 approved]

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Abstract

The prevalence of heart failure is expected to increase almost 50% in the next 15 years because of aging of the general population, an increased frequency of comorbidities, and an improved survival following cardiac events. Conventional treatments for heart failure have remained largely static over the past 20 years, illustrating the pressing need for the discovery of novel therapeutic agents for this patient population. Given the heterogeneous nature of heart failure, it is important to specifically define the cellular mechanisms in the heart that drive the patient’s symptoms, particularly when considering new treatment strategies. This report highlights the latest research efforts, as well as the possible pitfalls, in cardiac disease translational research and discusses future questions and considerations needed to advance the development of new heart failure therapies. In particular, we discuss cardiac remodeling and the translation of animal work to humans and how advancements in our understanding of these concepts relative to disease are central to new discoveries that can improve cardiovascular health.

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Competing interests: MSK is a co-inventor of patented intellectual property concerning the use of RSK3 inhibitors for the treatment of heart failure, by which he and the University of Miami may gain royalties from future commercialization. He is the manager of Anchored RSK3 Inhibitors, LLC (Miami Beach, FL, USA) and is on the board of directors of Cardiac RSK3 Inhibitors, LLC (Miami Beach, FL, USA), companies interested in developing RSK3-targeted therapies and in which he holds equity. CAE declares that he has no competing interests.

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Introduction

Heart failure, the common end stage of heart disease, is defined clinically by fatigue, shortness of breath, and fluid retention, including pulmonary edema¹. Heart failure is a syndrome of major public health significance, impacting 5.7 million worldwide with an incidence of 870,000 adults in the United States alone. The prevalence of heart failure is expected to increase by 46% by 2030, and this is due in large part to aging of the general population but also to the improved survival following events such as myocardial infarction and the increased prevalence of comorbidities such as obesity and diabetes². The cost to society is consequential. The 5-year mortality for heart failure remains approximately 50%, despite current therapies. Moreover, the financial costs associated with heart failure are expected to balloon to over \$70 billion per year by 2030³. As a result, the discovery of new drug targets for heart failure prevention or treatment (or both) remains an area of pressing concern.

The current approach to chronic heart failure therapy

Current therapies for heart failure are both medicinal and device-driven³. The mainstays of heart failure pharmacotherapy include β -blockers (β -adrenergic receptor antagonists such as carvedilol, metoprolol, and bisoprolol), angiotensin-converting enzyme inhibitors ([ACEI] e.g., enalapril and lisinopril), angiotensin II receptor blockers (e.g., losartan and valsartan), aldosterone antagonists, hydralazine and isosorbide dinitrate, and diuretics⁴. Ventricular assist devices, such as the implantable cardioverter-defibrillator, left ventricular (LV) assist device, and cardiac resynchronization therapy, are widely used, and cardiac transplant remains a therapy of last resort for some patients. There has been tremendous excitement this year as the first new drugs since 1999 have been approved by the US Food and Drug Administration for chronic heart failure. Ivabradine (Corlanor) is a sinoatrial node I_f current inhibitor that has been shown to have efficacy in a variety of clinical trials, including SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial)⁵⁻⁷. LCZ696 (Entresto™) is a combination drug including a neprilysin endopeptidase inhibitor (sacubitril) and angiotensin receptor blocker (valsartan). In the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, LCZ696 was shown to reduce mortality in comparison with enalapril⁸. Finally, ranolazine improved hemodynamic status in the proof-of-concept RALI-DHF (RAnoLazIne for the Treatment of Diastolic Heart Failure) trial⁹. However, even with these new drugs, heart failure morbidity and mortality are expected to increase substantially in the near future.

Heart Failure: HFrEF vs. HFpEF

In considering the future of heart failure therapies, it is important to remember that heart failure is not a homogenous entity but instead a clinical syndrome related to end-stage heart disease. Heart failure can be divided into two groups: (a) reduced ejection fraction (HFrEF) and (b) preserved ejection fraction (HFpEF) (ejection fraction >45%); the two forms confer a similar prognosis and have similar prevalence¹⁰⁻¹². As the names suggest, HFrEF includes prominent systolic cardiac dysfunction, whereas HFpEF is more closely associated with diastolic dysfunction. Although the current therapies for heart failure have been established in clinical trials involving HFrEF patients, none has been therapeutically

useful for HFpEF patients^{10,11,13,14}. Instead, exercise may be the only clinically effective, currently available HFpEF treatment¹⁵, and several small-scale clinical trials show that exercise improves cardiorespiratory variables such as oxygen consumption (VO_2), diastolic dysfunction, and quality of life in HFpEF patients¹⁶. The Exercise Training in Diastolic Heart Failure (EX-DHF) (ISRCTN 86879094) study will examine these findings on a larger scale and hopefully provide insight regarding the use of exercise to improve mortality. The lack of drug therapies for HFpEF may be due to the limited efficacy of current drugs to treat diastolic dysfunction. Alternatively, it was recently suggested that many patients with diagnosed HFpEF, typically older women with diabetes and obesity, do not have structural heart disease but instead exhibit fairly general signs that define heart failure due to non-cardiac problems¹⁷. For example, although pulmonary edema is usually a reliable indicator of LV dysfunction (and high diastolic pressures), it can also be caused by primary pulmonary disease (e.g., adult respiratory distress syndrome) or low plasma colloid oncotic pressure due to other etiologies¹⁸. HFpEF should also be distinguished from high-output heart failure, a form of heart failure that typically is secondary to a non-cardiac disease¹⁹. In high-output heart failure, the heart responds normally and reversibly to extra-cardiac stress, often undergoing physiologic hypertrophy that is induced by low afterload and volume overload on the heart. Thus, when novel approaches to the treatment of heart failure are considered, it is important to precisely define the cohort of patients being considered and whether the heart is in fact the relevant target for therapeutic intervention.

Pathological cardiac remodeling

A long-term goal of heart failure therapies is to reverse or prevent cardiac remodeling, the general term referring to the structural changes in the heart induced by chronic stress. While the heart can respond to acute demands for increased output by changes in chronotropy (heart rate), inotropy (contractility), and lusitropy (relaxation), the adult heart is generally limited to hypertrophy as a compensatory mechanism²⁰. Cardiac hypertrophy at the whole-organ level reflects non-mitotic growth of the cardiac myocytes. The generally cylindrical adult myocyte can grow in either width (diameter) or length, resulting in thickened ventricular walls or chamber dilation, respectively. In theory, concentric myocyte growth increases the width of cardiomyocytes, inducing parallel assembly of sarcomeres and thereby reducing ventricular wall stress (Laplace's law). In contrast, eccentric myocyte growth increases cardiomyocyte length, inducing serial addition of sarcomeres to accommodate greater ventricular volumes without stretching individual sarcomeres beyond the optimum length for contraction (Frank-Starling law)²¹. In pressure overload diseases, such as aortic stenosis or hypertension, there is increased systolic wall stress, and concentric hypertrophy initially predominates. In volume overload diseases, such as following a myocardial infarction or dilated cardiomyopathy, eccentric hypertrophy predominates, presumably in response to increased diastolic wall stress. Although sarcomeric assembly is considered initially compensatory, myocyte hypertrophy is eventually concomitant with altered myocyte gene expression, metabolism, excitation-contraction coupling, increased cell death, and myocardial fibrosis. Together, these factors contribute to systolic and diastolic cardiac dysfunction and promote pathological cardiac remodeling and subsequent heart failure.

Outstanding questions in heart failure research

The above description of heart failure is the basis for the underlying paradigm driving most research in the field, primarily the identification of potential drug targets that protect cardiac contractility and inhibit myocyte death and interstitial fibrosis^{22,23}. We propose the following issues as central to advancing the treatment of heart failure, including questions to stimulate discussion about the underlying assumptions concerning disease development:

1. A fundamental question concerns whether any of the features in cardiac remodeling are necessarily compensatory (i.e., can be safely targeted in the face of cardiac stress). For example, as recently discussed in a point-counterpoint editorial series in *Circulation*^{24,25}, concentric LV hypertrophy is often considered compensatory in diseases of increased afterload. The current first-line therapies for heart failure target the adrenergic and renin-angiotensin systems, having effects both on cardiac myocytes and on the vasculature²⁵. It has been argued that lowering afterload and LV wall stress is essential to the efficacy of these drugs in patients (whether by lowering blood pressure for hypertension or by contemporaneous aortic valve replacement for aortic stenosis) and that attenuating hypertrophy without lowering afterload would not be tolerated in humans²⁶. However, diverse studies in rodents using pharmacological agents such as cyclosporine, and more elegantly with genetically modified mice, have shown that inhibition of hypertrophy not only is tolerated in the face of persistent pressure overload but also can prevent or treat heart failure²².

2. It remains unclear which features in cardiac remodeling are co-regulated by signal pathways that may be targeted and which features may be specifically targeted independently of other aspects of remodeling. Although most studies show that hypertrophy and fibrosis are tightly associated in disease, recent findings by the Backs laboratory showed that mice lacking the γ and δ isoforms of Ca^{2+} /calmodulin-dependent protein kinase II had improved cardiac function and decreased fibrosis but persistent hypertrophy following transverse aortic constriction²⁷. Whereas some aspects of the changes in myocyte gene expression, metabolism, and excitation-contraction coupling may be detrimental (e.g., the decreased sarcoplasmic reticulum Ca^{2+} ATPase [SERCA2a] activity in heart failure), others may be beneficial (e.g., increased natriuretic peptide expression or concentric hypertrophy that decreases wall stress). These exciting findings suggest that the beneficial aspects of remodeling may be retained while therapeutically combatting the deleterious aspects that lead to heart failure.

3. It remains unclear what causes diastolic dysfunction, especially in HFpEF. Diastolic dysfunction is the result of reduced active relaxation or ventricular compliance. Active relaxation occurs in large part due to ATP-dependent Ca^{2+} reuptake during diastole primarily through SERCA2a, and reduced SERCA2a activity is associated with heart failure. Accordingly, in animal models, SERCA2a replacement has been effective in improving overall cardiac function²⁸. Decreased compliance and associated atrial hypertrophy have long been associated with interstitial fibrosis^{29,30}. However, the relative extent of fibrosis and altered Ca^{2+} reuptake can vary in different models for diastolic dysfunction^{30,31}, raising the

question of what should be targeted in diastolic dysfunction under different clinical scenarios. In numerous animal models, reversal or reduction of LV hypertrophy has been shown to improve diastolic function independently of hemodynamic alteration, implying that hypertrophy itself plays a role in diastolic dysfunction. However, clinical studies have shown that this relationship is less apparent in humans³². Finally, coronary vascular dysfunction may have a profound impact on myocardial oxidative capacity and diastolic dysfunction in heart failure³³. Recent work has shown that swine with diastolic dysfunction have myocardial oxygen supply/demand imbalance³⁴. This suggests that impaired coronary vasculature function may contribute to the inability of HFpEF patients to respond to situations of increasing stress by limiting ATP production and subsequent active relaxation.

4. Humans are not large mice. Little is known or being investigated about cardiac signal transduction in large mammals, despite the significant differences between large and small mammalian hearts. Instead, most of what is known about the regulation of myocyte hypertrophy and cardiac remodeling has been defined in mice and rats²⁵. Differences between large and small mammals include life span, heart rate, excitation-contraction coupling and Ca^{2+} handling, α : β -myosin heavy chain ratio, tolerance for myocardial injury, and rate of progression of cardiac remodeling²⁵. The successful development of therapeutics for human patients is dependent upon the identification of mechanisms that are in fact relevant to the large mammalian heart. For example, many question whether large animals subject to pressure overload can tolerate diminished hypertrophy similar to mice²⁴. A review by Dixon and Spinale discusses the importance of large animal models in translating basic science findings to the clinic and addresses the lack of studies using large animals to address pressure overload LV hypertrophy and its role in the development of heart failure³⁵. An advantage of large animal models is that key determinants of myocardial work and energy consumption, including LV wall tension, heart rate, and vascular wall-to-lumen ratios³⁶, are similar to those in humans. Thus, large animal models could provide an essential link to implement discoveries made in murines into models exhibiting functional and anatomical similarities more analogous to humans as a means to assess therapeutic potential for treating heart failure clinically. Significant financial challenges exist in generating, sustaining, and implementing large animal models of heart failure into research programs. Specific programs aimed at soliciting and supporting large animal cardiovascular research from both federal and private sources would help stimulate more large animal studies in the future and aid in bridging the gap between small animals, large animals, and humans.

Hope for the future

It is an exciting time to be involved in heart failure research. There are ample animal models, both small and large, addressing diverse types of heart diseases, as well as protocols to study cardiac cell types *in vitro*. Our knowledge of cardiac cell regulation continues to rapidly increase, and new tools, including novel methods for visualizing signaling in real time, are being developed³⁷. In addition, adeno-associated viruses are emerging as a viable therapeutic approach to deliver both small interfering RNA (siRNA) and

proteins *in vivo* for both scientific and clinical purposes³⁸. These advances portend the discovery of additional cardiac therapeutics in the coming years.

Competing interests

MSK is a co-inventor of patented intellectual property concerning the use of RSK3 inhibitors for the treatment of heart failure, by which he and the University of Miami may gain royalties from

future commercialization. He is the manager of Anchored RSK3 Inhibitors, LLC (Miami Beach, FL, USA) and is on the board of directors of Cardiac RSK3 Inhibitors, LLC (Miami Beach, FL, USA), companies interested in developing RSK3-targeted therapies and in which he holds equity. CAE declares that he has no competing interests.

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The referees who approved this article are:

Version 1

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