



EDITORIAL

Evolving targets for heart failure: the journey so far

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Abstract

The treatment of heart failure has included vasodilators, positive inotropes and most successfully neuro-hormonal blockade. Recent research has looked at metabolic and immune modulatory approaches, and implantable, mainly electrical devices. The near future in pharmacological research for heart failure remains focused on classic methodologies and small molecules, but despite significant improvements we still know relatively little of the complex interactions in heart failure, particularly for heart failure with preserved ejection fraction. Pharmacotherapy will in future be combined with advances in biotechnology, nanotechnology and devices and a digital revolution will help us to monitor patients at a distance, using wireless devices. Heart failure research has achieved much over the last 4 decades, but the pace of innovation and research has not abated and future advances in this disabling condition are indeed likely.

Key words: heart failure, therapeutics, randomized controlled trials.

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Introduction

Until the 1970s the only treatments for the management of heart failure (HF) were based on bed rest, restriction of physical activity, fluid restriction and pharmacological therapy limited to diuretics and digitalis. At the time research efforts in developing new heart failure treatments mostly focused on the kidney rather than the heart as a target. Since then, the evolution of the treatment of heart failure has been prolific, starting with the development of vasodilators, positive inotropes and more recently moving to neuro-hormonal blockade, metabolic and immune modulatory approaches, and implantable, mainly electrical devices.

Hemodynamics and inotropy

From the mid-1970s, vasodilators had been studied with the aim of reducing afterload and to increase cardiac efficiency and cardiac output.¹ It was thought that the effect of vasodilators on left ventricular ejection fraction, ventricular diastolic pressure and cardiac energetics would be advantageous for patients with heart failure. However, the vasodilator-heart failure trial showed that, despite short-term hemodynamic im-

provement, afterload reduction did not improve survival.² It soon became evident that the hemodynamic effects of vasodilators were not the main driver of longer-term benefits, and subsequently a series of trials showed that patients treated with pure vasodilators were at greater risk of developing worsening HF and mortality.³⁻⁶

The description by Sarnoff of ventricular function curves brought the idea of developing drugs aimed at improving ventricular contractility.⁷ Therefore, the possibility of shifting from one Starling curve to another by improving the *contractile* state of the heart became a major target. Overcoming the difficulties in measuring contractility, it became evident that improving the impaired contractility of the left ventricle in patients with chronic HF would be a meaningful target. Therefore, research focused on understanding the causes of the impaired myocardial contractility.

The recognition of a central role of abnormal calcium movements and energy starvation stimulated the development of novel inotropic drugs. These drugs were developed on the assumption that since left ventricular ejection fraction (LVEF) correlates with survival, increasing LVEF should improve prognosis. Despite a sound rationale it became evident that despite an improvement in cardiac performance, the early positive inotropic agents had a detrimental effect on survival. A few years later the picture was completed by the evidence that also cardiac gly-

cosides, the earliest inotropic agents, that had long been the mainstay of heart failure therapy, were not effective at improving survival in patients with heart failure in sinus rhythm.⁸

The neuroendocrine years

Starling's law of the heart and the neuroendocrine response were considered as compensatory mechanisms. In the 1980s Peter Harris of the National Heart and Lung Institute in London, and his group hypothesized that the neuroendocrine activation observed in patients with heart failure was a maladaptive response and not part of a maintained compensatory mechanism.⁹⁻¹³ This novel interpretation of neuro-endocrine activation led to a new way of treating heart failure and became considered a defining hallmark of the heart failure syndrome, persistent neuroendocrine activation. Consequently, this new approach led to the evaluation and later introduction of angiotensin converting enzyme inhibitors (ACEIs), β -blockers (BBs) and mineralocorticoid receptor antagonists (MRAs) as treatments for HF. ACEIs were the first class of drug to show a significant and sizeable reduction in the risk of death and hospitalization in patients with heart failure with reduced ejection fraction (HFrEF), regardless of its severity.¹⁴ BBs were introduced with more caution given the negative inotropic effect of first and second generation BBS. They were, indeed paradoxically found to improve left ventricular ejection fraction, improve symptoms and decrease mortality and hospitalization when administered chronically, provided of course the patient can be supported during a slow period of introduction and up-titration.¹⁵ Both classes of drugs, ACEIs and BBs were demonstrated to reduce left ventricular remodeling and to be beneficial regardless of the etiology of HF, age, race or gender.¹⁶

Later, the MRAs were shown to have a beneficial prognostic effect on top of therapy with ACEIs and BBs. The picture was completed with the development of newer angiotensin receptor blockers. At this stage of neuro-endocrine focused research, atrial natriuretic peptide was thought to be beneficial in heart failure because of its vasodilatory capacity.¹⁷ However, this peptide had not been shown in human studies to positively modify cardiac structure, function or improve survival.^{18,19}

The neuroendocrine story stimulated radical changes in the management of HF, from vasodilators to anti-renin angiotensin-aldosterone drugs, from positive inotropes to drugs with a short-term negative inotropic effect, such as BBs, that progressed to effectively become positive inotropes in heart failure over the medium to longer term due to their ability to induce left ventricular reverse remodeling and an increase in left ventricular function without increasing oxygen consumption.

The effect of BBs in HF highlighted the paradox of the altered relationship between heart rate and contraction. In normal physiological states, the contractile force of a healthy papillary muscle increases proportionately to the increase in its rate of contraction. In contrast, in HF this relationship becomes inverse, and the contraction strength decreases in re-

sponse to increased heart frequency. As a result, in HF, increasing heart rate is associated with a reduction of left ventricular ejection fraction.²⁰ This evidence led to the introduction of a newer class of drugs that selectively reduce heart rate and increase ejection fraction, whilst be devoid of any direct effect on cardiac myocytes or peripheral vascular resistance. Ivabradine, a specific inhibitor of the If current in the sinoatrial node, that induces a selective heart rate reduction, was found to have a positive effect on remodeling and ejection fraction.²¹⁻²³

The millennium

In the new millennium heart failure research turned to a combination of devices (which are beyond the scope of this chapter), molecular biology, genetics and stem cells. Despite huge excitement at their potential, the heralded benefit of these therapies has not yet been achieved clinically. Despite the demonstration of the molecular cause of a form of familial hypertrophic cardiomyopathy, a mis-sense mutation in the cardiac β -myosin heavy chain gene, being reported in the early 90s, the replacement of faulty genes with correct copies delivered by viral vectors has not been proven to be effective to date. A newly discovered type of regulation termed epigenetics has been more recently identified as a possible therapeutic target for heart failure therapies.²⁴ Linked to epigenetics is the concept of micro RNAs (miRNAs). These are small non-coding RNA segments that regulate gene transcription and protein formation by silencing selected messenger RNA strands. Preclinical research into miRNAs suggests the importance of these molecules for many cardiac myocyte functions in the failing heart, from calcium cycling to ventricular hypertrophy.²⁵

The enthusiasm for stem cell therapy led to the belief that stem cell implantation could re-generate the myocardium and improve cardiac function. Autologous bone marrow-derived mono nuclear cells were considered first for therapeutic purposes.

However, the results of their use have never been compelling, and this approach has been not found effective for clinical use.²⁶⁻²⁸ Subsequently, mesenchymal stem cells harvested from the adipose tissue were also considered, but they also have been found not to have a significant therapeutic effect in patients with heart failure.²⁹ Hope now has focused on the therapeutic use of autologous stem cells. The efficacy of this technology remains under investigation.²⁶ However, the challenges of finding the optimal cell type, quantity, processing method, administration route, and establishing efficacy and safety remain unsolved.

The future

The near future in pharmacological research for heart failure remains focused on classic methodologies and small mol-

ecules. The results in HF_rEF from the PARADIGM-HF study, in which a smart fixed dose combination of sacubitril and valsartan (LCZ696) significantly improved prognosis compared with treatment with the ACEi enalapril suggests that there is still room for further developments using this approach, even though other attempts at comprehensive neurohormonal modulation have failed, such as when vasopressin and/or endothelin antagonists were added to the triad of ACEIs, BBs and MRAs.

Areas of relative failure

The past decades have led to a significant improvement in our understanding and treatment of chronic HF_rEF, whereas in stark contrast, no effective therapies have been developed for acute HF or for HF_rEF.³⁰ These two conditions, however, are a mixed bag of different aetiologies that may well need differing and more differentiated therapeutic approaches. The identification of different phenotypes helping identify the multifaceted pathophysiology of these two conditions may be an essential precursor to the development of effective therapies.

We still lack the unifying hypotheses for both acute HF and HF_rEF that would allow more soundly based therapeutic approaches to be developed. We also lack for both conditions adequate surrogate end points that may shed the light on the efficacy of newer therapies at an earlier stage of the development pathway. Many promising compounds have failed in largescale randomized clinical trials in acute heart failure, despite the attractive conceptual foundations underpinning their use.³¹⁻³⁴ We are still missing the link between acute symptomatic relief and long-term risk reduction, which has not been achieved with any agent used in acute HF to date.

Conclusions

Despite significant improvements in our understanding of heart failure over 4 decades we still know relatively little of the complex interactions of the disorder. Pharmacotherapy is likely to play an integral role for the foreseeable future. This remains true, despite the fact that we live in a modern, technological world where advances in biotechnology, nanotechnology and devices continue to offer tantalizing possibilities of replacing failing cardiomyocytes with gene or stem cell therapy or to correct the dysfunctional cells using chimeric antigen receptors. The digital revolution will help us to monitor patients at a distance, using wireless devices. This may help to identify newer innovative approaches to heart failure management through a combination of health- and bioinformatics, personalized medicine and smart drug design. Heart failure research has achieved much over the last 4 decades, but the pace of innovation and research has not abated and future advances in this disabling condition are indeed likely.

Conflict of interest

The authors declare no potential conflict of interest.

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