The pathophysiology of heart failure: a tale of two old paradigms revisited

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ABSTRACT – Although our current appreciation of the detrimental role of neurohumoral activation in heart failure (HF) has been intellectually appealing and has led to neurohumoral antagonism that has reduced morbidity and mortality from HF, the persisting disability and death rates remain unacceptably high. In the search for novel strategies to improve on these outcomes, we must reacquaint ourselves with basic cardiac physiology at levels ranging from the molecular to the systemic in order to identify new targets for the treatment of HF. This approach has already begun to yield results; in this review, two such aspects will be focused on: diastolic ventricular interaction and cardiac energetics. These two examples will be used to illuminate how fundamental research has elucidated age-old, although mechanistically elusive, principles (for example, the Frank–Starling law), explained why existing and emerging therapeutic approaches (for example, biventricular pacing in HF) have proved successful, and successfully identified novel therapy modes (for example, perhexiline as an energy augmentation agent).

KEY WORDS: diastolic ventricular interactions, energetics, fatty acid oxidation, Frank–Starling law, glucose, GLP-1, heart failure, perhexiline, pulmonary embolism, trimetazidine, uncoupling

Introduction

Heart failure (HF) is a leading cause of morbidity and mortality in developed countries[1] and an emerging one in the developing world.[2] The identification of neurohumoral activation as a central detrimental feature of HF, coupled with an improved infrastructure for trialling and delivering neurohumoral antagonists, has led to great advances in the treatment of HF.[3] Nonetheless, the mortality of HF at five years remains about 50%, which is similar to the prognosis for many cancers.[4] Although combinations of neurohumoral antagonists – with respect to both the pathways antagonised and the degree of pathway antagonism – have been partially successful,[5] the limits of this approach have already been encountered.[6] Consequently, in order to identify new modes for the treatment of HF, a critical reassessment of fundamental cardiac physiology has proved essential. This review describes how this reassessment, which ranges from the study of basic molecular mechanisms to studies of systemic human physiology, has yielded insights that guide existing therapies and identified novel treatment avenues. Only with this translational approach can major advances in the management of disease be made.

Diastolic ventricular interaction

'Frank–Starling relation'

The relation between cardiac 'preload' and the force of ventricular contraction was studied by Otto Frank in the 1890s and Ernest Starling in the early twentieth century. Accordingly, the term 'Frank–Starling relation' is used to describe this phenomenon. Frank studied the relation between left ventricular stretch during diastole and force of contraction in the isolated frog heart.[7] Starling initially used a canine heart–lung preparation to study the relation between atrial pressure (which approximates to left ventricular diastolic pressure) and the force of contraction,[8] although he later went on to assess the relation between left ventricular stretch and force of contraction. 'Preload' thus has been expressed in terms of both left ventricular diastolic pressure and left ventricular diastolic stretch (Fig 1). Furthermore, the latter has been assumed to be proportional to the former, and as left ventricular end diastolic pressure (LVEDP) (or its surrogate pulmonary capillary wedge pressure) is simpler to measure, it has come to be used as the measure of 'preload' in clinical practice.

The relation between left ventricular stretch and force of contraction of the heart is analogous to that of the length–tension relation in skeletal muscle and is related to an increased number of actin–myosin interactions at higher sarcomere length. In skeletal muscle, excessive stretch may result in a reduction in developed tension, as actin–myosin interactions diminish at very high sarcomere length. Starling and coworkers demonstrated a similar phenomenon at very high levels of stretch in the heart. This is often referred to as the 'descending limb of the Starling curve'.[8] The presence of this 'descending limb' is

often used to explain the clinical observation that acute reductions in right atrial and pulmonary capillary wedge pressures in patients with HF (for example, as a result of administration of intravenous nitrates) markedly increase stroke volume. Howarth demonstrated this phenomenon elegantly by showing that venesection in patients with HF markedly reduced right atrial pressure while markedly increasing cardiac output.[9] Others have challenged the assertion that the cardiac sarcomere can be stretched in health or HF to an extent that causes the force of contraction to diminish.[10] More recently, Holubarsch *et al* showed that the developed force increased with increased stretch in whole explanted hearts and in cardiac muscle strips of patients undergoing transplantation.[11] How then do we explain the salutary effects of intravenous nitrates in acute heart failure? To do so, we need to stand back from cellular physiology and understand whole animal physiology.

The heart is surrounded by the pericardium. In health, pericardial pressure at rest is close to zero. Similarly, right ventricular end diastolic pressure (RVEDP) is close to zero. Accordingly, external constraint to the filling of the left ventricle is minimal and the degree of stretch of the left ventricle at end diastole is determined by the intracavitary LVEDP. In this setting, LVEDP and diastolic stretch parallel each other and are both valid measures of left ventricular 'preload.' The pericardium has a J-shaped stress–strain relation, however, and beyond a certain level of stretch, pericardial pressure begins to increase – and does so exponentially (Fig 2).[12] Because the right ventricle has thin walls, RVEDP increases in parallel with pericardial pressure (it is marginally higher, but this is within measurement error).[13] Studies in open-chest dogs have shown that pericardial pressure is about zero when LVEDP is lower than 8 mmHg but increases progressively with volume loading above this value of LVEDP.[14]

Why is this important?

When pericardial and right ventricular diastolic pressures are increased, they constrain the filling of the left ventricle. In these circumstances, LVEDP is no longer the distending force acting on the left ventricle at end diastole (that is, left ventricular preload). The actual distending force is LVEDP minus the external constraints from the pericardium and from the right ventricle via

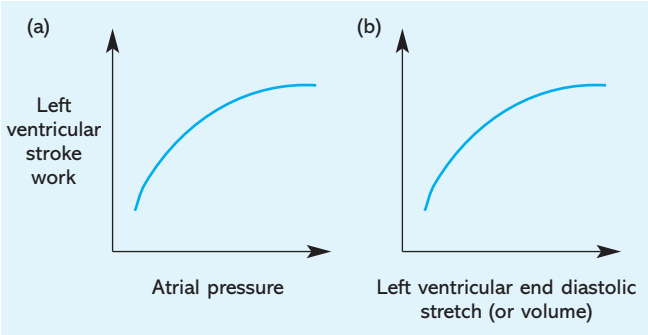

Fig 1. (a) Frank originally described the relation between increasing left ventricular stretch during diastole and increased force of contraction. (b) Starling showed that the force of left ventricular contraction increased as the atrial pressure (and therefore left ventricular end diastolic pressure) increased.

the interventricular septum. The impending effects of the right ventricle and pericardium on left ventricular filling are known as diastolic ventricular interaction (DVI) and pericardial constraint, respectively. Experimental studies in animal models have shown the physiological importance of pericardial constraint and DVI in situations associated with acute right ventricular volume and pressure overload. For example, Belenkie and colleagues undertook studies in a canine model of acute pulmonary embolism.[15] Volume loading in this model resulted in a decrease in stroke volume – a manifestation of the descending limb of the Starling curve! Although volume loading increased LVEDP, the increase in pericardial pressure and RVEDP was even greater, so 'true' left ventricular preload fell and the left ventricular area at end diastole fell. Accordingly, the fall in stroke volume was entirely explicable on the basis of a reduction in left ventricular stretch at end diastole (in accordance with Frank's observations).

The pericardium, however, can grow and therefore adapt to chronic increases in cardiac volume;[16] it therefore was assumed that although pericardial constraint and DVI might be important in acute situations, they were unlikely to be important in chronic HF. This was shown to not be the case. Central blood volume was reduced in healthy controls and patients with chronic heart failure by pooling blood in the pelvic and leg veins using lower body negative pressure. In about 40% of patients

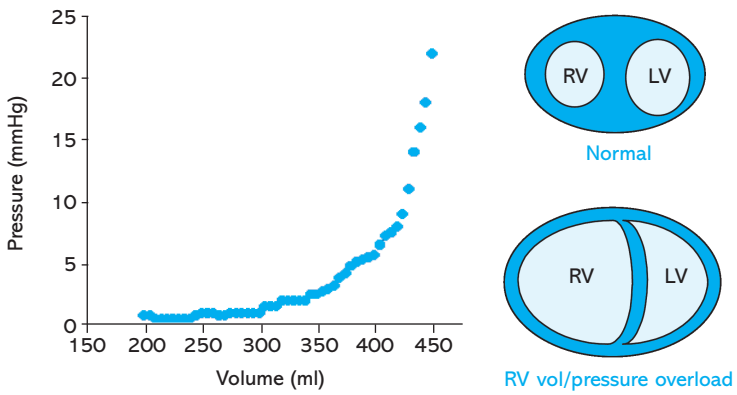

Fig 2. J-shaped stress–strain relation of pericardium. In health, pericardial pressure and right ventricular end diastolic pressure (RVEDP) are close to zero. In some situations associated with right ventricular pressure and volume overload (for example, in some patients with heart failure), the pericardium becomes stretched and pericardial pressure and RVEDP become markedly increased. In this setting, filling of the left ventricle becomes impeded by the pericardium (pericardial constraint) and by the right ventricle via the interventricular septum, which results in a flattening of the septum at end diastole (diastolic ventricular interaction). Adapted from Reference 12.

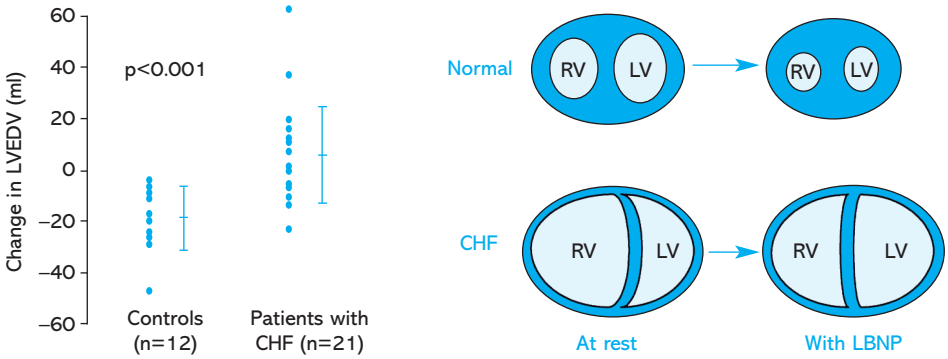

Fig 3. Effect of lower body negative pressure (LBNP) on left ventricular end diastolic volume (LVEDV). On application of LBNP, LVEDV reduced in healthy controls but increased in nearly half of the patients with heart failure. This was because reduced central blood volume reduced right ventricular volume and pressure and pericardial pressure (increasing left ventricular filling). CHF = chronic heart failure. Reproduced with kind permission of Elsevier.[17]

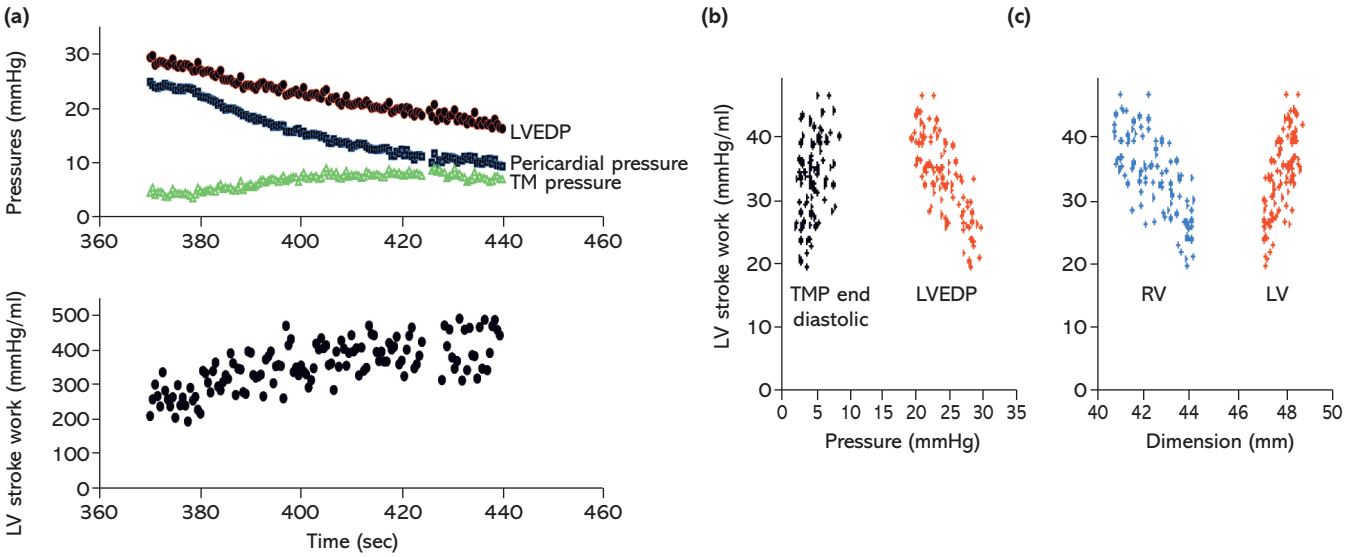

Fig 4. (a) Effect of constriction of inferior vena cava (IVC) on left ventricular ejection diastolic pressure (LVEDP) and left ventricular stroke work. In an animal model of heart failure, constriction of the IVC reduced LVEDP but increased left ventricular stroke work. **(b) Pericardial pressure.** Pericardial pressure fell more than LVEDP, so the distending pressure acting on the left ventricle (transmural pressure (TMP)) increased. **(c) Left ventricular diastolic dimension.** Changes in left ventricular diastolic dimension were reciprocal to LVEDP but parallel to left ventricular TMP. Reproduced with kind permission from *Am J Physiol Heart Circ Physiol*.[18]

with HF, right ventricular end diastolic volume (RVEDV) fell as right atrial pressure reduced but left ventricular end diastolic volume (LVEDV) increased (Fig 3).[17] This was due to pericardial constraint and DVI in a rapid pacing animal model of heart failure.[18] Constriction of the inferior vena cava reduced LVEDP but increased left ventricular stroke work (that is, a 'descending limb' of the Starling curve). As LVEDP fell, however, left ventricular end diastolic dimension increased. The changes in left ventricular stroke work were related to changes in left ventricular stretch during diastole (as shown originally by Frank). The reason left ventricular volume rose as LVEDP fell is that the fall in external constraint from the pericardium and right ventricle was even greater than the fall in LVEDP (Fig 4).

What is the implication of this? Firstly, it means that LVEDP (or its surrogate pulmonary capillary wedge pressure) is not a measure of left ventricular preload in situations where DVI and pericardial constraint are important and that changes in stroke volume and LVEDP may be reciprocal in this setting. Secondly, these observations highlight the importance of using potent venodilatators in this setting. Finally, are there other means of reducing DVI and pericardial constraint to improve cardiac output in patients with HF?

Biventricular and left ventricular pacing are now established treatments for patients with severe heart failure; they work, in part, by reducing dyssynchronous ventricular contraction.[18] Left ventricular pacing also markedly reduces DVI and pericardial constraint, which allows greater 'preload' (stretch) and therefore stroke volume for a given LVEDP. It presumably does so by advancing left ventricular filling in comparison to right ventricular filling and therefore reducing pericardial stretch at left ventricular end diastole.[19] The precise contribution of this mechanism of DVI resolution to the benefits of biventricular and left ventricular pacing in HF remains to be determined.

Cardiac energetics

Although it has been recognised for more than half a century that the heart is a pump and as such is fundamentally dependent

on an optimal energetic status in both health and disease,[20] the startling success of neurohumoral treatment meant that the determinants of cardiac energetics received less attention as putative therapeutic targets. Nevertheless, the heart is a major metabolic organ with a profound energy requirement. As the daily turnover of adenosine triphosphate (ATP) (about 35 kg) is very many times that of the myocardial ATP pool and, indeed, many times the weight of the heart itself,[21] even subtle variations in the efficiency of energy generation or utilisation may have a profound impact on cellular energy levels.[22]

Although the detailed evidence is beyond the scope of this article and has been reviewed extensively elsewhere, the myocardium in heart failure seems to be energy deficient.[22] Biochemically measured high-energy phosphate levels have long been known to be low in biopsies from failing hearts.[23,24] This recently was confirmed and expanded on by magnetic resonance spectroscopy, which has the capacity to non-invasively measure absolute cardiac energetics and energy fluxes.[22] Accordingly, although the data are preliminary, the most recent studies not only confirm a consistent reduction in creatine phosphate:ATP ratio (a marker of cardiac energy charge) but also demonstrate that cardiac ATP flux through creatine kinase (CK) is reduced by 50% in mild-to-moderate human heart failure (1.6±0.6 *v* 3.2±0.9 mmol/g of wet weight per sec ($p<0.0005$)).[25] Cardiac energetics are therefore of significant potential pertinence to cardiac physiology, especially in HF. Some authors have gone so far as to declare, 'These findings support the pursuit of new therapies that reduce energy demand and/or augment energy transfer in heart failure.'[25]

The heart is a metabolic omnivore; at rest in a healthy individual, it derives most of its energy (>70%) from free fatty acids (FFAs). The remainder is derived principally from carbohydrates (for example, glucose and lactate) and to a much lesser extent other fuels (for example, amino acids).[26] As FFAs are energy dense (burning with an enthalpy of 298 kcal/mol of C_2 units compared to 223 kcal/mol of C_2 units for glucose), this cocktail of substrates provides the heart with optimal fuel in health. In disease, such as HF, however, the burning of excess FFAs induced

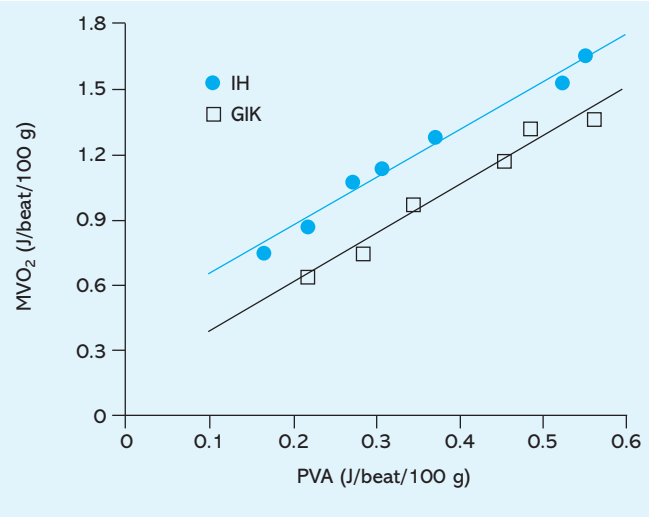

Fig 5. Relation between left ventricular pressure area (PVA) – a measure of left ventricular work – plotted against myocardial consumption of oxygen (MVO_2) in a pig model. During intralipid–heparin (IH) infusion, which increases cardiac utilisation of fatty acids, HVO_2 is about 40% greater for a given amount of cardiac work than during glucose–insulin–potassium (GIK) infusion, which increases myocardial utilisation of glucose. Reproduced with kind permission from *Am J Physiol Heart Circ Physiol*.[29]

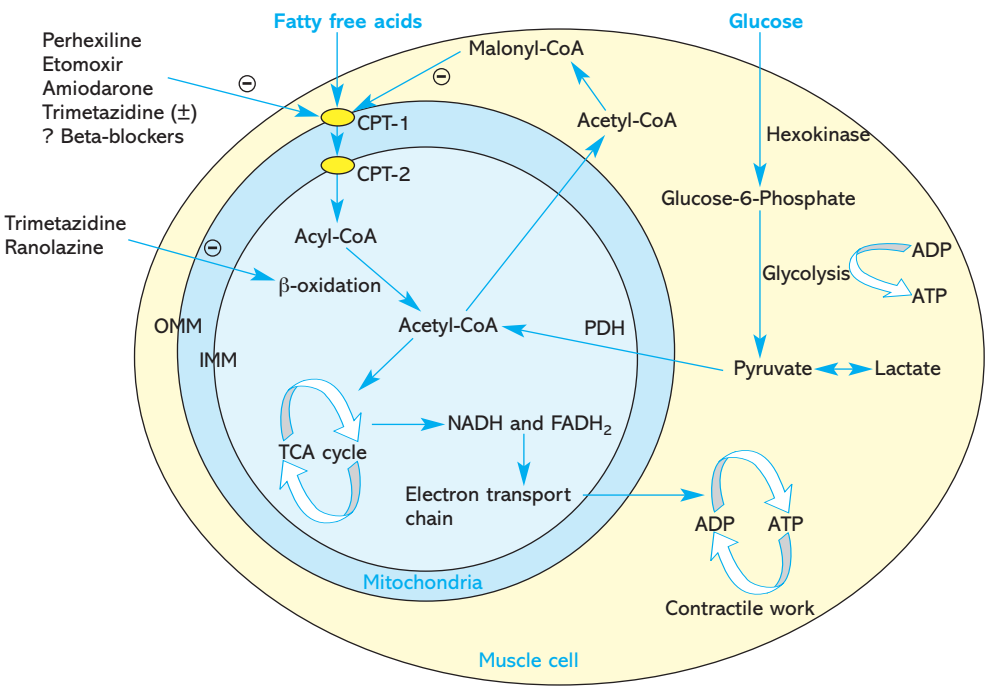

Fig 6. Pharmacological blockade of fatty acid metabolism occurs in two ways: inhibition of the enzyme carnitine palmitoyltransferase-1 (CPT-1), which prevents uptake of fatty acids into the mitochondria, and inhibition of fatty acid β-oxidation. ADP = adenosine diphosphate; ATP = adenosine triphosphate; CoA = coenzyme A; FAD = flavin adenine dinucleotide; IMM = inner mitochondrial membrane; NAD = nicotinamide adenine dinucleotide; OMM = outer mitochondrial membrane; PDH = pyruvate dehydrogenase; TCA = tricarboxylic acid. Reproduced with kind permission of Oxford University Press.[32]

by transcriptional and biochemical changes proves inefficient.[26,27] The cause for this inefficiency derives from the fact that FFAs produce less ATP per unit oxygen consumed than carbohydrates (2.8 *v* 3.17) but also that FFAs induce mitochondrial uncoupling that wastes energy in a futile fashion.[27] This is critical, as the myocardium in HF has dysfunctional mitochondria that render the heart energy vulnerable.[27] As a corollary, numerous studies since the 1970s have shown that hearts that are burning FFAs are markedly less efficient (about 40%) than those that are burning carbohydrate (Fig 5).[28,29] Based on these observations and a wealth of other preclinical data,[26] substrate modification was hypothesised to improve cardiac energetics and hence HF.

Although preclinical data supported this hypothesis,[26] manipulation of cardiac substrate recently has proved a promising strategy in the treatment of human HF. A number of studies with the partial fatty acid oxidation inhibitor (pFOXi) trimetazidine have culminated in a long-term study of more than a year in which trimetazidine conferred significant New York Heart Association (NYHA) functional class improvement, an increased ejection fraction from 36% to 43% (p=0.002), and an improvement in parameters on images from magnetic resonance imaging (MRI).[30] Although the findings of this study are encouraging in principle, trimetazidine is off-patent and unlikely to make an impact on the clinical management of HF.[31]

A similar study with perhexiline was performed for patients with advanced HF who were already optimally medicated. Perhexiline, another more powerful pFOXi that reduces transport of FFAs into mitochondria by inhibiting carnitine palmitoyltransferase-1 (CPT-1) (Fig 6[32]), was a successful antianginal agent in the 1970s.[33] It fell out of favour in the same decade due to unexplained cases of hepatotoxicity and neurotoxicity. In the ensuing decades, the basis of this toxicity has been attributed to abnormal metabolism of perhexiline in a small group of patients, labelled 'poor metabolisers,' due to defects in the CYP2D6 liver microsomal enzymes. Strict monitoring of levels of perhexiline in plasma is now known to allow its use with abolition of all toxicity.[33] In our randomised double-blind trial of 56 patients with ischaemic and non-ischaemic cardiomyopathy, perhexiline (monitored and adjusted according to levels in plasma) led to significant improvements in the primary endpoint of maximum oxygen consumption (from 16.1±0.6 ml/kg/min to 18.8±1.1 ml/kg/min; p<0.001), left ventricular ejection fraction (from 24±1% to 34±2%; p<0.001), and quality of life (Fig 7). These improvements are almost unprecedented whether judged against other pharmacological therapies or mechanical therapies. This data is highly promising and will usher in a new era in the therapy of HF if it is replicated safely in larger phase III trials.[34]

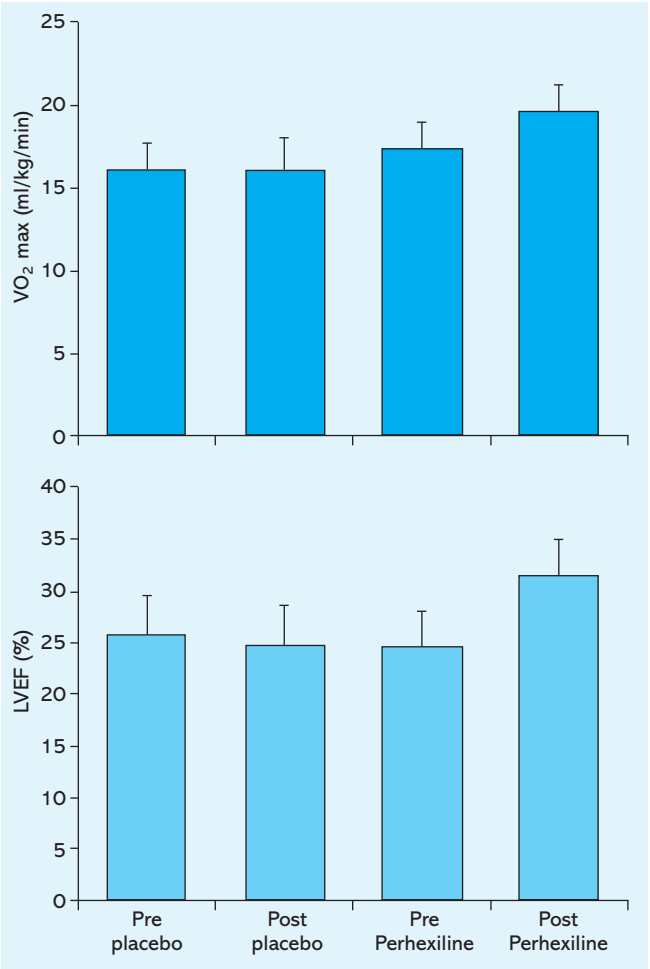

Fig 7. Perhexiline significantly increased maximal oxygen consumption (by approximately 3 ml/kg/min) and left ventricular ejection fraction (LVEF) (by about 10 percentage points). Reproduced with kind permission from *Circulation*.[34]

Conclusion

Although neurohumoral antagonism will continue to represent a central tenet in the treatment of HF, a more detailed understanding of the mechanisms of cardiac mechanics and inefficiency as manifested by DVI and energetics, clearly will make a significant therapeutic impact. These advances were facilitated by an improved basic understanding of the biochemistry and physiology of cardiac function and were specifically proved in human studies. As Professor David de Bono presciently noted, 'It is salutary to be reminded that patients with disease are often the most appropriate model for studying human pathophysiology.'[35] It is our earnest belief that continuing support for a better understanding of human physiology will not only lead to improvements in HF but will also translate into oft-unexpected bounty in other fields as well.

Acknowledgements

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Conflict of interests

MF and HA have applied for a method-of-use patent for perhexiline in heart failure.

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