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Review

A general theory of acute and chronic heart failure

David H. MacIver [a,*], Mark J. Dayer [a,1], Andrew J.I. Harrison [b]

[a] Department of Cardiology, Taunton & Somerset Hospital, Musgrove Park, Taunton, TA1 5DA, UK
[b] Department of Mechanical Engineering, Queens Building, University Walk, University of Bristol, Bristol BS8 1TR, UK

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ABSTRACT

Current concepts of heart failure propose multiple heterogeneous pathophysiological mechanisms. Recently a theoretical framework for understanding chronic heart failure was suggested. This paper develops this framework to include acute heart failure syndromes.

We propose that all acute heart failure syndromes may be understood in terms of a relative fall in left ventricular stroke volume. The initial compensatory mechanism is frequently a tachycardia often resulting in a near normal cardiac output. In more severe forms a fall in cardiac output causes hypotension or cardiogenic shock. In chronic heart failure the stroke volume and cardiac output is returned to normal predominantly through ventricular remodeling or dilatation. Ejection fraction is simply the ratio of stroke volume and end-diastolic volume. The resting stroke volume is predetermined by the tissue's needs; therefore, if the ejection fraction changes, the end-diastolic volume must change in a reciprocal manner.

The potential role of the right heart in influencing the presentation of left heart disease is examined. We propose that acute pulmonary edema occurs when the right ventricular stroke volume exceeds left ventricular stroke volume leading to fluid accumulation in the alveoli. The possible role of the right heart in determining pulmonary hypertension and raised filling pressures in left-sided heart disease are discussed. Different clinical scenarios are presented to help clarify these proposed mechanisms and the clinical implications of these theories are discussed. Finally an alternative definition of heart failure is proposed.

1. Introduction

The pathophysiological processes of heart failure are highly complex. Numerous different hypotheses have been offered to explain the condition. The multiple theories proposed include the hemodynamic, neurohumoral, muscle and diastolic heart failure hypotheses [1]. Heart failure remains incompletely understood by researchers and no single unifying framework has been proposed that has stood the test of time [2].

The heart is thought to have evolved from a simple two chamber peristaltic pump as observed in the Zebrafish [3]. Mammals have two pairs of pumps arranged in series, the right and left heart chambers. It is tempting to speculate that evolutionary success of the mammalian heart is partly down to the fact that the four pumps are anatomically and electrically connected resulting in (normally) identical rates between the chambers. When considering an abnormality of one pump it is essential to take into account the effects of the other pumps.

Recently it has been suggested that the features of chronic heart failure may be explained using a simplified conceptual framework and this article is written to be read in conjunction with that paper [4]. This viewpoint extends those hypotheses for chronic heart failure and broadens the framework to explain the diverse acute heart failure syndromes. The paper will discuss the clinical implications and, in the On-line supplement, we will illustrate the hypotheses using clinical examples.

2. Prevailing concepts of heart failure

The features of heart failure are a consequence of a diverse set of clinical abnormalities and diagnoses. Pathophysiological responses may cause both adaptive and maladaptive reactions that may in themselves create additional problems. Initially, a review of some of the existing hypotheses for the pathophysiological mechanisms of heart failure is presented.

Heart failure would have been a rare condition during the course of natural selection. Therefore the pathophysiological processes in heart failure are likely to have been appropriated from other cardiovascular regulatory mechanisms. These physiological mechanisms can be broadly outlined as apparent hypovolemia, similar to those invoked by hemorrhage or dehydration, and hypervolemia where there is an inappropriate increase in intravascular volume. This results in the apparent paradox of 'opposite' physiological mechanisms that were designed to reverse hypovolemia (e.g. the renin-aldosterone-angiotensin system and the sympathetic nervous system) and hypervolemia (e.g. elevated brain natriuretic peptide). In other words, the pathophysiological processes involved in

Abbreviations: HFPEF, heart failure with a preserved (normal) ejection fraction; HFREF, heart failure with a reduced ejection fraction.

* Corresponding author. Tel.: +44 1823 342130; fax: +44 1823 342709.
E-mail address: david.maciver@tst.nhs.uk (D.H. MacIver).
[1] Tel.: +44 1823 342130; fax: +44 1823 342709.

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heart failure make use of physiological systems originally determined by evolution to cope with other changes such as hemorrhage, dehydration and over hydration. In the longer-term additional adaptations may be 'borrowed' from other evolutionarily important physiological responses such as those that normally occur during the animal's growth, pregnancy and in response to exercise. Many of these initially helpful processes may become maladaptive or even harmful over time.

2.1. The hypotheses for fluid retention

One of the cardinal features of heart failure is intravascular fluid retention, although extravascular fluid accumulation is not universal. The mechanisms of fluid retention in chronic heart failure have been investigated for over a century [5,6] but remain incompletely understood. Fluid retention may occur in the setting of heart failure and preserved ejection fraction (HFPEF) even when the arterial pressure is normal or high. Body weight and plasma volume increase before venous pressure rises in chronic heart failure [7]. Renal flow is often normal in heart failure even though glomerular filtration rate and tubular re-absorption are increased [8,9]. Any fall in renal blood flow is often proportionally greater than the reduction in cardiac output [10]. One explanation is that renal vein flow may be reduced by an elevated venous pressure [11]. It is also suggested that the mechanism for fluid retention is through sympathetic activation, perhaps mediated by changes in the central nervous system perfusion, through stimulation of renin [12]. This may be located in the ventrolateral medulla (C1 neurons) increasing catecholamines and vasopressin [13]. Additional hypotheses for the mechanisms in heart failure are now discussed.

2.2. The conventional hemodynamic hypothesis

Heart failure has traditionally been considered a hemodynamic abnormality. In 1986 Harris proposed that reduced cardiac output, through a fall in blood pressure, was sensed by the baroreceptors, which in turn led to the features of heart failure [14]. This concept does not explain by what mechanism heart failure might occur in hypertensive heart disease or why the stroke volume and cardiac output are often normal in chronic stable heart failure [4]. Harris stated that "although the function of the circulation is to perfuse the tissues, the body monitors the adequacy of its perfusion, not through metabolic messengers carried from the tissues in the blood stream, but by sensing the arterial pressure; and the mechanisms evoked act to maintain the arterial pressure" [14]. Neurons are normally designed for rapid responses rather than longer-term adaptation; baroreceptors detect sudden changes in blood pressure and allow acute responses. Baroreceptors get 'reset' in hypertension and hypotension [15] and so probably have no real role in chronic compensated heart failure. If the Harris hypothesis was complete, standard drug therapy for heart failure that lower blood pressure should exacerbate the condition.

Pharmaceutical strategies designed to correct the hemodynamic derangements have been largely unsuccessful. Several therapeutic interventions designed to improve the hemodynamic status of patients such as using inotropic agents (e.g. flosequinan and milrinone) actually adversely affect their prognosis [16]. These findings raised further questions about the validity of this hemodynamic hypothesis. Due to the limitations of the original hemodynamic hypothesis authors have turned to alternative explanations such as the neurohumoral hypothesis.

2.3. The neurohumoral hypothesis

Hemodynamic abnormalities may help explain some of the symptoms of heart failure; however they are not sufficient to explain the progression of heart failure. Neurohumoral mechanisms are thought to play an important role in the progression of heart failure. Sympathetic nervous system and renin-angiotensin system activation appear to exert a detrimental long-term effect on the heart. Drug therapy that antagonizes these neurohumoral systems (e.g. beta-blockers and angiotensin converting enzymes) improves the natural history of heart failure. How much this benefit is through a change in hemodynamic factors such as vascular resistance and how much is due to direct effects of neurohumoral changes is unknown. These observations support the formulation of a neurohumoral hypothesis of heart failure and provided the foundation for the development of novel therapeutic strategies. However, conventional concepts do not provide a clear understanding as to how neurohumoral activation is instigated and maintained.

2.4. The muscle hypothesis

The muscle hypothesis for heart failure was introduced to explain the discrepancy between the clinical features of heart failure and the hemodynamic abnormalities observed [17,18]. The poor correlation of maximum oxygen consumption and ejection fraction is cited as an example. It is proposed that abnormal metabolism, function and atrophy in skeletal muscle are central abnormalities that may account for many of the symptoms of heart failure. The cause of the skeletal myopathy is unclear but mechanisms probably include disuse atrophy as well as changes related to an inflammatory milieu. An exaggerated ergoreflex is suggested to explain muscle fatigue and dyspnea [19].

2.5. The diastolic heart failure hypothesis

The term diastolic heart failure was introduced to describe a subgroup of patients with heart failure and a preserved ejection fraction (HFPEF) where other cardiac or non-cardiac causes, such as valvular and lung disease, have been excluded. The major abnormality is thought to be due to reduced left ventricular compliance and is effectively Hope's original backward failure hypothesis [20–22]. As ejection fraction is relatively normal in HFPEF it has been assumed that systolic function is also normal and consequently alternative explanations for the heart failure have been sought. Recent work has shown that although the ejection fraction may be preserved, other measures of systolic function such as shortening velocities, myocardial strain and strain rate are reduced [4,23,24].

HFPEF and heart failure with a reduced ejection fraction (HFREF) are compared in Table 2. Note that the main differences are their causes (e.g. hypertension vs. myocardial infarction respectively) and morphological findings (i.e. degree of end-diastolic wall thickness and end-diastolic volume). All other features overlap and may be dependent on severity rather than subtype (Table 2).

A shift in the end-diastolic pressure volume relation upward and to the left has been considered to be the hallmark of diastolic dysfunction. However, there is a variable shift in the ventricular end-diastolic pressure–volume relationship to lower, higher or normal volumes in HFPEF whereas one would expect only an upward shift if heart failure were due to diastolic dysfunction [25]. In addition, diastolic dysfunction is often worse in heart failure with a reduced ejection fraction (HFREF) than in HFPEF [26].

Furthermore there is a close interrelationship between systolic and diastolic dysfunction. During systole energy is stored by compression of the elastic elements of the myocardial tissues. Energy may be released in early diastole due to the elastic recoil. This may result in a fall in ventricular pressure, increasing the pressure gradient and improving forward flow into the ventricle during diastole (so called ventricular 'suction'). If contractile function is reduced less energy may be stored reducing the pressure gradient and reducing diastolic forward flow [27].

3. New concepts in heart failure

3.1. Background

The left ventricle is a displacement pump resulting in pulsatile flow and is beginning to be understood in terms of engineering