Heart Failure: The Dilemma of the 40-50% Ejection Fraction Range

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Abstract

The common pathophysiology contributing to fluid retention and dyspnoea in heart failure is a non-compliant and stiff myocardium with raised left ventricular end-diastolic pressure. With the rapid development of newer imaging technologies, particularly echocardiography, our understanding of the syndrome of heart failure has significantly changed. The most important imaging sign in the early eighties was reduced ejection fraction (HFrEF), with low values being used as an explanation for the development of signs and symptoms. In the early 2000s, similar Doppler echocardiographic signs became frequently recognised in patients with heart failure symptoms and signs who proved to have a relatively maintained ejection fraction (EF) of >40%, hence the description of the syndrome of “diastolic heart failure”. This was later rephrased as heart failure with normal ejection fraction (HFnEF) and more recently as heart failure with preserved ejection fraction (HFpEF). Since then, HFpEF has attracted the interest of many cardiologists and scientists worldwide, searching for specific features and treatment options for the syndrome. As for the features, two important findings have now been established, the first showed that LV systolic function mainly at the subendocardial level was abnormal in HFpEF, particularly manifesting during stress/exercise when the increase in heart rate was not associated with a commensurate increase in stroke volume and a second observation of a significant impairment of left atrial function (i.e. myocardial strain) and emptying fraction associated with increased left atrial pressures and the potential development of atrial arrhythmia in HFpEF. Such atrial abnormalities have been shown to be commonly associated with cavity enlargement and poor compliance. The latter observation has similarly been reported in patients with reduced EF. Despite the above similarities in cardiac physiology between HFpEF and HFrEF, treatments of the two conditions differ markedly. When comparing HFrEF and HFpEF, we can easily see that some patients fall into the grey area on the EF spectrum with values fluctuating above and below 40%, suggesting that the substrate for the expected drug effect may differ, possibly explaining the lack of consistent response in these patients. In addition, it should not be forgotten that most heart failure medications work on the circulation rather than the heart itself, hence the need for shared circulatory disturbances between the two conditions before we can reasonably expect identical treatment benefits when using the same medications in different clinical settings. Therefore, it is clear that classifying heart failure patients according to a single measure of LV function i.e. ejection fraction fails to help at least 50% of patients presenting with this syndrome. In contrast, aggregating such patients based on clear evidence for raised LA pressures, irrespective of EF, might show evidence for a more consistent response to vasodilators and conventional heart failure therapy, particularly those patients currently described as HFpEF.

Keywords: Heart Failure; HFpEF; HFnEF; Haemodynamics

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Introduction

In the absence of significant valve disease or arrhythmia, symptoms of heart failure e.g. exertional breathlessness and/or fluid retention are conventionally attributed to left ventricular myocardial disease, irrespective of its aetiology. The common pathophysiology contributing to these manifestations is a non-compliant and stiff myocardium with raised left ventricular end-diastolic pressure with its known consequences, i.e. raised left atrial pressure, pulmonary venous hypertension, and later on post-capillary pulmonary hypertension. In many cases, the presence of a third heart sound, on careful auscultation, supports the diagnosis and predicts an impaired prognosis. With even simple old-fashioned imaging investigations such as a chest X-ray that shows an increased cardiothoracic ratio and increased pulmonary vascular markings (the radiological accompaniment of audible râles), physicians would confidently confirm the diagnosis and commence heart failure treatment.
With the rapid development of newer imaging technologies, particularly echocardiography, our understanding of the syndrome of heart failure has significantly changed. The most important imaging sign in the early eighties was reduced ejection fraction (HFrEF), with low values being used as an explanation for the development of signs and symptoms. This was further supported by the pattern of left ventricular (LV) filling shown by spectral Doppler which clearly differentiated normal from slightly raised and documented a well defined restrictive filling pattern (1). Indeed, other signs such as an isovolumic relaxation time of zero have been shown to be consistent with an elevated left atrial pressure (above 30 mmHg). A short early diastolic filling velocity deceleration time of <140 ms is also consistent with raised LV end-diastolic pressure (2). These findings established the spectrum of LV disease associated with a heart failure presentation and suggested its contribution to patient’s symptoms and clinical signs. Later on, an increase in interest in diastolic function was generated by the publication of European and American guidelines for grading diastolic dysfunction (3). Those recommendations received further updating, based on age related normal changes, and are currently directed towards identifying patients with elevated filling pressures rather than the grade of diastolic dysfunction (4).

In the early 2000s, the same Doppler echocardiographic signs became frequently recognised in patients with heart failure symptoms and signs who proved to have a relatively maintained ejection fraction (EF) of >40%, hence the description of the syndrome of “diastolic heart failure”. This was later rephrased as heart failure with normal ejection fraction (HFmrEF) and more recently as heart failure with preserved ejection fraction (HFrEF). Furthermore, studies have shown that the underlying aetiology of this syndrome varies considerably with the commonest being a long-standing history of systemic hypertension, and frequent additional co-morbidities such as diabetes and coronary artery disease. Conditions such as amyloid infiltration of the myocardium and hypertrophic LV disease are relatively ignored and under-diagnosed because of their rarer contribution to the large bulk of patients presenting with HFrEF. (5) (6)

Since then, HFrEF has attracted the interest of many cardiologists and scientists worldwide, searching for specific features and treatment options for the syndrome. As for the features, two important findings have now been established, the first showed that LV systolic function mainly at the sub-endocardial level was abnormal in HFrEF (7), particularly manifesting during stress/ exercise when the increase in heart rate was not associated with a commensurate increase in stroke volume, as it should physiologically do according to the Frank Starling law (8). The second observation was a significant impairment of left atrial function (i.e. myocardial strain) and emptying fraction associated with increased left atrial pressures and the potential development of atrial arrhythmia in HFrEF. (9) (10) (11) Such atrial abnormalities have been shown to be commonly associated with cavity enlargement and poor compliance. The latter observation has similarly been reported in patients with reduced EF.

Despite the above similarities in cardiac physiology between HFrEF and HFrEF, treatments of the two conditions differ markedly. Guideline-recommended treatments for HFrEF are well established based on large scale randomised clinical trials and meta analyses; these include vasodilators (particularly ACE inhibitors and angiotensin receptor blockers), beta blockers, and diuretics for those with fluid retention. This treatment protocol has resulted in significant symptomatic improvement and an improved prognosis. In contrast, our recommended medical treatment of HFrEF has consistently constituted a clinical dilemma, since none of the same medications has shown clinical benefit in this patient population, even with spironolactone proving to lack significant benefit. (12)

One meta analysis has suggested a modest response of HFrEF to ACE-Inhibitors and/or angiotensin receptor blockers. (13) These findings explain the heterogeneous nature of the syndrome, not only in aetiology, but also in disease grades and most strikingly the wide range of EF (40-60% or more) the diagnosis is based on. Furthermore, when comparing HFrEF and HFrEF, we can easily see that some patients fall into the grey area on the EF spectrum with values fluctuating above and below 40%, suggesting that the substrate for the expected drug effect may differ, possibly explaining the lack of consistent response in these patients. In addition, it should not be forgotten that most heart failure medications work on the circulation rather than the heart itself, hence the need for shared circulatory disturbances between the two conditions before we can reasonably expect identical treatment benefits when using the same medications in different clinical settings. Even when LV re-synchronization therapy was tested as a potential therapy, it too failed in HFrEF compared to HFrEF (14).

Therefore, it is clear that classifying heart failure patients according to a single measure of LV function i.e. ejection fraction fails to help at least 50% of patients presenting with this syndrome. In contrast, aggregating such patients based on clear evidence for raised LA pressures, irrespective of EF, might show evidence for a more consistent response to vasodilators and conventional heart failure therapy, particularly those patients currently described as HFrEF. To further support this proposal, a recent sub-classification of patients with heart failure and EF >40% into mid-range EF 41-49% (HFrEF) and EF >49% (HFrEF) did not demonstrate any better refinement, neither in treatment nor prognosis (15). This reiterates the importance of identifying the pattern of cardiac physiology that explains patient’s symptoms and clinical signs that should guide towards optimum treatment, as we already do for other distinct cardiac conditions, treated with different strategies for different severities such as aortic stenosis.

Declarations of Interest
The authors have no conflicts of interest to declare.

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