Heart Failure with Preserved Ejection Fraction

a report by
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Definitions and Historical Considerations – The Misleading Role of Ejection Fraction

Chronic heart failure (CHF) is a heterogeneous syndrome with a complex pathophysiology. Although many different definitions for heart failure exist, we prefer the following: “a clinical syndrome characterised by symptoms and signs of increased tissue/organ water and decreased tissue/organ perfusion. Regardless of its aetiology, symptoms and signs may be related either to impaired left ventricular (LV) relaxation, suction and filling (predominantly diastolic pump dysfunction/failure) or to impaired output of the cardiac compression pump (predominantly systolic pump dysfunction/failure) but almost always to a combination of both.”

This definition of heart failure refrains from including any notion of LV ejection fraction. However, mostly driven by clinical trial design, heart failure has been dichotomised according to ejection fraction as ‘preserved’ (heart failure with preserved ejection fraction [HfPpEF]) or ‘reduced’ (heart failure with reduced ejection fraction [HFrEF]).

Recently, epidemiological surveys have revealed that the incidence of HfPpEF has been steadily increasing over the past 25 years. Currently, the LV ejection fraction is found to be preserved in >50% of cases of heart failure. Patients with HfPpEF appear to be older and are more likely to be female, have a history of hypertension and have less coronary artery disease. Once hospitalisation for ‘decompensation’ has occurred, the cardiovascular mortality and overall prognosis is as poor as for HFrEF.

Erroneously, the pathophysiology of HfPpEF and HFrEF were considered to be genuinely different. Whereas HFrEF was correlated with mere ‘systolic abnormalities’, these abnormalities were believed to be absent in HfPpEF. Instead, when ejection fraction was preserved, heart failure was correlated with ‘diastolic abnormalities’, and was thought to occur without abnormalities in systole. Inevitably, the connotations ‘systolic’ and ‘diastolic’ heart failure were introduced as they were estimated to reflect distinct diseases. However, recent observations have neglected to refine this view. Most importantly, it is now generally recognised that in systolic heart failure LV diastolic abnormalities are profound, and predict a patient’s symptoms better than systolic (dys)function. In contrast, in diastolic heart failure there are marked, previously overlooked LV systolic abnormalities, as revealed by novel cardiac imaging techniques. In fact, CHF, irrespective of ejection fraction (even when preserved), is emerging as a syndrome in which many pathophysiological processes interact. These processes include systolic dysfunction, diastolic dysfunction, circulatory volume overload, disturbed ventriculo-arterial coupling and activation of neurohormonal systems. Although the relative contribution of each of these factors may vary among individual patients, measurements of LV ejection fraction do not allow for exclusion of any of these factors. Accordingly, rather than being two separate identities, systolic and diastolic heart failure may be more closely related than previously thought. In fact, it is preferable to envisage CHF as a syndrome with a spectrum of diverse clinical presentations, in which most if not all cases are hybrids of diastolic and systolic heart failure (see Figure 1). The misleading connotations of systolic and diastolic heart failure should be abandoned to avoid biased clinical and scientific approaches.

Systolic Abnormalities in Heart Failure with Preserved Ejection Fraction – The Heart as a Muscular Pump

The recent unveiling of LV systolic dysfunction at normal LV ejection fraction by tissue Doppler imaging, magnetic resonance imaging (MRI) and speckle tracking is surprising at first glance. Nevertheless, these observations are just a reminder that LV ejection fraction is an index of global haemodynamic pump performance, insensitive to disturbances of ventricular muscle function (see Figure 2). A preserved ejection fraction often merely indicates that the radial (or circumferential) fibres of the ventricle have compensated for dysfunction of the longitudinal fibres; it does not necessarily imply that the systolic function of the muscular pump is normal. These considerations may have important diagnostic implications, since impaired longitudinal fibre function may be the single or most marked sign of cardiac dysfunction in HfPpEF. Systolic impairment of longitudinal fibre shortening strongly correlates with impairment of longitudinal fibre re-lengthening and with expression of brain natriuretic peptide (BNP) messenger RNA (mRNA) in subendocardial LV layers.
Heart Failure

Diastolic LV dysfunction is very common in, but not specific for, HFrEF. It often co-exists with – or is even caused by – other cardiovascular abnormalities such as systolic LV dysfunction, arterial stiffening and volume overload. More specifically, diastolic LV dysfunction is a consequence of impaired LV suction due to impaired LV systolic relaxation and reduced LV diastolic compliance. Causes of impaired relaxation are related to factors intrinsic and extrinsic to cardiomyocytes. The intrinsic factors include impaired inactivation processes (disturbed intracellular calcium homeostasis, myofilament function and cell energetics), whereas the extrinsic factors include pressure volume overload, ventricular dysynchrony and abnormal activity of soluble cardio-active factors (angiotensin, endothelin, nitric oxide). Decreased compliance of the LV is due to extracellular matrix or cytoskeletal abnormalities. Interestingly, none of the above mechanisms of diastolic dysfunction seems to be specific for HFrEF or HFrEF, although there is emerging evidence that passive forces and resting tension of cardiomyocytes from patients with HFrEF are higher than those from patients with non-ischaeamic HFrEF.

Clinical Aspects of Heart Failure with Preserved Ejection Fraction

Diagnosis

The clinical symptoms and signs of patients with HFrEF are the same as for those with HFrEF. During diagnosis, the finding of a normal ejection fraction obviously should not be used to doubt the clinical diagnosis of heart failure. Recently, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) has proposed novel diagnostic guidelines for heart failure when LV ejection fraction is preserved (see Figure 3). Within these guidelines, blood flow Doppler, tissue Doppler, serum BNP or N-terminal pro-BNP (NT-pro-BNP) concentrations and atrial diameters play a central role. The predictive values of BNP and NT-pro-BNP are still too vague to use as the gold standard for diagnosis in individuals, but certainly reflect the severity of disease when used in cohorts of HFrEF patients. In the absence of atrial fibrillation, left atrial size provides morphological and physiological evidence of chronic elevation in LV filling pressures.

Treatment of Heart Failure with Preserved Ejection Fraction

Randomised multicentre trials in patients with HFrEF are scarce. Therefore, the recommendations for the management of HFrEF are based on small clinical studies lacking a pathophysiological concept and validated diagnostic guidelines. Treatment of HFrEF should have two essential goals: reducing symptoms and improving prognosis by targeting the mechanisms of disease.

The diversity of CHF does not reside in the presence or absence of systolic or diastolic dysfunction, but rather in the degree and type of LV remodelling, developed along the pathophysiological progression of the disease. However, LV remodelling is not an all or nothing phenomenon, and it is influenced by many patient characteristics acting as ‘disease modifiers’. LV remodelling, when quantified as cardiomyocyte diameter, covers a wide, continuous spectrum over the whole range of LV ejection fraction. The ‘modifiers’ that influence LV remodelling include haemodynamic load, coronary arterial function, gender, age, metabolic disturbances (obesity, diabetes), physical fitness, cardiac endothelial function and genetic background, which may either promote or decelerate remodelling. Future unravelling of the cellular, molecular and biochemical puzzle of LV remodelling may reveal how these modifiers propel heart failure diversity over a wide spectrum of closely related disease phenotypes.
**Symptom-targeted Treatment**

Reducing the symptoms of individual patients with HFpEF can be challenging as they may be multifactorial. For example, exertional dyspnoea, the most common symptom of HFpEF, can be caused by increased LV diastolic pressures or reduced cardiac (chronotropic) reserve, but also by peripheral deconditioning. Optimising therapy in HFpEF is often a matter of trial and error, and can be frustrating when arterial blood pressure is normal. Diastolic LV pressure can be reduced by decreasing circulating or LV volume (with diuretics, venodilators or neurohormonal inhibitors), reducing heart rate to normal, reducing blood pressure and maintaining synchronous atrial contraction. As treatment with diuretics can vary substantially, it may be appropriate to start at a relatively low dosage, since a small change in diastolic volume may cause a large change in pressure and cardiac output, and may lead to hypotension. Blood pressure lability is often noted in HFpEF, not only due to passive ventricular stiffening, but also due to arterial stiffening.

Reducing heart rate in HFpEF acts as a double-edged sword. On the one hand, it may have a beneficial impact on ischaemia-related diastolic dysfunction, and may avoid the problem of incomplete relaxation seen at high heart rates. On the other hand, blunting exercise-induced increases in heart rate may also inappropriately impair an important mechanism of the (hypertrophic) heart to increase cardiac output, especially as some of these hearts manifest a small recruitable inotropic and preload reserve, and thus rely on chronotropy for adaptations of cardiac output to peripheral demands.15

**Mechanism-targeted Treatment**

Randomised clinical trials on mechanism-targeted treatment in HFpEF have been slow to develop. Thus far, none of the trials specifically targeting HFpEF has shown a significant effect of either digoxin, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor inhibitors on overall mortality. In the Digitalis Investigation Group (DIG), in those with ejection fraction >45% and ancillary sinus rhythm digoxin induced a significant reduction in heart failure hospitalisations, but also a trend towards more hospitalisations for non-heart failures. In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-preserved trial (heart failure with LV ejection fraction higher than 40%, but patient characteristics strongly diverging from HFpEF patients in the community), candesartan had a moderate but significant impact on preventing hospital admissions for heart failure.16 Similarly, in the Consistent with the conceptual physiological considerations explained in Figure 2 and throughout the article, the diagnostic criteria of heart failure with preserved ejection fraction (HFpEF) include the clinical demonstration of a normal haemodynamic pump performance and a dysfunctional muscular pump performance. The latter can be realised by invasive haemodynamic measurements, cardiac imaging techniques or using serum biomarkers.

**Perindopril for Elderly Persons with CHF (PEP-CHF) trial**, a study in elderly people with rather milder degrees of HFpEF (mean LV ejection fraction 65%), perindopril did not reduce overall mortality, perhaps because of low event rates (4% per year), but significantly reduced hospitalisations for heart failure.17 Of note, in some recent heart failure trials, inclusion criteria no longer include limitations for ejection fraction, thereby studying heart failure over the whole spectrum of ejection fraction. In one of such trials, the of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors With Heart Failure (SENORS) trial, nebivolol reduced the composite end-point of death or cardiovascular hospitalisation, but the modest trend towards improved mortality did not reach statistical significance.18

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