

EDITORIAL

Heart Failure with Preserved Ejection Fraction: A Common, Serious and Underrecognized Problem in Breathless Patients

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Heart failure is a major and increasing clinical problem. There are two broad populations of heart failure patients: those with left ventricular systolic dysfunction, a condition termed heart failure with reduced ejection fraction (HFREF), and those with a preserved ejection fraction, termed heart failure with preserved ejection fraction (HFPEF). Despite accounting for half of heart failure cases similar to HFREF, much less is known about HFPEF [1-2]. Whether HFPEF results in a similar or lower mortality than HFREF is still debatable. Initially, it was believed that mortality was similar in the two groups, as illustrated by two large studies [3-4]. However, a recent large meta-analysis of randomized controlled trials and observational studies encompassing over nearly 40,000 patients demonstrated lower mortality in HFPEF cohort compared to HFREF following adjustment for age, gender, aetiology, and history of hypertension, diabetes, and atrial fibrillation [5]. Nevertheless, just as their HFREF counterparts matched by age and gender, patients with HFPEF experience substantially reduced quality of life (QoL) as demonstrated on global well-being, general QoL, and disease-specific QoL questionnaires [6].

Whereas impressive advancements in treatment and reduction in mortality have marked HFREF, HFPEF mortality remains unchanged [3]. This is likely due to lack of successful pathophysiology- and evidence-based therapies [1]. Moreover, the treatment of HFPEF displays regional variations across the globe. In a comparison of over 70,000 patients with HFPEF admitted to United States (US) hospitals and international hospitals located in ten countries, patient demographics; length of stay; and pre-hospitalization, inpatient, and discharge therapy all differed significantly according to region [7]. For instance, US patients seem to represent a higher risk cohort, as they tend to be older and have more comorbidities such as renal insufficiency and chronic obstructive pulmonary disease than patients outside the US. The cause of this difference in admission criteria is unknown, but one postulation involves greater availability of care in the US preadmission ambulatory setting [7]. However,

overall the in-hospital mortality was similar. This finding implies that evidence-based treatment is lacking, which poses a major dilemma in the progress of HFPEF management.

While there is a simple diagnostic criteria for HFREF – left ventricular ejection fraction (EF) below 50% on echocardiography – and a well-established relationship between EF and morbidity and mortality, there is no diagnostic gold standard for HFPEF. This diagnosis is challenging and relies mainly on the judgement of individual clinicians in addition to echocardiography. Compared to their counterparts with reduced EF, HFPEF patients are more likely to be older, female, obese, hypertensive, diabetic, and hyperlipidemic. They are also frequently afflicted by other comorbidities including cerebrovascular disease, coronary artery disease, atrial fibrillation, and chronic kidney disease [8,9]. Hence, it is likely that HFPEF consists of a constellation of disorders associated with aging rather than a homogenous entity [10]. Early HFPEF research focused on diastolic dysfunction alone, but further investigations revealed a multitude of non-diagnostic pathophysiological dysfunction including left ventricular dysfunction, vascular stiffening, and chronotropic dysfunction [1,10]. Evidently, diagnosing HFPEF remains a challenge. The complex and still misunderstood pathophysiology of HFPEF represents a significant barrier to the development of consistently efficacious treatment.

The multitude of concurrent issues also renders it more difficult to pinpoint heart failure as the cause of patients' symptoms or mortality. Indeed, while classifying the mode of death is highly subjective, HFPEF patients are less likely than HFREF to die from definite heart failure or cardiovascular disease in general [11]. This may be in part explained by the difference in pathophysiology between the two conditions. For instance, arrhythmias leading to sudden cardiac death is more common in HFREF [12]. It has been postulated that the patchy fibrosis and eccentric remodelling seen in HFREF as opposed to the diffuse fibrosis and concentric remodelling of HFPEF is more conducive to potentiating arrhythmias. Moreover, the prevalence of non-cardiovascular mortality in heart failure patients is proportional to the number of comorbidities. As HFPEF patients tend to be older than HFREF patients, it is natural for them to be afflicted with more comorbidities both in terms of number and severity [12]. Unsurprisingly, therefore it has been noted that with advancing

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age, the difference in mortality between HFPEF and HFREF patients decreases, which is consistent with the relative decrease in cardiovascular deaths and increase in non-cardiovascular deaths [5]. The contribution of non-cardiovascular modes of death may also explain the inconsistent mortality rate found in different HFREF studies in different populations with different comorbidities.

In this issue of the *Netherlands Journal of Critical Care*, Franssen and Paulus review the literature on HFPEF pathophysiology, diagnosis and therapy in an attempt to provide better understanding of this still misunderstood syndrome [13]. The authors have summarized the current understanding of HFPEF and reemphasized the importance of continued investigational endeavours. They grouped pathophysiological aberrances such as diastolic dysfunction, systolic dysfunction, and exercise disturbances. Left ventricular diastolic dysfunction is attributed to myocardial stiffness due to excess collagen and altered cardiomyocyte cytoskeletal protein. Despite preserved left ventricular ejection fraction, systolic abnormalities are still present in the form of reduced longitudinal and radial shortening. The authors conclude that the 2007 European Society of Cardiology (ESC) guidelines have helped standardize the diagnosis but still fail to account for increased abnormal exertional changes and the

role of biomarkers [14]. They have identified that no large HFPEF drug trials, including angiotensin converting enzyme-inhibitors, angiotensin II receptor antagonist, beta-blockers, and digoxin, have yielded conclusive positive results. In part, this could be attributed to failure to adhere to the 2007 ESC diagnostic criteria when deciding on inclusion criteria. The authors also endorsed the ESC treatment recommendations for subsets of the HFPEF group. Though mortality in patients with HFPEF has remained steady, diagnostic criteria and our understanding of the mechanism of HFPEF is improving.

With the expected introduction of biological markers into the definition of the syndrome and further pathophysiological understanding, successful therapeutic interventions may be anticipated and a brighter future for patients with HFPEF is possible. Heart failure with preserved ejection fraction is a major burden on health care services and its investigation should retain a sense of urgency as the population ages and the incidence of heart failure continues to increase. In the meantime, before the advent of therapeutic trials demonstrating convincing impact on natural history of HFPEF, clinicians ought to take patients' complaints seriously despite normal EF and counsel on lifestyle modification believed by experts to be helpful in all forms of heart failure.

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