SCIENTIFIC EDITORIAL

Heart failure with preserved ejection fraction: Looking for new pieces of a complex puzzle

Insuffisance cardiaque à fraction d’éjection préservée : un puzzle complexe avec de nombreuses pièces manquantes

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Heart failure with preserved ejection fraction (HFpEF) is a growing public health problem \cite{1–3}. Indeed, studies of patients with heart failure (HF), such as Acute Decompensated Heart Failure National Registry (ADHERE) \cite{4}, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) \cite{5}, EuroHeart Failure Survey II (EHFS-II) \cite{6} and Épidémiologie et Traitement de l’Insuffisance Cardiace dans la Somme (ETICS) \cite{1}, indicate that 34 to 55% of patients hospitalized for HF have preserved left ventricular (LV) ejection fraction (EF). Clinical registries have consistently highlighted the clinical profile of patients with HFpEF; these individuals are predominantly elderly women with a high prevalence of hypertension, atrial fibrillation, diabetes mellitus and obesity with metabolic syndrome \cite{1–3}. The prevalence of HFpEF has increased over the past three decades, in parallel with the ageing of the population and the increasing prevalence of hypertension, atrial fibrillation and diabetes \cite{7}. In contrast, the prevalence of both coronary artery disease (CAD) and heart failure with reduced ejection fraction (HFrEF) has remained stable \cite{7}. Moreover, over the past three decades, survival has improved for HFrEF but not for HFpEF \cite{7}.

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According to current guidelines [8], the diagnosis of HFpEF requires the presence of the following conditions:

- signs or symptoms of HF;
- normal or mildly abnormal systolic LV function (LVEF > 50% and a LV end-diastolic volume index ≤ 97 mL/m²);
- evidence of diastolic LV dysfunction by echocardiography and/or haemodynamic invasive evaluation.

Unfortunately, these diagnostic criteria are often not appropriately applied to patients enrolled in clinical trials or registries, leading to great heterogeneity in the study populations. Thus, a review of 21 HFpEF studies found that the cut-off value for preserved EF (pEF) ranged from 35% to 50%, with only eight series using the recommended value of 50% [9]. Use of common diagnostic criteria in future clinical research is therefore imperative.

Echocardiography—the cornerstone for HFpEF diagnosis [10]—remains insufficiently used in elderly patients admitted to hospital for HF [11] despite the fact that early use of this technique appears associated with more intensive drug therapy and improved outcome in this population [11]. The echocardiographic features of HFpEF include increased LV mass and/or concentric LV remodelling, decreased LV longitudinal deformation, increased LV filling pressures, an enlarged left atrium, the presence of mild-to-moderate functional mitral regurgitation [12] and pulmonary artery hypertension [13,14]. The reestablishment of a compensated state in HFpEF is associated with a significant reduction in E/e’ ratio, mitral regurgitation and pulmonary pressure; this emphasizes the value of repeating an echocardiographic examination after the initiation of appropriate therapy [15].

Patients with HFpEF have a poor prognosis in general and notably display a significantly lower 5-year survival rate than age- and gender-matched controls from the general population (43% and 72%, respectively) [1]. One-year mortality rates in patients with HFpEF are dramatically lower in randomized clinical trials (4–5%) [16–19] than in registries (22–29%) because patients are frequently enrolled in the registries after hospitalization for HF and are therefore sicker than those enrolled in randomized trials [1–3]. While some registries have reported similar prognosis for HFpEF and HFrEF [2,8], randomized trials and a meta-analysis have reported better outcomes for HFpEF [20]. This apparent discrepancy may be explained by interstudy differences in the patient populations, aetologies and criteria used to diagnose HFpEF. The wide variability of CAD prevalence in HFpEF studies and the rarely documented functional significance of coronary lesions also emphasize these differences between study populations. Whether obstructive CAD presents a potential therapeutic target for reducing the high rates of death and hospitalization in a subset of patients with HFpEF certainly deserves further investigations. On the other hand, comorbidities such as diabetes, smoking, chronic kidney failure and anaemia are frequent and well documented predictors of death in patients with HFpEF [21–24]. This high comorbidity burden could explain why outcomes in recent trials of pharmacological treatments of HF were consistently found to be neutral in HFpEF [25]. Accordingly, the results of a community-based study suggested that the frequency of non-cardiovascular deaths among patients with HFpEF is high [21]. In contrast, a prospective registry found that 5-year cardiovascular mortality was similar in HFpEF and HFrEF groups [1]. Although the debate on whether HFpEF has a better or a similar prognosis to HFrEF is still ongoing, we do not consider this issue to be the most important. Given that HFpEF clearly has a documented poor prognosis, the main challenges in order to identify effective therapies and improve outcomes are to:

- better understand the complex pathophysiological features of this frequent condition;
- define subsets of patients according to aetiology;
- document the major causes of death.

Despite the presence of a large body of published data, it must be borne in mind that the pathophysiology of HFpEF is not fully understood. The involvement of many different mechanisms has been hypothesized, such as:

- increased myocardial stiffness with restrictive abnormalities of the left ventricle;
- hypertension-induced LV hypertrophy (resulting in LV diastolic dysfunction);
- impaired ventriculovascular coupling;
- combined vascular stiffening [26–28].

Peripheral changes may also have a major impact. Peripheral endothelial dysfunction in patients with HFpEF seems to be correlated with a poor outcome and future cardiovascular events [29]. Furthermore, patients with HFpEF exhibit intrarenal vascular haemodynamic alterations, the severity of which correlate with a poor outcome [30]. These findings prompted researchers to suggest that congestion can also result from extracardiac abnormalities (such as water and salt retention by the kidney). An increase in LV filling pressure could be the harbinger of water and salt retention rather than the primary cause of congestion [28]. Actually, there are many remaining unanswered questions concerning the physiopathology of HFpEF, as Burkoff et al. already pointed out in a thought-provoking editorial 10 years ago entitled ‘Have we failed to find a single effective treatment for HFpEF’ because diastolic dysfunction is too difficult to understand or manage, or is it because HFpEF has nothing to do with diastolic dysfunction at all?’ [31].

Cardiac resynchronization therapy is currently recommended as a means of relieving symptoms, boosting LV function and improving the prognosis in patients with moderate-to-severe HF, LV systolic dysfunction and prolonged QRS duration [32]. In this quest for the ‘holy grail’ (i.e. therapy that effectively improves outcomes in HFpEF), a number of landmark studies have reported mechanical dyssynchrony in patients with HFpEF. The KaRen study is a multicentre, international, prospective study designed to assess the prevalence of mechanical dyssynchrony in HFpEF [33]. In the present issue of the Archives of Cardiovascular Diseases, Donal et al. report on the study population’s baseline clinical profile [34]. The results are in agreement with the published literature: a high proportion of hypertensive women with a high comorbidity burden. The inclusion criteria were generally in line with current guidelines, although the LVEF threshold was 45%. However, it must be remembered that the test—retest variability of Simpson’s biplane technique can be as high as 6 ± 9% in stable patients, indicating that use of a cut-off value of 45% (rather than 50%) may not necessarily weaken future results from the KaRen
study [35]. The echocardiographic characteristics of the patient population are highly consistent with those of previous publications: LV hypertrophy, an enlarged left atrium and poor LV longitudinal and diastolic function. Importantly, electrical dyssynchrony was very uncommon in patients with HFP EF, since only 15.7% displayed lengthening of the QRS complex, 3.6% had left bundle branch block and 7.3% had right ventricle pacing. Although mechanical dyssynchrony was not frequently observed in the study population, a broad range of dyssynchrony parameters was found. For example, the tissue Doppler imaging time difference between the septal and lateral sides of the mitral annulus ranged from −94 ms to 301 ms. Similar results were found for strain data, indicating that marked mechanical dyssynchrony can be observed in some patients with HFP EF. Whether this mechanical dyssynchrony is linked to the clinical outcome and could be a specific therapeutic target is an important question that will require further analysis of the Kaufman registry data. Because the KaRen study population appears to be typical of HFP EF and has consistent clinical and echocardiographic findings, these data appear to form a solid basis for addressing the study’s primary objective: assessment of the role of dyssynchrony in the pathophysiology of HFP EF [36].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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