REVIEW

Heart failure with preserved ejection fraction: A systemic disease linked to multiple comorbidities, targeting new therapeutic options

Insuffisance cardiaque à fraction d’éjection préservée une maladie systémique liée à de multiples comorbidités orientant de nouvelles options thérapeutiques

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Summary
Heart failure is a pathology associated with severe morbidity and mortality. In this large field, heart failure with preserved ejection fraction (HFpEF) appears to be an increasing global health problem; it should be considered as a progressive syndrome, characterized by complex mechanisms of systemic and cardiac adaptation that vary over time, particularly with ageing. Multiple biological phenotypes contribute to the heterogeneous clinical syndrome. HFpEF emerges as a model with proinflammatory cardiovascular and non-cardiovascular coexisting comorbidities, leading to systemic inflammation and subsequent fibrosis and to diverse clinical HFpEF phenotypes. All of these aspects are often present in the elderly population, bordering on the emergence of a true geriatric syndrome. The therapeutic approach cannot be

Abbreviations: AF, atrial fibrillation; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle/ventricular; LVEF, left ventricular ejection fraction; NO, nitric oxide; NT-proBNP, N-terminal pro B-type natriuretic peptide; RV, right ventricular; sGC, soluble guanylate cyclase.

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Background

Heart failure (HF) is a pathology associated with severe morbidity and mortality and its prevalence varies from 1 to 3% in the adult population, regardless of age [1,2]. The number of individuals with HF will increase steadily over the next 20 years — the increase largely induced by projected changes in population demographics, especially related to ageing of the population [2]. In this context and in the large HF field, HF with preserved ejection fraction (HFpEF) appears to be an increasing global health problem [3].

Definition: which diagnostic and epidemiological profile for HFpEF?

Definition

HFpEF should be considered as a progressive syndrome, characterized by complex mechanisms of systemic and cardiac adaptation that vary over time, particularly in the elderly population. This progressive evolution is modulated by coexisting conditions (coronary artery disease, renal disease), tissue alterations (fibrosis, hypertrophy), anatomical alterations (dilatation, decreased contractility) and neurohormonal alterations [4], with step-by-step occurrence of haemodynamic disturbances. In 2006, a French group of HF specialists first proposed a diagnostic algorithm to confirm the existence of HFpEF with good accuracy [5]. This pragmatic proposal aimed to improve patient identification and, therefore, to allow better medical management of this population. After excluding other causes of symptoms (dyspnoea) in symptomatic patients with left ventricular ejection fraction (LVEF) ≥ 50 ± 5%, the algorithm took into consideration comorbidities often associated with HFpEF (obesity, diabetes, sleep disorders, etc.), excluding specific comorbidities that do not allow an HFpEF diagnosis (volume overload diseases, thyroid abnormalities). After this stage, consideration of the presence of structural cardiac disease was mandatory (myocardial hypertrophy, left atrial enlargement) to lead to an HFpEF diagnosis, which could eventually be confirmed after a final echocardiographic assessment of diastolic function. The following year, the Heart Failure and Echocardiography Associations of the European Society of Cardiology published a consensus statement that was very similar [6].

Recent international guidelines decided to focus on the value of LVEF as a clinically useful marker for individualizing the different types of HF [7–9]. Previously, according to the bimodal distribution of LVEF among patients with HF [10–12], HF had been classified as HF with reduced ejection fraction (HFrEF) when LVEF was < 40% and as HFpEF when LVEF was ≥ 40%. The most recent recommendations created a new subgroup — HF with mid-range (or borderline) LVEF, when LVEF is between 40 and 49% — thereby strictly
limiting HFpEF to patients with LVEF ≥ 50%. The European guidelines [8] defined some important criteria that must be present for the diagnosis of HFpEF. Symptoms and/or signs of HF must accompany the presence of LVEF ≥ 50%. However, elevated concentrations of natriuretic peptide (B-type natriuretic peptide [BNP] > 35 pg/mL and/or N-terminal proBNP [NT-proBNP] > 125 pg/mL) also have to be present, associated with at least one additional criterion: objective evidence of other structural alterations (left ventricular [LV] hypertrophy and/or left atrial enlargement) and/or functional alterations (diastolic dysfunction, mainly represented by increased filling pressures [E/e’ ≥ 13] and abnormal longitudinal relaxation [mean e’ septal and lateral wall < 9 cm/s]) underlying HF. In case of uncertainty, the recommendations suggest a stress test or invasively measured elevated LV filling pressures to confirm the diagnosis. The value of non-invasive assessment of LV filling pressures by echocardiography is always a matter of debate, but it may provide high feasibility and validation and, in particular, could be the most practical application [13].

Importance of assessment during stress
In normal subjects during exercise, LV diastolic function is important because the enhanced systolic function that underpins high levels of cardiorespiratory fitness must be matched by changes in LV filling; hence, LV diastolic dysfunction plays an early key role during stress [14]. The primary chronic symptom in patients with HFpEF, even when well compensated, is severe exercise intolerance [15]. Low peak oxygen consumption (VO₂) in patients with HFpEF is associated with reduced peak cardiac output, which is primarily caused by a blunted heart rate response, myocardial contractility and peripheral vascular vasodilator reserve [16–18]. In HFpEF, diastolic filling may be altered or associated with elevated LV pressures. Patients may have a limited capacity to increase early diastolic filling and cardiac output during exercise, without increasing filling pressures. The mechanisms that may underlie abnormal diastolic function at rest and influence functional reserve can be various [15,18] and are described later. Potential peripheral mechanisms may also limit exercise capacity, including decreased skeletal muscle mass, reduced type-1 muscle fibres and impaired blood flow in the active skeletal muscles [15,16]. Cardiopulmonary exercise testing, with or without invasive haemodynamic monitoring, may enhance the diagnosis and treatment of patients with HFpEF, particularly those with early stage disease, in whom abnormalities in haemodynamic and cardiovascular reserve may only occur during exercise, such as severe chronotropic incompetence and exaggerated blood pressure response to exercise [18].

Epidemiology
The prevalence of HFpEF increases with age, but is higher in women than in men at any given age, according to European data [2,19–21]. The overall incidence is more difficult to investigate. The values reported in Olmsted County, MN, USA, declined from 315.8 per 100,000 in 2000 to 219.3 per 100,000 in 2010, corresponding to a decline of 37.5% over the study period [2,22]. However, as for prevalence, the incidence increases with advancing age [2,23]. Age and female sex are two major risk factors associated with HFpEF [19–28], even if the higher percentage of women with HFpEF is, in part, related to the age distribution of the population at highest risk of HFpEF [2]. In the context of age, patients with HF, regardless of LVEF, also have multiple chronic conditions [12,29,30]. However, patients with HFpEF (both men and women) have more comorbidities (very often four or more) than those with HFrEF [2,29].

In the community, since the beginning of the 21st century, approximately 45–50% of patients with HF have HFpEF [2,31]. In the past, conflicting results about the mortality of HFpEF compared with HFrEF have been reported [21,24,26,27,32–36]. Two meta-analyses, including 24,501 and 73,597 individuals with HF, reported a significantly lower risk of death in HFpEF than in HFrEF [37,38]. More recently, data from the Get with the Guidelines — Heart Failure (GWGT — HF) registry showed that patients hospitalized for HFpEF had a similar poor survival at 30 days, 1 year and 5 years from admission compared to patients with HFrEF [31,33]; however, they had a lower risk of cardiovascular and HF readmission [31]. Causes of death distribution differ between HFrEF and HFpEF [39]. From data reported in randomized clinical trials, cardiovascular death in HFrEF represents about 80–85% of all deaths, predominantly consisting of worsening HF and sudden cardiac death. In contrast, cardiovascular death in HFpEF represents only about 60–70% of all deaths, and consists of worsening HF and sudden death, but also myocardial infarction, vascular death (aortic aneurysm, pulmonary embolism) and cerebrovascular death (intracranial haemorrhage, ischaemic stroke) [39,40]. Important causes of death are the result of other non-cardiovascular aetiologies, such as renal, respiratory, infectious or malignant diseases. Clinical experience suggests that HF death in HFrEF is not a classic pump failure, as in HFrEF, but in many cases involves progressive pulmonary hypertension, right ventricular (RV) failure, renal venous congestion and worsening renal function with ensuing multiorgan dysfunction [41–43], thereby misclassified as worsening HF in randomized trials. Similarly, sudden death may be presumed to be a sudden cardiac death related to a ventricular tachyarrhythmia [40], as in HFrEF. However, this linear pathway may not be true for many patients with HFpEF, because of the complexity of the disease process and the high rates of non-cardiovascular comorbidities [39]. Furthermore, more than half of all deaths can sometimes be attributed directly to right HF [44], showing that the right ventricle may be a meaningful therapeutic target in a subset of patients [45–47].

Pathophysiology: purely a diastolic cardiac disease or global systolic and diastolic dysfunction interplaying with multiple other altered mechanisms?
Recent concepts have now been well established: rather than being caused solely by diastolic dysfunction, HFpEF is caused by the complex interplay of multiple impairments, concerning many different organs in addition to the heart and vessels [48–51].
Diastolic dysfunction

Diastolic dysfunction is defined as the inability to fill the ventricle to an adequate preload volume at acceptably low pressures [52]. In the absence of hypertrophy, patients with HFP EF have either concentric remodelling or even normal LV geometry [53,54]. Thick and less elongated cardiomyocytes are associated with increased collagen content [55,56]. In a normal left ventricle (LV) at rest, the increase in pressure during diastole is minimal, with normal LV end-diastolic pressure despite large increases in LV chamber volume. At exercise, a dynamic reduction in LV minimal diastolic pressure occurs, related to enhanced LV early diastolic suction to prevent high left atrial pressures in response to an increase in venous return [48,57]. In HFP EF, the resting diastolic pressure-volume relationship is shifted up, with a prolonged relaxation time, indicating increased diastolic ventricular passive stiffness [51]. In addition to delayed relaxation, some mechanisms (speed of relaxation, mitral annular longitudinal motion, LV untwisting occurring during early diastole and end-systolic volume achieved in the preceding contraction cycle) are impaired [48,58], leading the LV to be filled only at the expense of high left atrial pressures. At exercise, a further shift upwards occurs, reflecting inadequate LV early diastolic suction, and contributing to a dramatic increase in LV end-diastolic pressure filling, leading to a need for high left atrial pressures to push blood into the chamber [48,57]. Thus, an abnormal LV diastolic response to exercise (defined by an exercise-induced increase in the E/e’ ratio) is a major haemodynamic abnormality in HFP EF [59]. Abnormal diastolic and systolic responses to exercise are associated with an increased risk of adverse clinical outcomes in HFP EF, including both death and hospitalization. These exertional measurements of E/e’ and LV myocardial deformation appear to be superior to those obtained at rest, in terms of prognosis [60].

Systolic dysfunction

HFP EF cannot be considered only as a disorder characterized by LV diastolic alterations. Systolic dysfunction may always be involved, even if the LVEF value remains in the normal range [61]. In the past, pathophysiological progression of chronic HF has been visualized by depicting cardiac performance as a time trajectory, declining progressively over time with three successive, somewhat arbitrary, major phases: systolic activation, systolic dysfunction — both with “preservation of ejection fraction” — and, finally, haemodynamic pump failure with deterioration of LVEF [61]. Preserved ejection fraction merely indicates that overall cardiac performance as a haemodynamic pump is adequately compensated, despite substantial systolic dysfunction of the muscular pump [61]. LV radial function is often long preserved, with consequent preservation of ejection fraction. However, there is an early alteration to LV longitudinal contraction, leading to subtle systolic dysfunction [62,63]. Myocardial strain assessed by two-dimensional speckle tracking identifies early the subtle systolic component as a result of structural abnormalities, even in asymptomatic subjects [64,65]. Clinical meta-analysis confirms that the longitudinal systolic function of the LV is significantly altered in a high proportion of patients with HFP EF, despite a normal LVEF range [66], with high prognostic value [66–68]. Furthermore, a correlation exists between the degree of longitudinal dysfunction, assessed by two-dimensional speckle tracking, and circulating biomarkers of fibrosis in patients with hypertension or diabetes and HF [69]. These subtle abnormalities in systolic function might have severe consequences during stress. Although LVEF is preserved at rest, enhancement in LVEF with stress is markedly limited in HFP EF [48,70], related to the inability to reduce chamber volume to a sufficiently low end-systolic volume, rather than to a limitation in the increase in end-diastolic volume. Thus, limited stroke volume reserve coupled with the common presence of chronotropic incompetence significantly limits limits cardiac output in response to exercise in HFP EF [48,71].

Left atrial dysfunction and atrial fibrillation

The left atrial cavity is in direct contact with the LV during the diastolic phase, so it is exposed to LV pressures throughout the diastolic time. Left atrial remodelling and dysfunction may represent a picture of chronic average LV pressure history [72]. Patients with HFP EF may be more reliant on left atrial contraction to achieve LV filling compared with healthy controls. In advanced HFP EF, progressive atrial dilatation and loss of atrial contractile reserve occur, particularly with stress [73]. Occurrence of left atrial remodelling, leading to loss of atrial function, is an important factor in the evolution of HFP EF. A complete left atrium assessment by echocardiography, combining a volumetric approach and a functional approach by strain measurement [74,75], should be integrated into the algorithm for evaluating LV filling pressures [74]. However, the evaluation and combination of several echocardiographic variables are probably needed, with the association of an instantaneous, but also chronic marker of filling pressures.

Atrial fibrillation (AF) is common in HF; HF predisposes AF and vice versa. HFP EF and AF are age-related conditions that are increasing in prevalence, commonly coexist and share clinical features [76]. The prevalence of HFP EF in patients with AF varies between 8 and 24%, and HFP EF is more common in those with a longer AF duration [76,77]. The prevalence of AF in patients with HFP EF varies between 15 and 41% [76]. The prevalence of AF decreases with decreasing LVEF; however, the prevalence is higher in men, and increases with age [78]. Adverse event rates (deaths, HF hospitalizations and cerebral events) are slightly greater in HFP EF than in other LVEF groups and considerably worse in AF versus sinus rhythm [78].

Pathophysiological mechanisms [76] may involve common risk factors (systemic inflammation, neurohormonal dysregulation, endothelial dysfunction, valvular alterations, chronotropic incompetence) and comorbidities (ageing, hypertension, obesity, obstructive sleep apnoea syndrome) that predispose to both conditions simultaneously. Furthermore, mechanisms such as structural and functional remodelling of the left atrium, by which HFP EF gives rise to AF and mechanisms by which AF leads to HFP EF (reduced ventricular filling, LV myocardial fibrosis, systolic dysfunction induced by left atrial dilatation, impaired atrial...
function and atrial fibrosis) are also involved in the complex relationship between AF and HFP EF.

### Right heart dysfunction

It is now well recognized that right heart dysfunction is common in HFP EF, and contributes importantly to poor prognosis [44–47,79]. Increased RV diastolic stiffness, ventricular interdependence and pulmonary hypertension are mainly involved in RV dysfunction [46,48,79,80]. Cardiac and non-cardiac comorbidities frequently present in HFP EF are known to alter RV myocardial structure and function independently [30,79,81]. A meta-analysis [80] has shown that both RV dysfunction (assessed by measuring tricuspid annular plane systolic excursion and fractional area change [82]) and pulmonary hypertension are associated with poor outcome in HFP EF.

### Other involved cardiovascular abnormalities

Ventricular dyssynchrony is prevalent and in relation to the importance of diastolic dysfunction [48,81,83,84], even if electrical dyssynchrony appears to be very uncommon in patients with HFP EF [85]. In addition, evidence exists that chronotropic incompetence, witnessed by limitation of increase in heart rate at exercise, is associated with autonomic dysregulation in HFP EF [17,86].

Vascular stiffness is responsible for the inability to vasodilate, which—in association with limitations in systolic reserve—leads to dynamic limitations in ventricular-arterial coupling in patients with HFP EF [48,87]. Central aortic stiffness, increasing systolic load and negatively affecting ventricular-vascular coupling, may accelerate HF development in at-risk patients. Aortic stiffness increases with age, particularly in women with hypertension, and is a precursor of incident HFP EF [49,88,89]. In older adults, wave reflections travel quickly, arriving back in the proximal aorta while the LV is still ejecting blood in systole. This early arrival of wave reflections increases the mid-to-late systolic workload of the LV and profoundly impacts the LV loading sequence (late relative to early systolic load). When LV pump function is preserved, the reflected wave typically induces a late systolic pressure peak in the pressure waveform, augmenting aortic pressure in mid-to-late systole [90]. Combined ventricular-vascular stiffening is a hallmark of HFP EF [49,53,91].

A recent study has shown that coronary microvascular ischaemia is independently associated with diastolic dysfunction, a detectable increase in troponin being significantly associated with diastolic dysfunction only in the presence of coronary microvascular ischaemia, even in the absence of obstructive coronary artery or overt structural heart disease [92]. Microvascular endothelial dysfunction decreases nitric oxide (NO) bioavailability, and increased profibrotic cytokine signalling may contribute to the reduced coronary microvascular density or rarefaction and increased myocardial fibrosis observed in HFP EF [30,92,93].

So, many cardiac and extracardiac factors are involved in the pathophysiology of HFP EF (Fig. 1), leading to difficulties in managing and treating the disease.

### Comorbidities: simple risk factors or effective aetiologies?

Many comorbidities may be involved in the pathophysiology of HFP EF [29], influencing pathophysiological pathways, either by each acting on a separate vascular or myocardial target with a global additional effect or by one comorbidity alone acting on all targets together, leading to the same results in terms of consequent abnormalities [50]. In a recent study [94] using the predefined MAGGIC risk factors [95], patients with HFP EF had relatively fewer cardiovascular and extracardiac risk factors than patients with HFrEF. Conversely, the demographic burden was higher in patients with HFP EF. There was a clear association between the incremental burden of extracardiac disease and risk of cardiovascular outcomes, irrespective of LVEF. However, extracardiac burden contributed more than cardiac burden to death, HF hospitalization, myocardial infarction and stroke in patients with HFP EF [96]. Thus, complex associations between comorbidities themselves, as well as between comorbidities and the cardiovascular system, lead to the development of HF—both HFP EF and HFrEF [97]. It has been suggested that HFP EF is the result of a constellation of comorbidities, including being overweight/obese, diabetes mellitus, chronic obstructive pulmonary disease and hypertension, which induce a systemic proinflammatory state [12,30,98]. For these reasons, HFP EF is not a well-defined clinical entity: it rather appears to be the result of an amalgam of cardiovascular, metabolic, renal and geriatric conditions [98–100].

Five comorbidities are highlighted below, to illustrate the different clinical phenotypes, all of which may be involved in the development of HFP EF.

### Systemic hypertension: a model for HFP EF as a complex comorbidity-related disease

Hypertension and age are major risk factors for HFP EF [20,21,25–27,32]. Four common clinical HFP EF phenotypes have been described, combining hypertension with ageing, obesity, pulmonary hypertension and coronary artery disease [100]. However, hypertension is one of the major modifiable risk factors in the development and progression of HFP EF [9,101,102]. The traditional model of HFP EF pathophysiology emphasizes the role of systemic hypertension causing increased afterload on the LV, leading to LV hypertrophy and subsequent LV diastolic dysfunction [51,103–105]. However, while diastolic dysfunction and LV hypertrophy may lead to HF, a significant proportion of patients with HFP EF do not have evidence of LV hypertrophy or concentric remodelling on their echocardiogram, or have normal diastolic function [53,106]. Conversely, many older adults have LV hypertrophy with preclinical LV diastolic dysfunction, but do not have clinical evidence of HFP EF. This suggests that, while hypertension is an important factor in the development of HFP EF, the true mechanisms are more complex than the traditional model implies [102]. A new paradigm for HFP EF development was proposed recently, where comorbid conditions (including hypertension, diabetes, obesity and chronic obstructive pulmonary disease, which are among the most frequent comorbidities
involved) promote a systemic proinflammatory state that starts a downstream cascade, leading to the development of HFrEF [12,100,102,107,108]. It is postulated that systemic inflammation leads to coronary microvascular endothelial dysfunction [92], with subsequent reductions in NO bioavailability, cyclic guanosine monophosphate (cGMP) content, and protein kinase G activity. The reduction in protein kinase G activity promotes cardiomyocyte hypertrophy, as well as decreased titin protein phosphorylation, which increases passive stiffening. Endothelial dysfunction also allows for migration of inflammatory cells into the interstitial space, causing collagen deposition and further ventricular stiffening [30,102,109,110]. Finally, in addition to increased afterload and LV hypertrophy, hypertension might contribute to a proinflammatory state that is potentially associated with multiple pathophysiological mechanisms described above (abnormal ventricular stiffness, ventricular-arterial coupling, peripheral microvascular function, systolic reserve and chronotropic response) [99,102].

Being overweight/obese: a model for HFrEF as a distinct phenotype-related disease

Increased body mass index is a recognized risk factor for both types of HF [111,112], particularly for the development of HFrEF in association with hypertension, age and sex [111]. Obesity has reached epidemic proportions worldwide, and is a common modifiable risk factor for HFrEF [50,113]. Obesity has been associated with LV hypertrophy and incipient LV dysfunction [114,115], and was reported in one third of the participants in the I-PRESERVE trial [116]. Central obesity is a major determinant of arterial stiffness [117,118]. Obesity has many deleterious effects on the cardiovascular system, mediated by cardiac loading, tissue metabolism and systemic inflammation, thereby promoting HFrEF progression [119–121]. It has been shown that patients with the obese HFrEF phenotype display greater plasma volume expansion, more biventricular remodelling, greater RV dysfunction, worse exercise capacity, more profound haemodynamic derangements on exercise and impaired pulmonary vasodilation compared with control patients and non-obese patients with HFrEF [121]. All the pathophysiological disturbances previously described can be present in obese people, and cause the development of HFrEF [100,121]. Increased adiposity promotes inflammation, hypertension, insulin resistance and dyslipidaemia, and impairs diastolic and systolic LV function, vascular function, skeletal muscle and physical function [122–125], all of which are abnormal in patients with HFrEF, and contribute to its pathophysiology [30,123,126]. Inflammation induces dysregulation of the NO-cGMP-protein kinase G signalling cascade. Adiposity-induced inflammation has cardiac and vascular adverse effects, including endothelial dysfunction and mitochondrial dysfunction [30,124].

HFrEF is common in those who are overweight or obese [113,116,127]. This phenotype is frequently associated with insulin resistance, characterizing the metabolic syndrome, which combines abdominal obesity, dyslipidaemia, hypertension and type-2 diabetes. Insulin resistance decreases myocardial energy supply [128,129]. In a second step, reductions in cardiac efficiency, adenosine triphosphate (ATP) production, myocardial perfusion and relaxation constitute remodelling processes, often based on insulin resistance, leading to myocardial cell damage, then to contractile dysfunction and/or HF [30,113,130,131]. These abnormalities can be responsible for the establishment of a metabolic cardiomyopathy [129,132,133].

Kidney disorders: a model for HFrEF as a cause- or consequence-related disease

It has long been recognized that HF and renal dysfunction form a detrimental combination [134,135]. Kidney dysfunction has been suggested to be involved in the pathogenic processes of HFrEF [136–138], with an increased risk of mortality [134,135,139]. In patients with
HFpEF, chronic kidney disease is independently associated with increased cardiac remodelling and significantly worse cardiac mechanics and outcome [139]. Renal insufficiency causes systemic inflammation and oxidative stress. Abnormal kidney function is probably also required to produce salt-sensitive hypertension [140]. However, fluid overload may be even more important than the presence of hypertension itself. Furthermore, in patients with chronic kidney disease, cardiovascular events are more likely in those with modest degrees of fluid overload, with or without concomitant hypertension [141]. Abnormalities in the ability of the kidney to maintain sodium and fluid balance might precede the development of HFpEF [137,142]. The syndrome of volume overload confers further cardiovascular injury and risk, and may perpetuate the condition of HFpEF in a vicious cycle, thereby leading to HFpEF possibly being considered as a cardiorenal syndrome [137]. Uremic toxins increase oxidative stress, leading to vascular smooth muscle cell dysfunction [143]. Moreover, dialysis might alter microvascular dysfunction and cause myocardial stunning [81,143,144]. On the other hand, cardiac remodelling in HFpEF might cause worsening renal function. HFpEF presents with both increased filling pressures and an alteration in arterial-ventricular coupling, resulting in reduced renal blood flow and the establishment of renal dysfunction [81]. Furthermore, common pathophysiological alterations are frequently found in HFpEF and kidney disease, such as activation of the renin-angiotensin system and endothelial dysfunction [30,138]. It is often difficult to know which is the chicken and which is the egg!

**Lifestyle and socioeconomic risk factors: a model for HFpEF as a behavioural disease**

Comorbidities for HFpEF are often diagnosed and treated in the clinical setting to prevent or improve HFpEF, given the lack of effective primary treatments for the disorder [145]. In this context, lifestyle risk factors, such as physical inactivity and obesity, play an important role in the development of HFpEF [111,146,147]. Low fitness and physical inactivity, reflecting a sedentary lifestyle, are associated with many of the underlying cardiac and skeletal muscle abnormalities often present in HFpEF [148–150], thereby contributing to diastolic dysfunction and concentric hypertrophy, both of which are determinants in HFpEF development [148]. There is a dose-response relationship between physical activity level and incident HFpEF, but not HFrEF, as well as a dose-response relationship between body mass index and increased risk of HFpEF [151]. The protective effects of leisure-time physical activity against HFpEF risk may be related to the direct effect of regular physical activity and fitness on the key pathophysiological determinants of HFpEF development, including systemic inflammation, cardiac structure and function, visceral adiposity and peripheral (skeletal muscle) oxygen extraction and utilization [113,124,152,153]. The potential humoral factors involved in the pathogenesis of sedentary lifestyle-induced cardiac and extracardiac dysfunction (and amelioration with exercise) appear to be multiple [154].

In the same manner, a relationship between socioeconomic deprivation and mortality exists in HF [155,156], mixed with the impact of physical and psychological impairment, assessed by frailty [157]. Among socioeconomic factors, limitations of activities of daily living may be the independent pejorative socioeconomic factor most strongly associated with all-cause and cardiovascular mortality in HFpEF [158], particularly in elderly people [159]. In addition, living alone or not having a professional occupation is independently associated with higher cardiovascular mortality [158]. It is well known that in the elderly, being married is associated with a lower risk of depression [160,161], and depression is reported to be associated with poor prognosis in elderly patients with HF [162].

**Aging: a model for HFpEF as a true geriatric syndrome**

Important changes occur in the cardiovascular system when healthy adults grow old [163]: thickening and stiffening of the large arteries, leading to an increase in systolic blood pressure; increased end-diastolic stiffness as a result of concentric wall thickening of the LV, not accompanied by changes in the cavity size; and progressive age-related decline in early diastolic relaxation, associated with an increase in late diastolic filling as a result of atrial contraction preserving end-diastolic volume [163–165]. These age-related changes are associated with an accelerated reduction in exercise capacity in the elderly [159,163,166], even if diastolic function is well preserved in healthy older subjects who have exercised throughout their lives [15]. This cardiovascular ageing reflects the normal evolution of the heart and vessels, and does not appear as pathological in the absence of symptoms or signs. However, many comorbidities are often present in older adults, associated with lifestyle alterations, and can introduce a destabilization of the frail “normal” cardiac function that is already presenting some pathophysiological disturbances, leading to the appearance of the clinical status of HFpEF, thereby bordering on the emergence of a true geriatric syndrome [48,167].

So, many comorbidities are present in HFpEF, and can be strongly related to HFpEF, as either causes or consequences of the disease, by means of many different biological pathways, largely as a result of proinflammatory coexisting conditions (Fig. 2).

**Treatment: is it possible to find an effective therapy for HFpEF?**

No proof of efficacy for any drug

Survival improved over three 5-year periods (1987–1991, 1992–1996 and 1997–2001) among patients with HFrEF, but not among patients with HFpEF [27]. This probably reflects the lack of efficacy in HFpEF of new drugs that have appeared successively in the HF therapy field. However, in a European survey, it appeared that whatever the drug prescribed, the effect on morality (beneficial or detrimental) was similar for each type of drug in patients with HFrEF or HFpEF, with a lack of statistical evidence for a heterogeneous effect of any agent [26]. Large pharmacological intervention trials were thus necessary, and were applied in
HFpEF, based principally upon effective therapies in HFrEF prescribed to control neurohormonal abnormalities, with the hope of achieving a similar gain in terms of reduction in morbimortality rates [8,9]. Unfortunately, these different classes of drugs appeared to be unsuccessful in HFpEF: angiotensin-converting enzyme inhibitors (perindopril in the PEP-CHF trial) [168]; angiotensin-receptor blockers (can- desartan in the CHARM-Preserved trial and irbesartan in the I-PRESERVE trial) [169,170]; aldosterone-receptor blockers (spironolactone in Aldo-DHF and TOPCAT trials) [171,172]; and beta-blockers (nebivolol in the SENIORS study) [173].

As an elevated heart rate appears to be a predictive factor for worse outcomes and increased mortality in patients with HFpEF [174], a recent trial (EDIFY) [175] assessed ivabradine in a proof-of-concept study, based on its ability to reduce cardiac fibrosis and improve vascular stiffness and LV diastolic function [176,177], in addition to having a favourable effect in terms of heart rate reduction. Unfortunately, as for all other drugs tested in HFpEF, the study failed to show any beneficial effect on the specified outcome criteria, despite a significant heart rate reduction [178]. Secondary to the results of the TOPCAT study, some differences were shown according to the international geographical regions of the patients included. These differences were notably greater for HFpEF than for HFrEF, mainly for HF hospitalization [172]. A retrospective analysis of some large HF trials showed consistent results with those of TOPCAT [179]. Possible explanations might be found in international geographic variations in the diagnosis and management of patients with HFpEF, in the type and frequency of comorbidities (smoking habits, diabetes, cancers, but also differences in lifestyle) and in possible differences in patient selection, including physician or patient willingness to enrol [180] and local health-care system organization and practice [181].

Considerable efforts have been made with risk stratification to identify patients and potential mechanisms that might be targets for therapy while strong benchmarks are missing. Moreover, an integrative and comprehensive approach is essential, with careful consideration of mimickers and may help in the design of future clinical trials. In this context, patients with HFpEF are often elderly with many comorbidities [45]. Thus, trial-selected patients might be poorly representative of patients treated in routine clinical practice. Pooled analyses of observational cohort studies, with or without use of propensity score analysis, showed that renin–angiotensin–aldosterone inhibitors were associated with reduced mortality in HFpEF, even if no benefit was seen in the pooled analysis of randomized controlled trials [180,181]. Similarly, meta-analyses, with or without pooled analysis of observational cohort studies and with or without propensity score analysis, showed that beta-blockers were associated with improved survival. However, beta-blocker use was not significantly associated with a reduced risk of HF hospitalization [182–184]. Given the difficulties associated with demonstrating strong efficacy for the usual cardiovascular classes of HF drugs in HFpEF, patient education programmes might be of great value, and are recommended in the care management of patients with HF [8,9]. It appears that a patient education programme can be effective in reducing all-cause mortality in HFpEF, independent of the treatment used [185].

What are the therapeutic hopes for the future?

Some new mechanistic approaches have been proposed and should be now tested in randomized placebo-controlled trials. Natriuretic peptides represent a first conceptual approach; they are secreted in response to cardiac myocyte stretch because of increased myocardial wall tension to defend the heart from volume and pressure overload—a deficient protective mechanism early in the development
of HFpEF [186]. Nephrilysin inhibition, by blocking the breakdown of natriuretic peptides, should increase this endogenous defence mechanism [187]. In the PARAMOUNT study [187], the angiotensin receptor nephrilysin inhibitor LCZ696 reduced NT-proBNP to a significantly greater extent than valsartan after 12 weeks of treatment in patients with HFpEF, with an additional reduction in left atrial size, indicative of reverse left atrial remodelling [187]. A large mortality trial (PARAGON-HF) is now under evaluation [188].

NO stimulation therapy is a second form of therapeutic approach. The haemodynamic effects of nitrates might attenuate pulmonary congestion caused by exercise and improve exercise capacity in HFpEF [189]. Data from previous studies indicate that 15–50% of patients with HFpEF are treated with nitrates [168–170,172]. However, in the NEAT-HFpEF trial [190], isosorbide mononitrate did not improve the daily activity level, submaximal exercise capacity or perceptive exercise tolerance in patients with HFpEF. The lack of improvement in exercise tolerance and the adverse effect on daily activity levels may relate to the pathophysiological abnormalities common in HFpEF, thereby limiting the haemodynamic benefits of nitrates [91,189,191]. Moreover, like NO donors, phosphodiesterase-5 inhibition by sildenafil did not improve exercise capacity and clinical status in patients with HFpEF [192,193].

Molecular targets for therapy might also be candidate pathways that could be promising, including the systemic inflammatory axis, endothelial and microvascular dysfunction and cGMP/protein kinase G signalling [113,194], all of which are potentially influenced or induced by the comorbidities related to HFpEF. Insufficient generation of cGMP by soluble guanylate cyclase (sGC) may contribute to the pathophysiology of HFpEF via cardiac, vascular and peripheral mechanisms [110,195]. Direct stimulators of sGC differ from other agents targeting the cGMP pathway in their NO-independent capacity to increase sGC activity [196] and could be promising therapeutic agents in HFpEF [195]. The novel once-daily sGC stimulator vericiguat was studied in the SOCRA TES programme, in which the SOCRA TES-PRESERVED study aimed to characterize the safety, tolerability and pharmacodynamic effects of vericiguat in patients with HFpEF [197]. The study showed that NT-proBNP concentrations and left atrial enlargement were not reduced by vericiguat in patients with HFpEF compared with placebo at 12-week follow-up. However, patient-reported symptoms and physical limitations were improved in patients receiving the two higher doses of vericiguat [198], supporting the hypothesis that cGMP elevation in response to the direct sGC stimulation capacity in the absence of NO by vericiguat differs from NO donors or phosphodiesterase-5 inhibitors.

Devices have been also tested in the therapeutic field of HFpEF. Cardiac resynchronization remains under evaluation [48,59,81,84], although electrical dys synchrony appears to be very uncommon in patients with HFpEF [85].

Transcatheter renal denervation is an investigational technique that can reduce the activity of the sympathetic nervous system [199]. Renal denervation has been shown to improve natriuresis, diuresis and cardiac and renal function in HFrEF, which are also important endpoints in HFpEF [199]. Furthermore, in patients with hypertension, renal denervation reduces LV mass, stiffness and filling pressures, which are common pathological features of HFpEF [200]. While the procedure appears to be relatively safe (although two patients did require intraprocedure renal artery dilatation), the study testing transcatheter renal denervation in HFpEF was unable to show improvement in quality of life, exercise function, biomarkers and left heart remodelling because of early termination and underpowering caused by difficulties in recruitment [201].

Effort intolerance in HFpEF is associated with an increase in left atrial pressure during exercise, with consequent pulmonary congestion [57], leading to symptoms and increased morbidity and mortality [202]. An appropriate iatrogenic left-to-right atrial shunt might attenuate exercise-induced increase in left atrial pressure in patients with HFpEF [203]. A randomized blinded sham-controlled trial was designed to test this hypothesis [204–206], and recently showed that a greater reduction in capillary wedge pressure during exercise was obtained compared with a sham control procedure after creating an 8 mm interatrial communication in patients with LVEF ≥ 40%. The procedure was safe, suggesting a need for a larger-scale randomized clinical trial.

What are the therapeutic recommendations?

Given all the comorbidities associated with the many pathophysiological mechanisms and/or biological pathways involved in HFpEF, it is evident that a single drug or class of drugs cannot be efficient in the therapeutic management of the disease. Defining HFpEF solely as a cardiac disease is thus not possible; it appears, rather, to be a systemic heterogeneous syndrome. Hence, successful treatment of HFpEF requires a thorough understanding of these contributing entities [113,207,208]. The European recommendations [8] establish that no treatment has yet been shown to reduce morbidity or mortality convincingly in patients with HFpEF. However, as these patients are often elderly and highly symptomatic, and frequently have a poor quality of life [209], an important aim of therapy may be to alleviate symptoms and improve well-being [210]. Regarding the proposals made by Margaret M. Redfield [12], the medical treatment strategy for HFpEF might consider the systemic heterogeneous disease. First, the volume overload, if present, must be treated with diuretics. After this first step, the second stage is the treatment of all coexisting conditions separately, with the appropriate therapies. The last step is to educate patients about HF and self-care and to propose aerobic exercise training. This approach has been chosen by the European recommendations, proposing treatment of both cardiovascular and non-cardiovascular comorbidities (class I, level of evidence C), and diuretics for congested patients (class I, level of evidence B) [8]. The future medical and non-medical treatment strategies should take into consideration the different systemic and myocardial signalling present in HFpEF, as well as the diverse phenotypes involved in the HFpEF patient population [113,207,208] (Fig. 3).

Conclusions

HFpEF is not a true cardiac disease, but rather a systemic disease with morphological and functional heterogeneity. Clinical manifestations of HFpEF appear to be the consequences of other underlying pathologies not or insufficiently
New therapeutic options for HFrEF

Figure 3. An integrative and comprehensive therapeutic strategy in heart failure with preserved ejection fraction (HFrEF). First, the strategy should combine symptomatic therapies and the separate appropriate therapies for all coexisting conditions. Future medical and non-medical treatments will be based on the different systemic and myocardial signalling and the various phenotypes involved in HFrEF. Last, but not least, patient education and exercise training should always be considered systematically. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; cGMP: cyclic guanosine monophosphate; GLP: glucagon-like peptide; HDL: high-density lipoprotein; HFrEF: heart failure with reduced ejection fraction; IL: interleukin; MRA: mineralocorticoid receptor antagonist; NO: nitric oxide; PDE: phosphodiesterase; RNA: ribonucleic acid; SERCA: sarco/endoplasmic reticulum calcium adenosine triphosphatase; sGC: soluble guanylate cyclase.

HFrEF

Phenotype treatment strategies considering associated comorbidities
- Systemic hypertension
- Overweight/Obesity/Diabetes mellitus
- Renal dysfunction
- Coronary artery disease
- Chronic obstructive pulmonary disease
- Ageing specific conditions

Symptomatic treatment
- Pulmonary congestion
- Pulmonary hypertension
- Chorea
tic incompetence
- Muscle deconditioning

Device therapies
- Resynchronization
- Ventricular shunt

Which place for traditional neurohormonal modulation?

Failure of usual recommended drugs in HFrEF:
- ACE inhibitors (perindopril)
- ARBs (candesartan, irbesartan)
- MRA (spironolactone)
- Beta-blockers ( nebivolol)
- I/ blockers (ivabradine)

Lifestyle management
- Exercise training
- Patient education

Future pharmacological approaches of biological pathways involved in the proinflammatory comorbidity-related state
- Systemic inflammatory axis
  - Cytokin inhibitors
  - IL-1 antagonists
  - Colchicine
- cGMP/protein kinase G signalling
  - NO donors (nitrate, nitrates)
  - Activators of endothelial NO-synthase
  - PDE family (PDE-5 and PDE-9) inhibitors
  - Direct sGC stimulators (vericiguat, riociguat)
- ARB/Neprolysin inhibitors
- Extracellular matrix and collagen controlling
  - Spironolactone
  - Torasemide
  - Matrix métalproteinase inhibitors
- Modulation of calcium homeostasis
  - RAN sliding receptor stabilizers
  - SERCA-2 modulators
- Modulation of myocardial energy
  - GLP-1 analogues
  - Sodium-glucose cotransporter-2 inhibitors
- Other future potential therapies
  - Cell therapy
  - HDL stimulators
  - MicroRNAs

HFrEF

treated. HFrEF emerges as a model with proinflammatory cardiovascular and non-cardiovascular coexisting comorbidities, frequently present in the elderly, constituting a potential geriatric syndrome. The therapeutic approach cannot be uniform, and must involve management of the different comorbidities according to a phenotype treatment strategy, respecting the pharmacological approaches to the biological pathways involved in the proinflammatory comorbidity-related status. Future studies should consider these multiple, potentially distinct HFrEF phenotypes, in the hope of improving survival in a disease that is the most common cardiovascular disorder with no effective therapies.

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