Is heart failure with preserved ejection fraction a 'dementia' of the heart?

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Abstract

Heart failure with preserved ejection fraction (HFpEF) remains an elusive entity, due to its heterogeneous clinical profile and an arbitrarily defined nosology. Several pathophysiological mechanisms recognized as central for the development of HFpEF appear to be in common with the process of physiological aging of the heart. Both conditions are characterized by progressive impairment in cardiac function, accompanied by left ventricular hypertrophy, diastolic dysfunction, sarcomeric, and metabolic abnormalities. The neurological paradigm of dementia—intended as a progressive, multifactorial organ damage with decline of functional reserve, eventually leading to irreversible dysfunction—is well suited to represent HFpEF. In such perspective, certain phenotypes of HFpEF may be viewed as a maladaptive response to environmental modifiers, causing premature and pathological aging of the heart. We here propose that the 'HFpEF syndrome' may reflect the interplay of adverse structural remodelling and erosion of functional reserve, mirroring the processes leading to dementia in the brain. The resulting conceptual framework may help advance our understanding of HFpEF and unravel potential therapeutical targets.

Keywords HFpEF · Cardiac aging · Dementia · Calcium handling · Myocardial fibrosis · Left ventricular hypertrophy

Under the broad label of heart failure with preserved ejection fraction (HFpEF) lays diverse entities, with partially diverging clinical trajectories [1]. At least three HFpEF phenotypes have been recognized: the subset of patients with clear structural and functional cardiac abnormalities prevailing over systemic impairment (i.e. what could be defined as 'cardiocentric' HFpEF), as opposed others in which extracardiac abnormalities prevail and cardiac modifications are less pronounced, such as the obese-HFpEF phenotype and the renal-HFpEF phenotype [2–5]. Multiple pathophysiological mechanisms have been described and applied across the HFpEF spectrum, in an attempt to find a unifying paradigm for all phenotypes—yet, HFpEF remains a composite entity and largely a diagnosis of exclusion.

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This gap in knowledge has two substantial implications. First, it contrasts with the epidemiological importance of the condition—HFpEF currently accounts for > 50% of HF cases [6, 7]. Second, HFpEF remains difficult to interpret, due to its heterogeneous and arbitrarily defined nosology [1–3]. For example, patients enrolled in dedicated clinical trials with a diagnosis of HFpEF often lack its defining hallmarks, such as, in up to one-third of cases, diastolic dysfunction or left ventricular hypertrophy (LVH) [1, 2]. Furthermore, primary myocardial diseases are generally excluded from the definition of HFpEF, even though they often present with a clear 'HFpEF syndrome' [4], instrumental to our understanding of this composite entity [8].

Several pathophysiological mechanisms recognized in HFpEF appear to be in common with the process of physiological aging of the heart [9]. Both conditions are characterized by progressive impairment in cardiac function accompanied by LVH, diastolic dysfunction, and sarcomeric and metabolic abnormalities. In a perspective in which biological age supersedes chronological age, HFpEF might therefore be viewed as a maladaptive response to stress causing premature aging of the heart [10] (Fig. 1). It may be both hypothesis-generating and clinically useful to envisage such pathophysiological continuum, in order to achieve a broader understanding of each condition in the light of novel acquisitions (Table 1). In the present work, focusing on the 'cardiocentric' HFpEF phenotype, the core mechanisms of physiological cardiac aging and of HFpEF will be reviewed and the two conditions will be ultimately compared to the neurological paradigm of dementia, intended as a multifactorial organ damage with age-related decline of functional reserve, leading to irreversible impairment [11].

Is HFpEF a dementia of the heart?

Dementia is an acquired syndrome, age-related and highly prevalent worldwide, characterized by progressive cognitive decline in more than one neuropsychological domain and functional impairment [12]. Dementias are classified as neurodegenerative (associated with abnormal depositions of proteins in the brain) or non-neurodegenerative (i.e. associated with vascular damage) [11]. However, dementia is rarely the product of a single pathological hit. Rather, it represents a final common pathway of multiple substrates and modifiers including genetic predisposition, pre-morbid

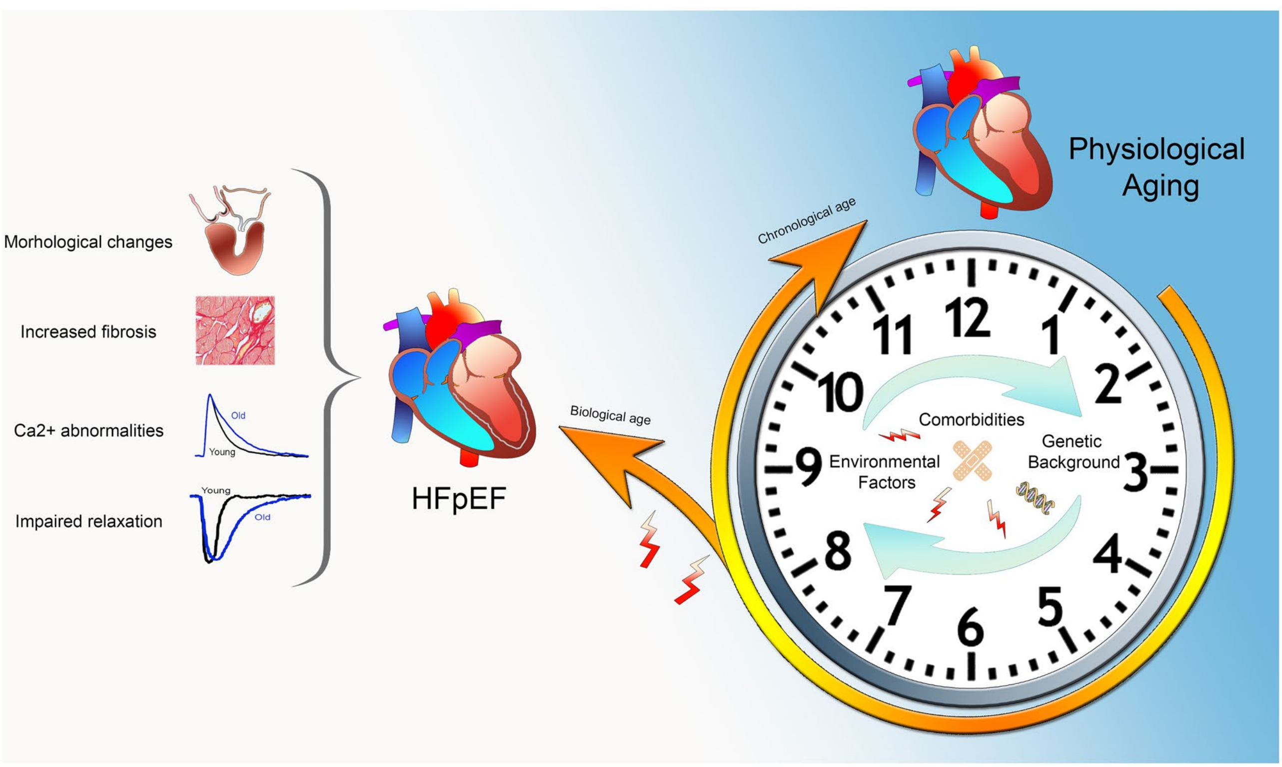

Fig. 1 The pathophysiologic continuum of cardiac aging and HFpEF. Physiological cardiac aging and HFpEF share many core biological mechanisms. In the latter, however, biological age supersedes chronological age, resulting in an accelerated aging of the heart and manifesting as a maladaptive response to stress. Morphological and molecular features of HFpEF are in common with those of cardiac aging, such as diastolic dysfunction (reproduced from [64]), ECM remodelling (reproduced from [28]), and impaired calcium handling (reproduced from [64]) (ECM, extracellular matrix; HFpEF, heart failure with preserved ejection fraction)

Table 1 Comparison of epidemiological, clinical, morphological and molecular features of physiological cardiac aging and HFpEF

	Physiological cardiac aging	HFpEF
Epidemiology and context		
Average age of clinical presentation (years)	≥75–80 [21]	65–75 [6, 7]
Prevalence	Virtually universal [21]	50% of HF patients [6, 7, 42]
Genetics	+/− [21, 23]	+/− [27, 53]
Comorbidities/environment	++ [21]	++ [42, 49]
Clinical and morphological features		
Limiting/HF symptoms	+ [20]	++ [3, 6, 7]
LVH	+ [20, 23]	++ [2, 6, 43]
Diastolic dysfunction	+ [20, 23]	++ [2, 6]
LA enlargement/Atrial fibrillation	+ [23]	++ [2, 3, 47]
Myocardial fibrosis	++ [20, 23]	++ [3, 48]
Microvascular dysfunction	+ [29]	++ [47, 49]
Molecular profile		
Sarcomeric abnormalities	+ [23, 31]	++ [3, 27, 32]
Abnormal collagen turnover	++ [27]	++ [3, 27]
Impaired calcium handling	++ [34, 35]	++ [2, 3]
Mitochondrial dysfunction/oxidative stress	++ [23]	++/+++ [, 53]
Telomere shortening and damage	+/− [39, 40]	+/− [10]

HFpEF heart failure with preserved ejection fraction, *HF* heart failure, *LVH* left ventricular hypertrophy, *LA* left atrial

functioning (i.e. cognitive decline), cardiovascular (CV) risk factors and comorbidities, microvascular functioning, and inflammation [11]. The ultimate and most important risk factor for the development of dementia is aging, which, physiologically, may itself be associated with a progressive decline in cognitive skills [13]. Nevertheless, it is not only a condition of the elderly, and specific types may even affect young individuals (i.e. in the case of genetic aetiologies). Differentiating physiological aging of the brain from the early stages of pathological cognitive decline is challenging [11, 12]. Moreover, differential diagnosis among dementias relies on the identification of the main determinant of disease—i.e. presence of pathological amyloid and tau aggregates in Alzheimer's disease. However, it is well recognized that a number of core mechanisms participate in different nosological entities, with a central role of microvascular dysfunction [14]. For example, also in non-vascular dementias, functional status and outcomes are frequently influenced by the extent of chronic vascular damage [15]. Likewise, accumulation of misfolded pathological proteins may be present in patients with vascular dementia and contribute to functional decline [16, 17]. Pathological protein accumulation and white matter damage due to vascular lesions coexist and contribute to cognitive decline, via a progressive erosion of cognitive and brain reserve, which may initially only cause transient functional impairment (with normal or near-normal performance in inter-critical stages), but eventually leads to overt dementia [18] (Fig. 2).

The paradigm of dementia is well suited to explain HFpEF (Fig. 2), which may be similarly conceived as a maladaptive response of the myocardium to aging. Dementia and HFpEF are both age-related conditions affecting organs with high energetic and metabolic demands, constituted by terminally differentiated cell types, that appear, at least in a subset of patients, particularly prone to misfolded protein damage [19] and microvascular dysfunction [14]. We propose that the 'HFpEF syndrome' may in part reflect the interplay of adverse structural remodelling of the myocardium, unfavourable gene-environment interaction, and erosion of the cardiac functional reserve, mirroring the processes occurring in the brain. HFpEF phenotypes share a multifactorial predisposition resulting in a maladaptation to CV stressors. As in patients with cognitive decline and dementia, the initial phases of HFpEF are characterized by episodic and transient failure, with no or only subtle evidence of disease during inter-critical stages. Ultimately, however, the impairment becomes severe and irreversible (Fig. 2).

Physiological aging of the heart

Epidemiology and context

In Europe, more than 20% of people are aged ≥ 65 years [20, 21]. Although the aging process is consistently preserved

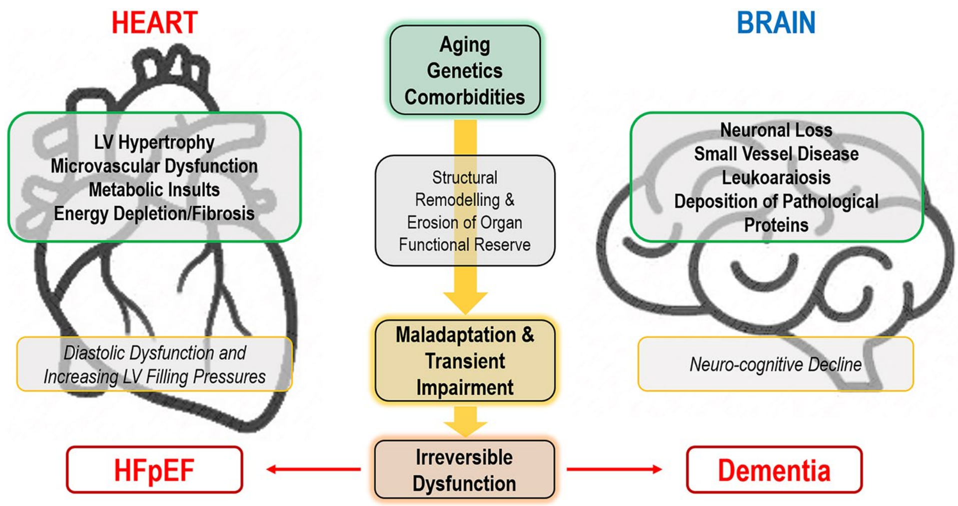

Fig. 2 Determinants, features, and progression of heart failure with preserved ejection fraction and dementia. HFpEF and cognitive decline dementia are age-related conditions characterized by progressive erosion of organ reserve, initially presenting with fluctuating functional impairment, ultimately resulting in irreversible impairment (LV, left ventricle; HFpEF, heart failure with preserved ejection fraction)

across species, the heritability of human lifespan is as low as 12%, underlining environmental factors as critical components of the aging process [21]. Indeed, older age is seldom disease-free, and the increased life expectancy is associated with comorbidities as diabetes, hypertension, HF, and dementia [22]. Based on this perspective, multimorbidity is seen as the multisystem expression of the so-called aging phenotype, rather than a coincidence of unrelated diseases [22].

Clinical and instrumental features

Aging-associated cardiac remodelling is characterized by LVH and decline in myocardial compliance [23], in the presence of preserved resting LVEF [24]. Moreover, the hearts of elderly healthy individuals show a reduced LVEF on exercise due to inability to reduce end-systolic volumes as well as impaired arterial-ventricular (A-V) coupling caused by augmented ventricular and vascular stiffness [25]. Of note, A-V coupling at rest is maintained, since the increase in LV stiffness—related to LVH, extracellular compartment remodelling, and increased collagen content—is counterbalanced by an increase in vascular stiffness and peripheral resistance [26]. In response to exercise or other stressors, however, the myocardium is less capable of increasing its elastance to meet the augmented stiffness of the vascular counterpart [25].

Molecular profile

Changes in extracellular matrix (ECM), neurohormonal activation, coronary microvascular dysfunction, calcium homeostasis, and mitochondrial function progressively occur with aging, qualitatively similar (although milder) to those described in the failing heart. ECM composition is modified with reduced collagen turnover rate, increased collagen deposition, reduced elastin component, and an imbalance between matrix metalloproteinase and their tissue inhibitors [27, 28]. Furthermore, ECM remodelling occurs due to impaired endothelial function and coronary microvascular dysfunction, responsible for transient ischemia and fibrosis [29].

The neurohormonal hyperactivation observed with aging is critical to maintaining adequate tissue perfusion over time. Even in healthy subjects, however, age-related enhancement in renin-angiotensin-aldosterone system (RAAS) and β-adrenergic signalling reduces myocardial compliance while providing inotropic support to overcome the increased peripheral resistances [20]. RAAS hyperactivation leads to myocyte hypertrophy, independent of pressure overload, and myocyte apoptosis [23, 30]. It also causes hyper-phosphorylation of the sarcomeric protein titin [31], leading to adverse sarcomeric changes in cardiomyocyte passive tension and increased myocardial stiffness [32]. Finally, RAAS activation increases cytoplasmic calcium levels, inducing activation of the Ca^{2+}/calmodulin-dependent protein kinase, responsible for myocyte hypertrophy and reduced cardiac relaxation [23, 30]. These effects are also partially shared with β-adrenergic hyperstimulation [33].

Aging is associated with disruption of the calcium handling machinery at multiple levels [23, 34]. Animal models showed age-related impairment of the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), resulting in reduced clearance of calcium from the cytoplasm during diastole and prolonged diastolic relaxation time [33, 34]. The extended duration of cardiac action potential associated with aging, meant to provide inotropic support, further contributes to cytoplasmic calcium overload [34, 35]. Finally, damage and reduced clearance of cellular compartments and mitochondria are observed with aging [9, 23]. Reduced autophagy indeed plays a pivotal role in accelerating aging [36]. Mitochondrial dysfunction promotes cardiomyocyte death, fibrosis, and generation of reactive oxygen species (ROS) [9, 23]. Defects in clearance of damaged mitochondria, i.e. the so-called mitophagy, are associated with accelerated aging, while a preserved process of mitophagy contributes to preservation of system physiology and, therefore, promotes healthy aging [23, 37]. Interestingly, telomere damage, a cellular hallmark of aging, has been linked to molecular and mitochondrial abnormalities, in a vicious circle involving ROS production and activation of pro-apoptotic pathways [38, 39].

Heart failure with preserved systolic function

Epidemiology and context

There is general consensus that 50% of HF cases show preserved LVEF [7] and that HFpEF incidence is increasing [40, 41]. The epidemiology of HFpEF, however, is largely unresolved [6], due to lack of a consistent definition [1]. Notably, in a landmark analysis reporting the prevalence of HFpEF among hospitalized patients, the definition was based solely on LVEF, with no information regarding patients' clinical profile or diastolic function [41]. The same study showed a clear prevalence of elderly and female patients in the HFpEF group, as well as a significant burden of obesity, hypertension, and atrial fibrillation. Similar epidemiological characteristics have been reported in more recent analyses, although with younger age at presentation (65 versus 75 years) [42]. Moreover, in a smaller proportion of patients, HFpEF may present at even younger ages, likely reflecting the complexity and variety of myocardial structural remodelling, gene-environment interaction, and comorbidity burden underpinning its development [3, 43].

Clinical and instrumental features

LVH and left atrial (LA) enlargement are considered characteristic of HFpEF [42, 44] and are presented as contributing diagnostic criteria in the European HF guidelines [6]. However, they are present in combination in only about one-third of HFpEF patients enrolled in major trials [1, 2]. Strikingly, the same is true for overt diastolic dysfunction [1, 2]. While LVH is a determinant of myocardial stiffening and a potential cause of HFpEF, LA enlargement reflects elevated LV end-diastolic pressures and therefore is an epiphenomenon of myocardial stiffening and/or impaired relaxation [45]. In addition, myocardial stiffness in HFpEF is often coupled with an equally stiff vascular compartment [26]. As in physiological aging, the coexisting impairment of LV and arterial elastance result in preserved A-V coupling at rest, but reduced coupling reserve during exercise, due to impaired vasodilatory response and myocardial energetics [26]. Notably, HFpEF and hypertensive heart disease show a similar increase in LV elastance, and the only difference between the two conditions with regard to A-V uncoupling stands in the reduced indexes of myocardial contractility found in HFpEF [46]. Finally, coronary microvascular dysfunction is very prevalent in HFpEF subjects [47], as reported by both in vivo and autoptic studies [48].

Molecular profile

The molecular profile of HFpEF might resemble an accelerated aging process [49]. Several morphofunctional features of HFpEF are attributed to an inflammatory state induced by the most frequently associated comorbidities [50, 51]. Systemic inflammation causes reduction in nitric oxide production by coronary endothelial cells, resulting both in microvascular dysfunction and alterations in phosphorylation of titin, and other molecular abnormalities promoting LVH and diastolic dysfunction [51]. In the myocardium of hypertensive HFpEF patients, higher levels of titin phosphorylation were found as compared to controls and non-HFpEF hypertensive subjects [27]. Accordingly, HFpEF patients showed greater diastolic impairment in vivo. Microvascular ischemia, inflammation, and impaired myocardial energetics all lead to extracellular expansion due to increased collagen deposition and fibrosis [27, 48]. In a recent cohort of HFpEF patients who underwent endomyocardial biopsy [42], LVH was highly prevalent, but mostly mild or moderate. Likewise, fibrosis was common but mild and was found with a similar prevalence in controls with reduced EF (HFrEF). Finally, indexes of myocardial inflammation were higher as compared to controls, but similar to those of elderly individuals and patients with renal disease [42].

Abnormalities in mitochondrial function have been described in HFpEF, as well as in HFrEF and in primary myocardial disease including hypertrophic cardiomyopathy [4]. Abnormal mitochondrial activity has multiple downstream effects including impaired cardiac metabolism, ROS production, and cytosolic calcium overload [52]. Calcium reuptake is indeed strictly related to myocardial energetics. As persistently elevated cytosolic calcium concentrations promote prolonged actin-myosin cross-bridging, diverse HFpEF models have been generated postulating calcium leaks from the sarcoplasmic reticulum or reduced SERCA activity [2]. Altered post-translational regulation of calcium handling-related proteins also contributes to the increased cytosolic Ca2+ levels [53]. Moreover, dysregulation of CISD2, an endoplasmic zinc-fingers protein at the crossroads between endoplasmic reticulum, mitochondria, and calcium handling proteins, disrupts Ca2+ homeostasis promoting HFpEF [54]. Of note, experimental evidence suggests reduced energy reserve both in myocardial and in skeletal muscle mitochondria of HFpEF subjects [55, 56].

While little is known about potential genetic mechanisms underlying HFpEF, both post-transcriptional and post-translational modifications of sarcomeric proteins, including phosphorylation and histone deacetylation [57], seem to contribute to its development [2]. Titin may exist in two different splicing isoforms, and overexpression of the stiffer N2B has been demonstrated in the myocardium of decompensated HFpEF patients [58], although this finding was not replicated [27]. Post-transcriptional modifications of titin are influenced by the RNA-binding motif protein-20 [32], whose inhibition in a mouse model has been shown to improve diastolic function [59].

Towards a unifying perspective

The concept of HFpEF as an all-encompassing category, aimed at mirroring HFrEF, has failed to work and appears to have inherent limitations [2, 3, 43]. The conceptual framework adopted worldwide for cognitive decline and dementia may help advance our understanding of HFpEF, building on existing research from overlapping fields. As reviewed, the 'cardiocentric' HFpEF phenotype may be conceived as an accelerated and exaggerated expression of many elements of physiological cardiac aging, not dissimilar to what happens in the brain with dementia, particularly of the vascular type (Fig. 2). The role microvascular dysfunction—a pivotal pathophysiological mechanism in both HFpEF and cognitive decline dementia—is a specifically suitable case in point [14], reflecting the combined effects of aging and comorbidities [14, 29, 60]. Indeed, as dementia presents features of neurological aging, but it is not only a condition of the elderly, in HFpEF a core of mechanisms—similar to those of cardiac aging, but not exclusive of this condition, and possibly including genetic predisposition—interplay to ultimately lead to the clinical syndrome. This concept endorses the view of maladaptive stress causing premature aging as a common pathway transversal to different conditions and may help direct future research towards the identification of molecular pathways common to aging and HFpEF, unravelling shared therapeutic targets. As an example, recent insights into the pathophysiology of hypertrophic cardiomyopathy (a near-monogenic condition) have shown that myosin abnormalities typical of the disease cause an important state of energy depletion, resulting in LVH and ultimately predisposing to HFpEF [62, 63].

A shift toward mechanism-based approaches has been recently advocated in HF, irrespective of LVEF nosology [61]. Addressing such diversity would be a welcome change of direction from the dominant 'one-fits-all' approach to HFpEF endorsed by major trials, which have led to consistently disappointing results. Novel therapeutic approaches are surfacing in CV medicine, targeting specific molecular mechanisms such as sarcomere protein function, intracellular calcium handling, and fibrosis. Each may prove beneficial in different subsets of patients across the spectrum of HFpEF, and beyond. Recognizing HFpEF as part of the continuum encompassing all 'HFpEF-like' conditions, including aging, may be an important step in the right direction.

Author contribution GT, AC, MC, and IO contributed to manuscript conceptualization and design. GT, AC, and IO contributed to first draft writing. All authors contributed to manuscript writing and critical review. All authors have read the final version of the manuscript and agreed to its submission.

Declarations

Conflict of interest The authors declare no competing interests.

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