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REVIEW ARTICLE

Heart failure with preserved ejection fraction (HFPEF). Impact of change in the paradigm of isolated diastolic dysfunction

José Antonio Magaña-Serrano, Martín Rosas-Peralta, Carlos Candanosa-Arias, Salvador Valencia-Sánchez, Martín Garrido-Garduno, Roberto Arriaga-Nava and Moisés C. Calderon-Abbo*

UMAE, Cardiology Hospital, Centro Médico Nacional SIGLO XXI, IMSS, México, D.F., México

Abstract

Heart failure with preserved ejection fraction is a significant and growing public health problem, since it currently represents half of all patients with heart failure. Despite improvements in the understanding of the disease, there is no benefit from treatments tested at all. Advances in diagnostic imaging and invasive evaluation algorithms will allow a more accurate and early diagnosis so that treatment of earliest forms in the progression of the disease are applied since the potential for benefit may be higher. Although important progress has been made in our understanding of the pathophysiology, cardiac catheterization, and cellular of diastolic failure mechanisms and not diastolic mechanisms of disease, further research is required promptly to determine how best to address these anomalies to reduce the significant burden of morbidity and mortality in this form of heart failure, which is reaching pandemic proportions. (Gac Med Mex. 2015;151:592-603)

Corresponding author: *Martín Rosas-Peralta, mrosas_peralta@hotmail.com*

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Introduction

Clinical interest on heart failure with preserved ejection fraction (HFPEF) arose from the confluence of two lines of investigation dealing with (i) left ventricle (LV) diastolic dysfunction in hypertrophied hearts, and (ii) LV remodeling after small myocardial infarctions.

In the late 70's, the first studies showed that the onset of LV diastolic dysfunction might significantly contribute to heart failure (HF) in hypertrophic cardiomyopathy[1,2], aortic stenosis[2,3] and hypertensive heart disease[4].

Soon after this incursion in the small niche of LV diastolic dysfunction in hypertrophied hearts, HFPEF was also identified and addressed in studies. These studies, in general, were a "by-product" of large HF trials investigating the use of angiotensin-converting enzyme inhibitors (ACEI) in HF with reduced ejection fraction (EF) (HFREF) and in post-infarction LV remodeling[5-7].

HFPEF populations deriving from the last studies were, however, clearly different, since they consisted of patients with limited and small myocardial infarction, but at risk for untoward LV eccentric remodeling. This HFPEF ambiguous origin contributed to the confusion surrounding this entity as a differentiated diagnosis[8-10],

Correspondence:
*Martín Rosas-Peralta
UMAE
Hospital de Cardiología del Centro Médico Nacional SIGLO XXI
IMSS
Av. Cuauhtémoc, 330
Col. Doctores, Del. Cuauhtémoc, C.P. 06725, México, D.F., México
E-mail: mrosas_peralta@hotmail.com

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and given the neutral result of many large trials on HFPEF, further studies are still necessary[11,12].

True cardiac hypertrophy has little in common with limited myocardial infarction, and in both conditions, the underlying mechanisms that drive LV remodeling are likely to be different and, actually, they react differently to drug treatment. Recently, stringent criteria have been proposed for the diagnosis of HFPEF, which consist not only of signs and symptoms of heart failure and a preserved left ventricular ejection fraction (LVEF), but also of LV diastolic dysfunction evidence[13,14].

This caused most current HFPEF patients being those with LV concentric remodeling, generally secondary to systemic arterial hypertension, obesity and diabetes, all these without evidence of epicardial coronary artery disease. A low prevalence of coronary artery disease has been recently proposed as a strategic measure for inclusion of the correct patients in clinical trials on HFPEF[15].

In the past, HFPEF was often referred to as an equivalent to "diastolic" HF (DHF) as opposed to the already traditional "systolic" HF (SHF), which corresponded to HFREF. Since LV diastolic dysfunction is not exclusive to HFPEF but is also observed in patients with HFREF, the term DHF has been abandoned in the last decade and replaced by HFPEF[16,17] or else, by HF with normal LVEF (HFNEF)[17]. However, the terms HFPEF and HFREF have their shortcomings as well. The notion of a preserved LVEF implies knowledge of a pre-existing LVEF, which is almost always absent, and the exact range of LVEF "normality" is difficult to define; i.e., nobody can guarantee that a 50% LVEF is normal for an individual who usually had 65%[18,19].

It has not been established if HFPEF and/or HFREF represent different forms of HF or if they coexist as part of the "continuum of HF"[13]. In spite of the different patterns of the ventricular chamber and the myocellular remodeling observed in couplings with dissimilar responses to medical therapies, all of it would be suggestive that these are two distinct processes of the disease. HFPEF is currently observed in about 50% (38-60%) of patients with HF, and the results are close to those observed for HFREF[20]. The somber prognosis is probably a reflection of the complex multi-systemic and multi-factorial involvement that characterizes all types of HF, regardless of the LVEF, including systems such as the skeletal muscle and vascular dysfunction, pulmonary hypertension, anemia and atrial fibrillation[21]. The prevalence of HFPEF as related to HFREF is increasing at an alarming rate of approximately 1% per year, which is rapidly turning HFPEF into the most prevalent HF phenotype for the next decade; however, in contrast with HFREF, no improvement in therapeutic results has been achieved over the past two decades[20]. In spite of these worrying epidemiological trends, the underlying pathophysiological mechanisms of HFPEF and diagnostic strategies or therapeutics remain uncertain[21,22]. Therefore, the present review has the following:

Objectives and methods

To conduct a systematic review with the exploration, reduction and synthesis method, and focusing on our epidemiological rates of associated risk factors. Using the online PubMed and Google Scholar digital browsers in English, French and Spanish languages, at least on their abstracts, the authors selected 102 original articles, the 7 most recent reviews, as well as editorials and related structured summaries.

Pathophysiology

The key studies on HFPEF were explained within the context of HF in the presence of LV preserved EF, but with LV diastolic dysfunction, which consisted of LV isovolumetric relaxation prolonged times, LV slow filling and LV increased diastolic rigidity[1-4]. However, our group also considered the hypothesis of diastolic dysfunction associated with a transient systolic dysfunction (TSD).

With the advent of Doppler echocardiography, LV diastolic dysfunction can be easily appreciated from the parameters through the mitral valve or pulmonary vein flow velocity recordings[23]. However, the recordings of abnormal mitral flow velocity suggestive of LV diastolic dysfunction have been considered as non-specific for HFPEF, as they are found with high frequency in the elderly[24], and in patients with HFREF[25]. The importance of LV diastolic dysfunction for HFPEF has been recently reevaluated by invasive studies, which showed consistent presence with LV slow relaxation at rest with elevated diastolic rigidity[26], and this elevated rigidity has also been shown to limit cardiac output during atrial stimulation and exercise[27,28]. This new estimation has also been made evident in the recent guidelines for the diagnosis of LV diastolic dysfunction by the European and American echcardiography associations[13,14].

The reevaluation of LV diastolic dysfunction as an important HFPEF underlying mechanism does not imply that it represents the only mechanism contributing

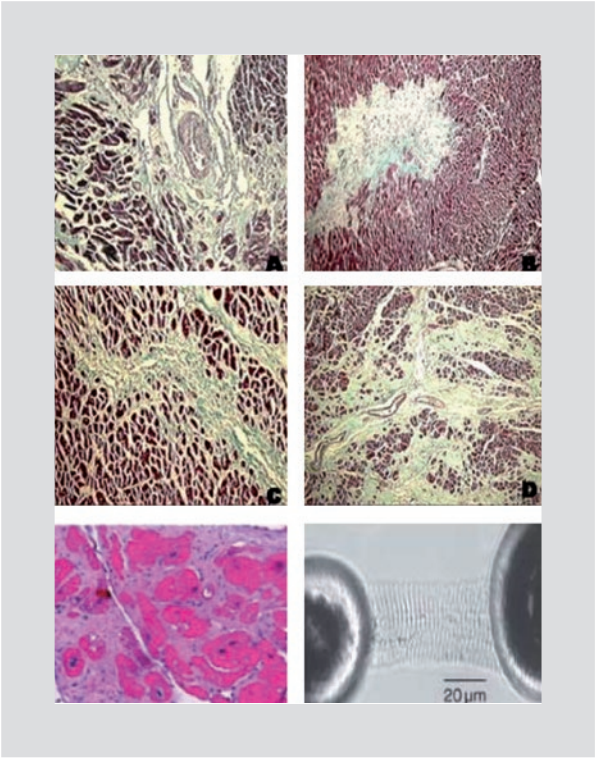

Figure 1. *Photographs showing the contribution to ventricular rigidity mediated by the extracellular matrix (***A, B, C, D;** *below left) and the cardiomyocytes own function (below right).*

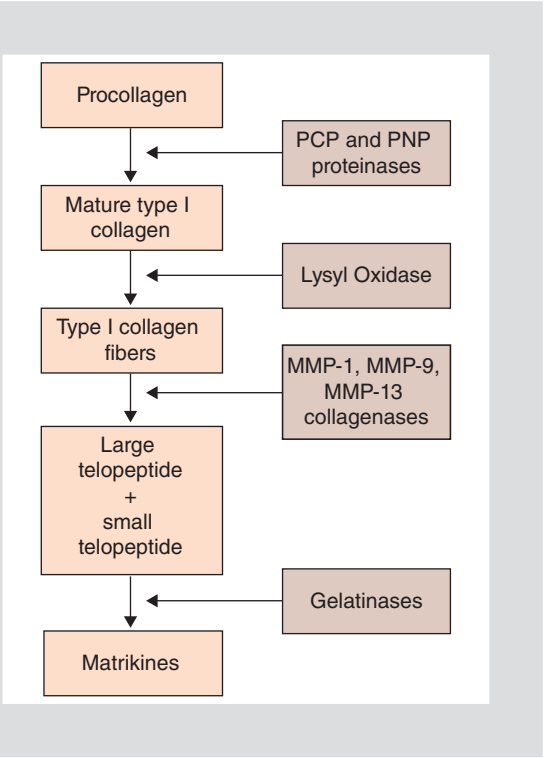

Figure 2. *Steps on type I collagen synthesis and degradation. PCP: type I procollagen carboxyl-terminal proteinase; PNP: type I procollagen N-terminal proteinase; PICP, PINP, carboxyl-terminal and amino-terminal propeptides; MMP: extracellular matrix metalloproteinase.*

to the pathophysiology of the disease. Many other mechanisms have been recently identified as components that play an important role. These include exercise-induced systolic dysfunction[29-35], exercise-induced ventricular-vascular altered coupling[33,34,36,37], and vasodilation-mediated abnormal flow[28,31-33], chronotropic incompetence and pulmonary arterial hypertension[31,33,34,38].

LV diastolic dysfunction

In the absence of endocardial or pericardial disease, LV diastolic dysfunction is considered as a manifestation of myocardial increased stiffness. Two compartments within the myocardium regulate its diastolic rigidity. These compartments are (i) the extracellular matrix (ECM), and (ii) the cardiomyocytes themselves. A rigidity change within one compartment is also transmitted to the other comparment by mechanoreceptor proteins of the ECM (Fig. 1).

ECM

The ECM rigidity is largely determined by collagen through: (i) regulation of its total quantity, (ii) the relative abundance of type I collagen, and (iii) the degree of intertwining of collagen itself. In patients with HFPEF, all three mechanisms appear to be involved.

The excessive deposit of type I collagen is the consequence of an imbalance between excessive synthesis and reduced degradation[41]. Several steps appear to be implicated in the type I collagen synthesis process (Fig. 2).

Of clinical relevance is the observation that the type I procollagen carboxyl-terminal propeptide, which is cleavaged by type I procollagen PCP, is released into the bloodstream and, therefore, is a potential biomarker of the PCP-PCPE system activity[42,43]. Type I collagen excessive accumulation can result not only in exaggerated synthesis, but also in a decreased degradation rate. In hypertensive patients with HFPEF[44] and in patients with aortic stenosis[45], there is a decrease in ECM degradation because of down-regulation of ECM metalloproteinases (MMP) and up-regulation of tissue inhibitors of ECM metalloproteinases (TIMP). TIMP-1 plasma levels have been recently proposed as a potential biomarker of HFPEF development in patients with arterial hypertension[46]. Conversely, in patients with dilated

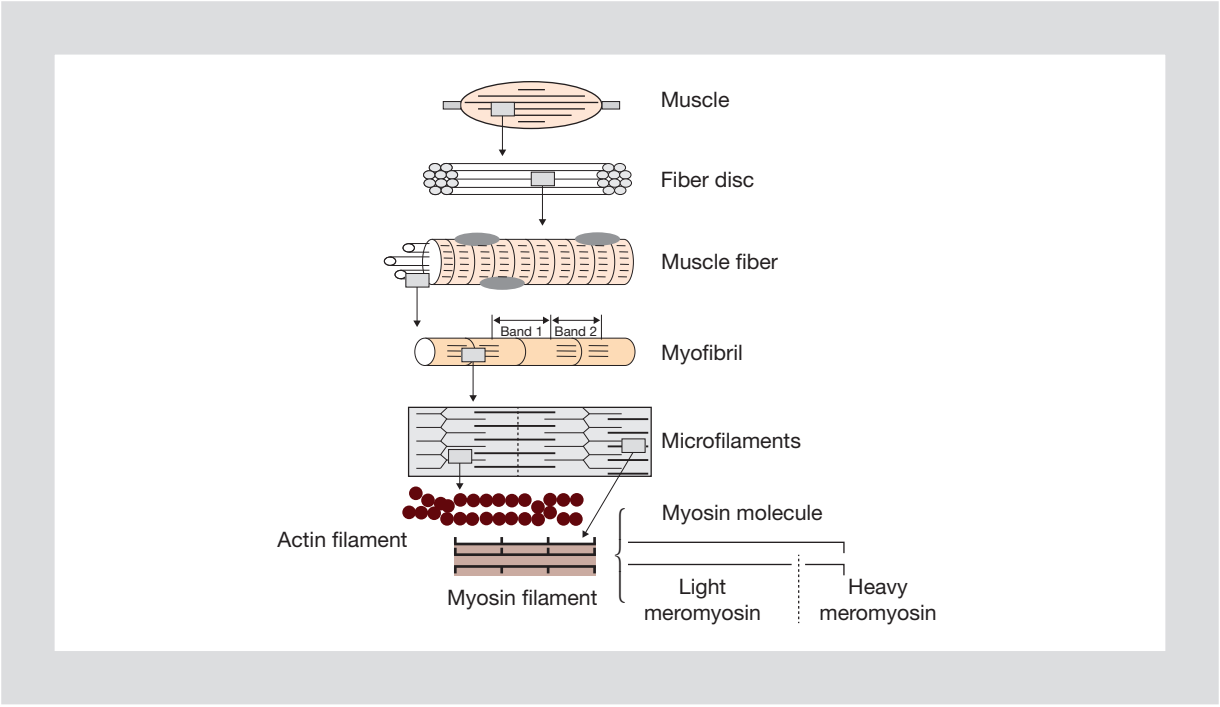

Figure 3. *Diagram of the sarcomere and its structure.*

cardiomyopathy, there is more ECM degradation due to MMP up-regulation[47]. These MMP and TIMP distinct expression profiles correspond also with uneven patterns of collagen myocardial deposit with interstitial fibrosis especially in diastolic dysfunction, as well as with degradation and replacement of interstitial fibrosis in dilated cardiomyopathy[48]. In patients with aortic stenosis who develop a depressed LVEF, there is reversion of the balance between collagen anti-proteolysis and proteolysis[49].

Cardiomyocytes (Fig. 3)

In LV endomyocardial biopsies, one third of the patients presenting with HFPEF have an apparent normal collagen concentration volume fraction[50]. However, their end of systole parietal tension of left ventricular end-diastolic pressure (LVEDP), their LV mobility pattern and rigidity have been comparable to those of patients with a marginally high collagen volume fraction. This finding suggests that, in addition to collagen deposit, intrinsic cardiomyocyte stiffness also contributes to LV diastolic dysfunction in HFPEF[50].

Thus, some studies have suggested that the cardiomyocyte intrinsic rigidity is indeed elevated in patients with HFPEF[48,50,51], as well as in patients with ventricular hypertrophy due to congenital heart disease[52]. This cardiomyocyte rigidity elevation has been associated with the cytoskeletal protein known as “titin”.

Titin (Fig. 4 and 5) is an elastic giant protein that is expressed in cardiomyocytes in two main isoforms; (i) N2B (more rigid spring), and (ii) N2BA (more indulgent spring)[53]. Previous works demonstrated that the proportion of the N2BA isoform expression increased in eccentrically remodeled hearts explanted from patients with myocardiopathy when compared with control donors’ hearts[54-56].

Although the switching of titin isoforms is a confirmed mechanism for passive myocardial stiffness adjustment, recent studies suggest that insufficient myocardial passive rigidity increase can also arise from abnormalities in the titin phosphorilation status[57-59] or from oxidative stress-induced disulfide bonds formation within the titin molecule itself (Fig. 5)[60].

A characteristic feature of LV relaxation in HFPEF is its slowness or delay, which may contribute to LV systolic volume reduction, especially at high heart rates[61,62].

This finding is opposed with normal heart, where LV relaxation is accelerated at high heart rates. Left ventricular relaxation depends on both (i) the detachment of crossed bonds, and (ii) Ca^{2+} reuptake by the sarcoplasmic reticulum[63].

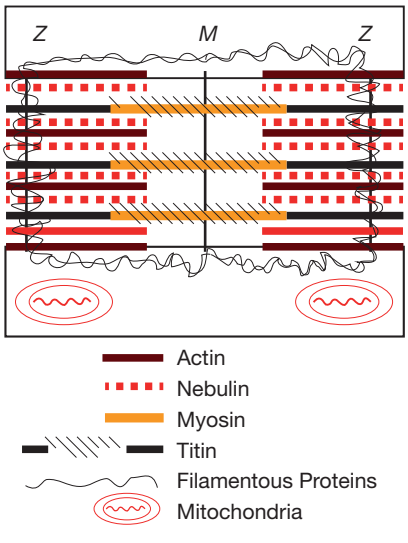

Figure 4. *Titin: support protein.*

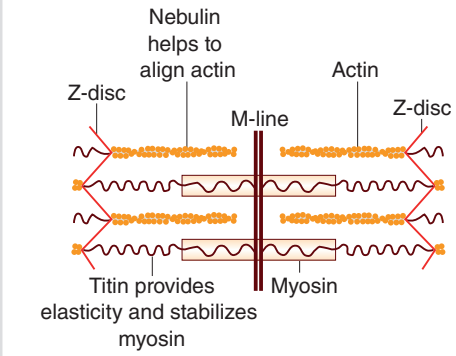

Figure 5. *Titin function.*

Nitric oxide (NO) signalling mechanisms are also implicated. Its down-regulator, cyclic guanosine monophosphate (cGMP) reduces the myofilament sensitivity to Ca^{2+} and, therefore, facilitates the detachment of cross-linked bonds[64].

The implication of ON on this was also recently reevaluated due to the close correlation between asymmetric dimethylarginine and diastolic dysfunction in the LV of human hearts[65,66] There is an uncoupling of NO-synthase-1, which induced HFPEF in an animal model[67]. Since the detachment of cross-linked bonds is an energy-consuming process, slow LV relaxation can also result in myocardial energy deficit. Recent studies using phosphorus magnetic resonance spectroscopy in infarction showed a lower creatine triphosphate/myocardial adenosine phosphate ratio in patients with HFPEF in comparison with normal controls[35,68], consistent with a decrease in the myocardial energy reserve.

ECM proteins

The induction of ECM mechanosensitive proteins affects the fibroblasts' function and regulates cardiomyocytes hypertrophy and survival[69]. By binding to collagen, cell-surface receptors and MMP, the ECM proteins appear to improve both the quality of the matrix and the cardiomyocyte function[70]. Their role in HFPEF remains unexplored (Fig. 1).

Systolic failure

EF is preserved in HFPEF, but LVEF has been considered more precisely as a measure of ventricular-arterial coupling and not only of contractility[3]. In 2002, two relevant studies reported that regional systolic function measurements, evaluated by tissue Doppler, were affected in HFPEF in spite of a normal LVEF[29,71]. This has driven our group to advocate the hypothesis of cardiac failure with TSD. Numerous subsequent studies have similarly demonstrated a depressed longitudinal shortening[72,73] and radial systolic function in HFPEF[74]. However, the importance of these anomalies remains to be elucidated[75], since systolic function global measurements appeared preserved in HFPEF[76]. Recently, a large epidemiological study demonstrated that both at the chamber and at the myocardial contractility level they are "subtly" but significantly reduced in HFPEF, in comparison with hypertensive and healthy controls[30]. It is important to note that the degree of contractile myocardial dysfunction was associated with increased mortality in HFPEF, which suggests it can be a mediator or nominally a marker of more serious disease[30].

End-systolic elastance (ESE), defined by the slope and the intersection of the end-systolic pressure-volume ratio, is a gold standard contractility measure that, in contrast with other measures, is elevated in HFPEF[30,36,76,77]. The coexistence of elevated end-systolic elasticity (ESE) and systolic function reduction in other indices has been difficult to conciliate. However, in addition to being sensitive to contractility, ESE rigidity is also influenced by the geometry of the ventricular

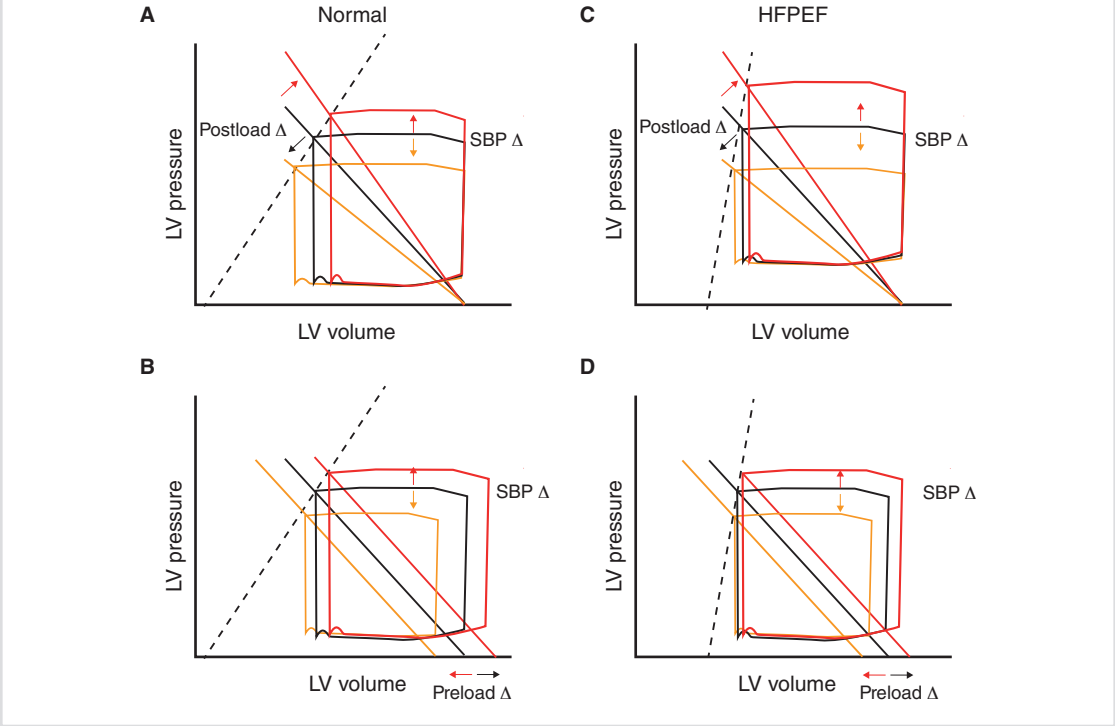

Figure 6. *In comparison with normal controls (**A** and **B**), the slope of the pressure-end-systolic volume ratio (end-of-systole elastance; esE, dotted lines) is increased in heart failure with preserved ejection fraction (HFPEF) (**C** and **D**). This leads to blood pressure exaggerated increases and decreases by the postload (**A** and **C**) or preload change itself (**B** and **D**) in HFPEF, which represents more predilection for crisis and/or hypotension and azotemia with hypertension and excessive diuresis or excessively vigorous vasodilation.*

chamber in the rest/effort cycle. ESE is elevated in HFPEF in spite of a contractility depression, when measured across each pattern of the ventricular chamber geometry[30]. The same processes that promote ventricular diastolic stiffness in HFPEF are thought to increase ESE and contribute to contractility in infarction by limiting the systolic reserve as well. The systolic function is not as clearly deteriorated in HFPEF as it is in HFREF[73], but recent studies have demonstrated that even mild basal contractility limitations in HFPFS can turn out to be more problematic with tension adjustment during exercise[31-35], where incapacity to improve contractility can be associated with deteriorated cardiac output reserve, thus making intolerance to exercise and decreased aerobic capacity symptoms more severe.

Defects in the ventricular-arterial coupling

Ventricular and vascular rigidity is known to increase with age, systemic arterial hypertension and diabetes, and it is elevated in patients with HFPEF[20,77]. Reduced aortic distensibility in HFPEF is strongly associated with reduced exercise capacity[78]. Some authors[36] demonstrated that both arterial distensibility (arterial elastance, aE) and ESE are elevated in tandem in HFPEF, thus explaining the arterial pressure labile changes commonly seen in HFPEF[79]. Combined ventricular-arterial rigidity drives to greater arterial pressure lability, by means of the creation of a "high-gain" system with arterial pressure amplified for any preload and/or postload alteration (Fig. 6)[37]. Postload acute elevation in the context of ventricular-arterial rigidity results in higher increase of arterial pressure, which may then further deteriorate diastolic relaxation[80,81], thus producing an important increase in the filling pressures under stress conditions (Fig. 7). Recent studies have also highlighted the importance of abnormal ventricular-arterial coupling during exercise in HFPEF[33,34], where stunned contractility and the reduction of arterial post-load impairments that with stress cotribute each to effort intolerance are increased[82]. Therapies directed to improve

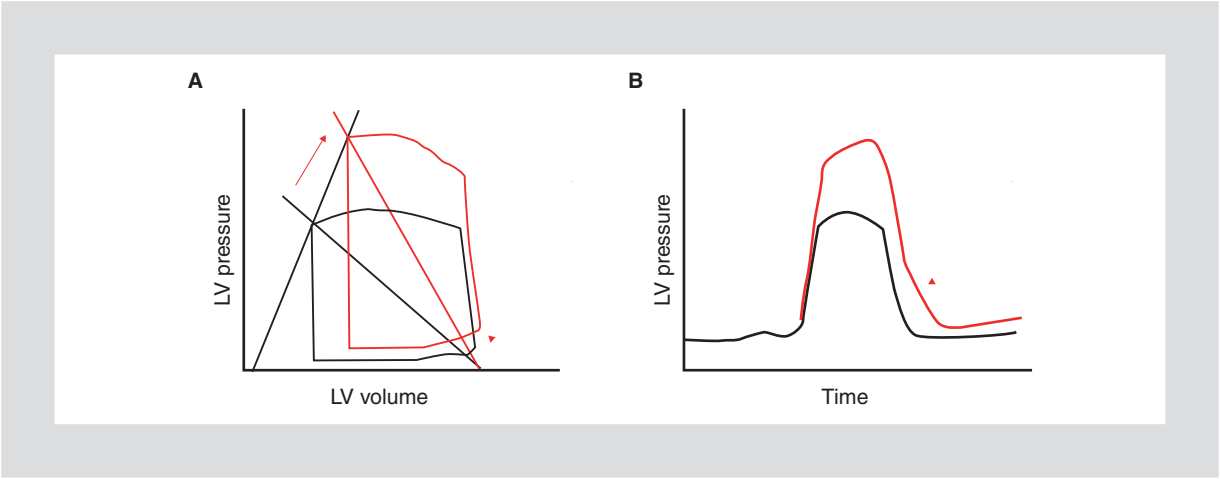

Figure 7. A: *arterial ventricle rigidity combined in heart failure with preserved ejection fraction can lead to dramatic blood pressure elevations with postload increase (grey arrow). This leads to a new increase of the end-diastolic LV pressures (arrowhead), by alteration of the slope or position of the diastolic pressure-volume ratio, and/or (***B***) by prolongation of the LV pressure fall during isovolumetric relaxation (arrowhead).*

the effort ventricular-arterial interaction in hypertensive elderly patients[83] suggest its possible role in HFPEF.

Systemic vasorelaxation with exercise is atennuated in HFPEF[31-33], which promotes alteration in blood-flow delivery to skeletal muscle. Vascular dysfunction in HFPEF may be due in part to endothelial dysfunction, as shown in a recent study, which demonstrated flow-mediated deteriorated vasodilation in HFPEF in comparison with healthy controls matched by age[33]. The dyspnea and fatigue symptoms in heart failure may be related to this ergoreflex pathological activation, which is also related to NO bioavailability[84].

Curiosly, the degree of flow-mediated vasodilation (an endothelial function marker) is related to the seriousness of effort intolerance symptoms during low intensity exercise in HFPEF[33], with an emphasis on the complex between peripheral processes and the perception of symptoms in HF[85]. These data provide a further explanation of possible therapies targeting NO in HFPEF.

But vascular dysfunction is not limited to systemic circulation in HFPEF, since pulmonary hypertension is very frequently observed as well[40]. Among old-age patients with normal LVEF and high pulmonary artery pressure, HFPEF is usually the most common etiology[86]. Pulmonary pressures increase with aging and have been correlated with systemic vascular rigidity; both, common risk factors for HFPEF[87]. Pulmonary hypertension in HFPEF appears to be due both to elevated telediastolic pressures of the heart's LV and to high pulmonary vascular resistence, which can develop as a response to the former[40]. In the early stages of HFPEF, pulmonary vasodilation with exercise is preserved, and effort pulmonary hypertension is passive and mainly secondary to high pressures of the left heart[28]. Pulmonary artery elevated pressures can predict an increase in HFPEF mortality[40] and might represent a new therapeutic target, although arterial pulmonary unbalanced vasodilation can lead to pathological elevations in the left pressures of the heart or even to overt pulmonary edema, and further studies are required to define the possible role of pulmonary vasodilators in HFPEF[88].

Chronotropic response and cardiovascular reserve reduction

Most patients with HF do not complaint about symptoms at rest, but rather with physical effort. A number of recent studies have emphasized on the importance of cardiovascular reserve function alterations at exercise stress in the physiopathology of HFPEF[31-35,38]. During physical exertion, cardiac output is augmented through comprehensive improvements in the venous return, contractility, heart rate and peripheral vasodilation[89].

Abnormalities in each one of these components of the abnormal reserve function in response to exercise have been identified in HFPEF and all of them may contribute to the pathophysiology in individual patients (Fig. 8).

Normal diastolic reserve with exercise allows for the ventricle to fill up to a larger preload volume, in a short period of time, with no increase in filling pressures[90]. An old heart is indeed more labile than normal as a result of an increase in preload reserves to compensate

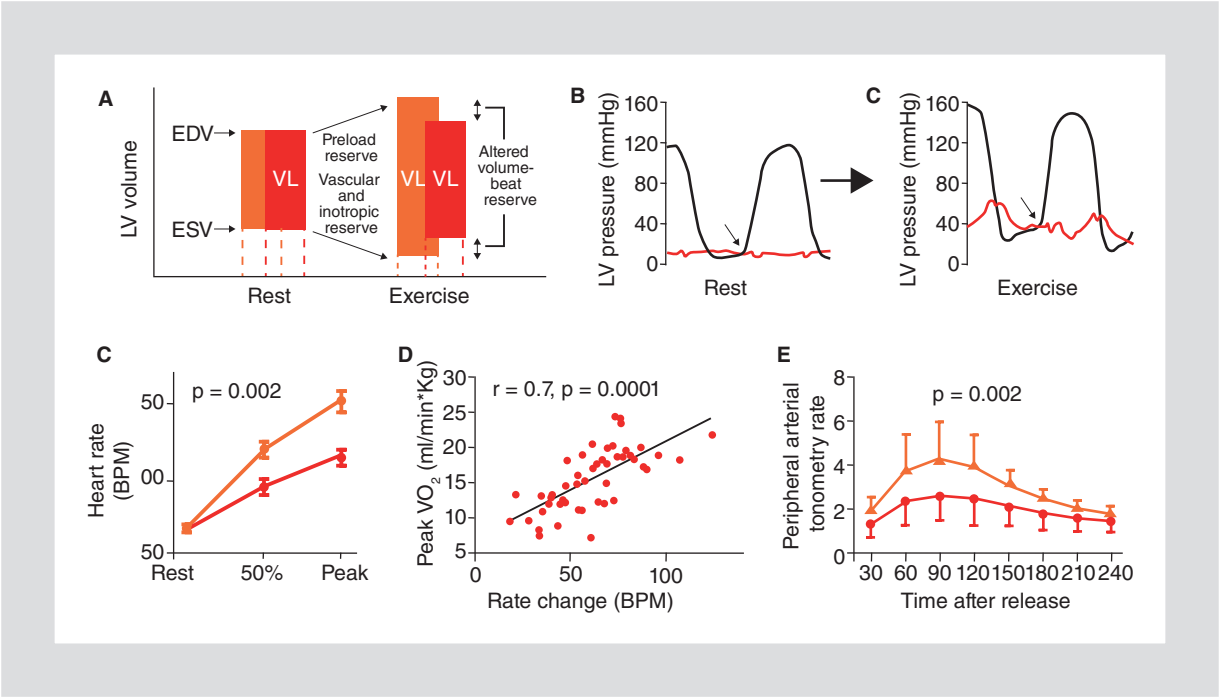

Figure 8. (A) *the chamber volume and LVEF are shown to be similar at rest in heart failure (HF) with preserved ejection fraction (HFPEF) (dark grey) vs. controls (light grey), but patients with HFPEF are less capable to improve the preload volume (end-diastolic volume, EDV), as well as to manage to minimize end-systolic volume (ESV) during physical effort. These differences are related to diastolic and systolic dysfunction and dysfunction of the vasodilator reserve, which contribute to systolic volume (SV) deterioration with physical exercise in HFPEF.* **B:** *in spite of less EDV improvement with exercise, there is much larger increase in LV filling pressures, measured as the LV diastolic-end pressure (arrow) or the pulmonary wedge pressure (dark grey).* **C:** *the chronotropic response during sub-maximal and maximal work load is affected in HFPEF (dark grey) in comparison with controls (light grey) and the degree of chronotropic deterioration is associated with a more severe decrease of the aerobic capacity* **(D).** *The peripheral vascular function is also affected in HFPEF, which can be related to endothelium-dependent altered vasodilation, measured as an increase in peripheral arterial blood-flow after superior arm cuff occlusion* **(E).** *(Data published in Borlaug et al.[28,33]).*

the age-related reductions in the contractile and chronotropic reserves[91]. In the same way the diastolic function is altered in HFPEF, the diastolic function is also reduced, with patients showing effort-induced preload volume increases, in spite of marked elevations in the filling pressure[28,92]. This is probably related to an increased rigidity of the chamber[27] and inadequate improvement of early relaxation[61,62] in spite of modulation by the pericardium and improvement of ventricular interaction, which may also contribute[93].

The systolic reserve (SR) is also altered with exercise in HFPEF, causing non sufficient EFs, with stunned contractility and systolic-longitudinal shortening velocities during exercise[31-35]. Exercise-induced stress can "unmask" mild deficits in the systolic function rest, and incapacity to reduce the telesystolic volume, combined with lower increase in end-diastolic volume, which largely limits the systolic volume responses during exercise. The causes of SR and diastolic reserve (DR) remain unclear, but may be related to myocardial ischemia (epicardial/microvascular coronary disease or vascular distensibility alterations), to beta-adrenergic system deteriorated signalling[94], to myocardial energetics[34,68] or to abnormal management of calcium[95].

The chronotropic reserve is depressed in HFPEF[31,33,34,38,96], even in comparison with controls, older of the same age and use of rate-deceleration-independent drugs. Similar to HFREF[97], this is probably associated wit downwards deficits in beta-adrenergic stimulation, since the increase in plasma catecholamines with exercise is similar in HFPEF and in healthy controls[31]. Autonomic dysfunction can contribute to chronotropic incompetence, since baroreflex sensitivity[31] is reduced and heart rate recovery is altered in HFPEF[31,96].

Patients with HFPEF show exercise-induced reductions in mean vascular arterial resistance and distensibility, together with endothelial function and dynamic ventricular-arterial coupling alterations[31-33]. Many of these anomalies are observed with normal aging and are symply more abnormally marked in HFPEF, consistent with the idea that HFPEF developes as an exaggerated, progressive and pathological form of aging in

Table 1. Echocardiographic parameters to measure the degree of diastolic dysfunction

					Severe reversible failure	
		Normal	**Mild failure**	**Moderate failure**	**Yes**	**No**
MF	E/A	0.75-1.5	< 0.75	0.75-1.5	> 1.5	> 1.5
	TD	> 140 ms	> 140 ms	> 140 ms	> 140 ms	
MF(VSL+)	E/A	< 0.5	< 0.5	< 0.5	< 0.5	< 0.5
TDI	E/E'	< 10	< 10	> 10	> 10	> 10
	S:D	>	>	<	<	<
PVF	DurAr:RA	<	<	> + 30 ms	> + 30 ms	> + 30 ms
	LVR	Normal	Altered	Altered	Altered	Altered
	LVC	Normal	Normal or ↓	↓↓	↓↓↓	↓↓↓↓
	LAP	Normal	Normal	↑↑	↑↑↑	↑↑↑↑

MF: mitral flow; MF(VSL +): mitral flow with Vasalva maneuver; TDI: tissue Doppler imaging; PVF: pulmonary venous flow; S:D: pulmonary venous flow (systolic peak:diastolic peak); DurAr:RA: atrial-pulmonary reflow duration:atrial-pulmonary reflow peak; LVR: left ventricular resistance; LVC: left ventricular compliance; LAP: left atrial pressure.

hypertensive heart disease[82]. Patients with HFPEF are more prone to show higher number of slight individual anomalies in the ventricular and vascular reserve; recent evidence suggests that the acquisition of a sufficient number of individual abnormalities in the reserve promotes the transition of asymptomatic to symptomatic diastolic function in hypertensive HFPEF[33]. This way, HFPEF can be conceived as a fundamental disorder of the complex: cardiovascular reserve, of the diastolic, systolic, chronotropic and vascular function. Furter investigation is required to determine how these abnormalities can be efficaciously treated.

Diagnosis

In contrast with HFREF, the HFPEF diagnosis is more laborious, especially in patients who attend an outpatient clinic with effort dyspnea and multiple comorbidities, but without evident physical signs of fluid overload. To avoid low specificity in the diagnosis of HFPEF, effort dyspnea and a normal LVEF, should be complemented with objective measurements of LV diastolic dysfunction, left ventricular hypertrophy, left atrial (LA) compliance and area, or plasma levels of natriuretic peptides (NP), such as BNP.

So far, several guidelines have been published for the diagnosis of HFPEF[13,98-100]. All of them require the simultaneous and mandatory presence of signs and/or symptoms of HF, "normal" LV systolic function tests and evidence of LV diastolic dysfunction, such as LV hypertrophy, LA compliance and size, atrial fibrillation or plasma BNP elevated levels. The first working group on myocardial function is the European Society of Cardiology[98]. A second group of guidelines was provided by the Framingham Heart Study[99]. A third series of guidelines was proposed by Yturralde and Gaasch[100], who implemented in their assessment a major and minor criteria scoring system and the use of LV hypertrophy and LA size, as well as surrogate markers of LV diastolic dysfunction. Finally, the last group of guidelines was provided by the Heart Failure and Echocardiography associations of the European Society of Cardiology[13]. According to this last group, the diagnosis of HFPEF requires signs or symptoms of HF, a > 50% LVEF, a telediastolic volume < 97 ml/m^2, and evidence of LV diastolic dysfunction; additionally, LVEDP > 16 mmHg, PCP > 12 mmHg and/or a E/E' ratio > 15, this providing independent evidence of LV diastolic dysfunction, whereas BNP should always to associated with a E/E' > 8, a signal of the Doppler mitral flow velocity showing a E/A ratio < 0,5, deceleration time (DT) + > 280 ms, a signal of the pulmonary vein flow velocity showing an Ard-Ad index > 30 ms (where Ard: pulmonary vein flow duration at reverse atrial systole; Ad: atrial waves mitral valve flow duration), a LA size > 40 ml/m^2, or a LV mass > 149 g/m^2 (males) or > 122 g/m^2 (females) (Table 1).

Recently, our group has validated these indices in Mexican population. Valuable validation efforts made also by the Heart Failure and Echocardiography associations of the European Society of Cardiology have already addresed the subject to a certain extent, including (i) the diagnostic value of E/E' against a LV stiffness model calculated based on multiple LV volume-end-diastolic pressure points observed during balloon occlusion of the vena cava[101,102]; (ii) the diagnostic value of LA > 40 ml/m^2, LV mass > 149 g/m^2 (males)

or > 122 g/m^2 (females), Ard-Ad > 30 ms and E/A ratio < 0,5 DT + > 280 ms against E/E'[103], and (iii) the diagnostic value of NT-proBNP > 220 pg/ml against E/E'[104].

In contrast with recent criticism on the validity of E/E' as a measure of the LV filling pressures in patients with acute decompensated HFPEF[105], a direct comparison of E/E' against the flotation catheter derived from LV diastolic dysfunction models yielded a sensitivity of 83%, specificity of 92% and an area under the ROC curve of 0,907 for E/E' > as a measure of the high-rigidity model in HFPEF patients[102].

These results have suggested that an E/E' value > 8 can be able to provide independent evidence of LV diastolic dysfunction, without further need of non-invasive tests[106]. Hence, the distinctive value of E/E' can be explained as an indirect measurement of the LV filling pressures in HFREF and HFPEF[107]. A direct comparison between the diagnostic values of E/E' and pulmonary flow velocity showed that the latter is even poorly reliable for the diagnosis of LV diastolic dysfunction[103]. In contrast, however, a LA size > 40 ml/m^2 provides both high sensitivity and high specificity to detect E/E' > 15.

Effort test: An underestimated risk marker?

HFREF is characterized by dilation of the chamber and low LVEF, easily detectable by echocardiography. In HFPEF, the size of the chamber and the LVEF are normal, and the main hemodynamical alteration is an elevation of filling pressures[26].

When pressures are high and congestion is present at rest, HFPEF is easily diagnosed based on history and physical examination, x-rays, BNP levels and echocardiographic parameters[13].

However, many patients with early-stage HFPEF have significant effort intolerance symptoms in the absence of apparent volume overload. In some patients, an invasive evaluation can reveal pathological elevation of the filling pressures that was not previously suspected[108], and a recent study found that even among patients with normal echocardiographic tests, BNP levels and normal hemodynamics at rest, many can anyway develop pathological elevations in the filling pressures that are characteristic of HFPEF during exercise-induced stress[28]. The HFPEF diagnosis could only be made by using hemodynamical evaluation with exercise, since in these patients it was also a strong predictor of HFPEF. Pulmonary artery pressures give a very good idea of the left heart filling pressures in the early stages of HFPEF[28]. Therefore, assessment during effort is highly recommendable and necessary.

The E/E' ratio is one of the cornerstones in the non-invasive assessment of diastolic function at rest[13,14], and some groups have started using evaluations based on tissue Doppler imaging (TDI) during exercise, with the first studies showing reasonable correlations with invasive measurements[109]. However, E/E' can be less robust in the tachycardia and hyperventilation settings and in the fusion of early and late transmitral filling velocities. In patients not fulfilling the established criteria for positive HFPEF diagnosis[13], but in whom there is reasonable strong clinical suspicion, invasive assessment should be seriously considered when available measures on stress with exercise and at rest are normal[28].

Conclusions

HFPEF is an important and growing public health problem, given that currently it accounts for half of all patients with HF. In spite of improvements in the understanding of the disease, there are no treatments with entirely proven benefits. The advances on diagnostic algorithms, imaging projection and invasive assessment will allow for more accurate and early diagnosis, in order for treatments to be applied earlier in the progression of the disease, since the potential for benefit can be greater. Although important advances had been made in our understanding of the pathophysiology, hemodynamics and cell mechanisms of diastolic failure, as well as non-diastolic mechanisms of the disease, further investigation is urgently needed to determine how to better direct these abnormalities in order to reduce the important burden of morbidity and mortality of this form of HF, which is reaching pandemic proportions.

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