

# Heart failure with preserved ejection fraction (HFpEF): a basic and clinical perspective

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## Abstract

Up to 50% of patients with heart failure have a relatively normal ejection fraction; this is called “heart failure with preserved ejection fraction” or HFpEF. These patients are more likely to be older, female, hypertensive, obese, or to have metabolic syndrome or atrial fibrillation. They suffer substantial mortality and morbidity, but there are currently no treatments available proven to improve outcomes. Abnormal left ventricular diastolic function is thought to be a major feature of HFpEF, and its detection (or the detection of cardiac structural abnormalities that predispose to diastolic dysfunction) is a requirement for positive diagnosis in most diagnostic guidelines. However, noninvasive detection of left ventricular diastolic dysfunction and its distinction from normal cardiovascular aging may be difficult. Clinical assessment of patients during exercise or similar stress can be very valuable. The clinical pathophysiology of HFpEF is heterogeneous and involves not only diastolic dysfunction but also abnormalities in heart rate, heart rhythm, microvascular resistance, aortic stiffness, and ventricular-vascular coupling, resulting in impaired systolic and diastolic reserve capacity upon exercise. The mechanisms underlying these abnormalities are poorly understood. The phenotype bears similarity to normal cardiovascular aging and could involve similar abnormalities in inflammation and oxidative stress levels. Abnormalities in nitric oxide/cyclic guanosine monophosphate (cGMP) signaling also possibly contribute. To develop effective therapies for HFpEF, more rigorous clinical phenotyping and classification are probably needed to facilitate a better understanding of the disease pathophysiology and the development of more personalized treatments. ■ *Heart Metab.* 2016;71:4-8

**Keywords:** diastolic dysfunction; HFpEF; ventricular-vascular coupling

## Introduction

Chronic heart failure (CHF) affects nearly 6 million people in the United States and similar proportions in other industrialized countries.<sup>1</sup> The prevalence is projected to rise substantially over

the next 15 years, particularly in the >65 age group. It causes substantial mortality and morbidity and represents a major disease and socioeconomic burden. CHF is a systemic syndrome involving the heart, vasculature, kidneys, and other organs, but it develops primarily as a result of diverse acquired and/

### Abbreviations

**cGMP:** cyclic guanosine monophosphate; **CHF:** chronic heart failure; **EF:** ejection fraction; **HFpEF:** heart failure with preserved ejection fraction; **HFrEF:** heart failure with reduced ejection fraction; **HYVET:** HYPertension in the Very Elderly Trial; **LV:** left ventricular; **NO:** nitric oxide; **NOS:** nitric oxide synthase

or genetic structural and functional abnormalities of the heart. Forty percent to 50% of CHF patients have a form of heart failure in which left ventricular (LV) systolic function, as assessed by ejection fraction (EF) at rest, is relatively well preserved. This type of heart failure has come to be termed heart failure with preserved EF (HFpEF). The outcome of patients with HFpEF is on average slightly better than for those with reduced EF (HFrEF), but they still have substantial morbidity and mortality, eg, 23% mortality over 3 years in a large meta-analysis.<sup>2</sup> Furthermore, the prevalence of HFpEF relative to HFrEF is rising. Although many trials have had limited power, treatments used for patients with HFrEF (eg, inhibitors of the renin-angiotensin-aldosterone system,  $\beta$ -adrenergic blockers, biventricular pacemakers, and implantable defibrillators) have not been shown to reduce mortality in HFpEF. Current treatment is thus focused on comorbidities.<sup>3,4</sup> To develop effective specific treatments, there is a compelling need to better understand the pathophysiology of this type of heart failure.

### Diagnosis of HFpEF

The diagnosis of HFpEF is more difficult than HFrEF and more likely to be inaccurate. It is generally accepted that abnormal LV diastolic function (with or without other cardiovascular pathology, as discussed later) is a fundamental component of HFpEF. Current American Heart Association (AHA) guidelines require the presence of signs or symptoms of heart failure, a preserved EF (EF $\geq$ 50%), and objective evidence of LV diastolic dysfunction to diagnose HFpEF.<sup>3</sup> Because symptoms may be nonspecific and difficult to distinguish from those related to aging and comorbidities, such as obesity, and because EF is preserved, the demonstration of LV diastolic dysfunction becomes critical, especially in those without definitive signs (such as pulmonary edema). However, noninvasive

assessment of LV diastolic function is not always easy. Assessment during exercise—when diastolic abnormalities are more evident—is particularly valuable though not routinely performed. The most recent European Society of Cardiology (ESC) guidelines have added the presence of elevated natriuretic peptide (NP) levels as an essential requirement for the diagnosis of HFpEF.<sup>4</sup> However, not all patients with HFpEF (including those characterized by definitive invasive assessment) have elevated NP levels<sup>5</sup>; the use of these new criteria may therefore exclude important subsets of patients with HFpEF.

### Risk factors and heterogeneity

Whether HFpEF and HFrEF are distinct conditions or part of a spectrum has been debated, but it is clear that patient characteristics differ between the groups. HFpEF is especially common in the elderly. Patients with HFpEF are more likely to be female, have hypertension, obesity, metabolic syndrome, diabetes, atrial fibrillation, and to lead a sedentary lifestyle than those with HFrEF, and they are less likely to have ischemic heart disease. Transition of HFpEF to HFrEF may largely occur only in those who develop myocardial infarction.

There is significant phenotypic and probably pathophysiologic heterogeneity among patients with HFpEF. An important question is whether defining more homogeneous subpopulations might allow a better understanding of the underlying pathophysiology and identification of groups that respond favorably to specific therapies. This idea is supported by a recent unbiased clustering analysis of nearly 400 carefully diagnosed HFpEF patients; in the analysis, three distinct patient groups could be identified, which differed in clinical and cardiac structural/functional characteristics as well as outcomes.<sup>6</sup>

### Clinical pathophysiology

HFpEF was historically considered primarily to be a disorder of LV diastolic function (so-called “diastolic heart failure”). Although this is undoubtedly a major feature, it is now evident that HFpEF results from a complex and variable interplay of multiple defects in LV hemodynamic and reserve function, including abnormalities of heart rate and rhythm, vascular stiffness and resistance, and ventricular-vascular coupling.

LV diastolic dysfunction in HFpEF usually comprises both an impairment of active LV relaxation and an increase in passive (late diastolic) stiffness that together increase LV filling pressures. The latter may be especially evident during exercise, highlighting that the problem is essentially one of reserve capacity (as in CHF more generally).<sup>7</sup> The left ventricle is typically concentrically remodeled and hypertrophied but rarely dilated. Concentric LV remodeling and interstitial fibrosis contribute to elevated diastolic stiffness in HFpEF, but an important additional factor may be an increased cardiomyocyte sarcomeric stiffness, influenced by the giant elastic protein titin and its phosphorylation status.<sup>8</sup> In diabetic patients, increased stiffness related to advanced glycation end products may be important. Impairment of the myocardial energetic state on exercise, knowing that energy metabolism is crucial for active myocardial relaxation, may also contribute to diastolic dysfunction.<sup>9</sup>

Chronic elevation in LV filling pressure leads to pulmonary hypertension in many HFpEF patients, especially upon exercise. An associated impairment of right ventricular function predicts worse outcomes. Elevated filling pressures also predispose to atrial fibrillation, which is poorly tolerated because HFpEF patients are highly dependent on normal left atrial function to adequately fill the left ventricle. Many patients with HFpEF have an inadequate increase in heart rate upon exercise, related to abnormalities in autonomic balance, which impairs cardiac output and exercise capacity.

Vascular dysfunction is an important feature of HFpEF. An increase in aortic stiffness and central aortic pressure increases vascular hydraulic load on the left ventricle, adversely affects LV relaxation, and contributes to chronically increased wall stress that may drive concentric LV remodeling.<sup>10</sup> Myocardial perfusion reserve is often reduced, independent of coronary artery disease, which may in part be related to the increased vascular load. The potential importance of hypertension in HFpEF is illustrated by findings from the HYVET (HYpertension in the Very Elderly Trial) study, where indapamide (either with or without perindopril) compared with placebo reduced fatal or nonfatal heart failure events by 64% in patients with preexisting hypertension who were aged 80 years or more (but did not significantly reduce cardiac deaths).<sup>11</sup> Although the type of heart failure was not specifically defined in this study, the characteristics of the patients were such that a

substantial proportion of the heart failure would have been HFpEF. Patients with HFpEF also have reduced vasodilatation during exercise, which impairs their ability to increase stroke volume.<sup>12</sup> A defining characteristic of HFpEF is therefore vascular dysfunction and abnormal ventricular-vascular coupling, which compromises optimal hemodynamic function.

Although EF at rest is normal or only mildly reduced in HFpEF, the preceding discussion indicates that there is significant systolic impairment during exercise. Indeed, more sensitive indices of contractile function than EF readily identify subtle abnormalities of systolic function even at rest. However, there is a clear difference between HFpEF and HFrEF, with the left ventricle typically being concentrically remodeled and nondilated in HFpEF, whereas HFrEF is characterized by substantial LV thinning, dilatation, and systolic impairment at rest.

### Disease mechanisms

The underlying mechanistic basis for the multisystem abnormalities in patients with HFpEF is unknown and may vary among patients. Hypertension is an important factor in many patients. The *in vivo* dissection of potential disease mechanisms is quite challenging; at the same time, there are few reliable animal models of HFpEF.

Many pathophysiologic abnormalities found in typical HFpEF resemble those observed in normal aging (which is a dominant risk factor for HFpEF), albeit much more exaggerated. HFpEF could therefore be considered a form of premature cardiovascular aging.<sup>13</sup> The mechanisms underlying cardiovascular aging are complex and incompletely understood.<sup>13,14</sup> However, there is a consensus that there is a general disorder of multiple aspects of the signaling cascades and molecular pathways required to maintain cellular and organ homeostasis, driven for example by increasingly dysfunctional cellular defense pathways and by increased oxidative stress. It has been suggested that the cardiovascular aging phenotype is the consequence of inflammatory defenses generated by cells in an attempt to limit this molecular and signaling disorder.<sup>14</sup> From this perspective, a proinflammatory aging-related milieu may be an important aspect of the underlying mechanism in HFpEF.

Recently, it has been proposed that dysregulated nitric oxide (NO) signaling is an important contributor

to HFpEF pathophysiology.<sup>15</sup> NO generated by NO synthases (NOSs) regulates multiple aspects of cardiovascular function, including vascular tone, myocardial function, growth, energetics, and autonomic function. Endothelial NOS (eNOS) is expressed in endothelial cells and to a lesser extent in cardiomyocytes, whereas neuronal NOS (nNOS) is found in nerves, cardiomyocytes, and potentially in vascular smooth muscle. NO signaling involves the elevation of cyclic guanosine monophosphate (cGMP) and cGMP-dependent protein kinase (PKG) activity or the S-nitrosylation of specific protein targets. The potential of PKG to modulate cardiomyocyte stiffness via titin phosphorylation may be particularly relevant to HFpEF.<sup>8</sup> Interestingly, recent studies in small groups of highly selected HFpEF patients identified increased cardiomyocyte stiffness in myocardial biopsies, which was related to a reduced PKG-mediated phosphorylation of titin.<sup>16</sup> These authors proposed that HFpEF involves systemic endothelial dysfunction (most risk factors predisposing to HFpEF impair endothelial function) involving impaired bioactivity of endothelium-derived NO, for example, due to increased oxidative stress. It should be noted that randomized clinical trials of agents that enhance NO release (eg, the  $\beta$ -blocker nebivolol) or prevent cGMP breakdown (eg, the phosphodiesterase type 5 inhibitor sildenafil) were unsuccessful in HFpEF.<sup>17,18</sup> However, ongoing trials are assessing agents that directly stimulate cGMP formation (eg, vericiguat; NCT01951638).

Table 1 shows the potential pathophysiologic abnormalities that may be influenced by antihypertensive agents or by agents that target the NO-cGMP pathway.

Mechanism	Effects of antihypertensive treatment	Effects of NO-cGMP pathway modulation
Increased filling pressures	Reduced by diuretics	Some diuretic effect
Increased passive diastolic stiffness (structural)	Reduced by regression of LVH Possible specific effect of spironolactone	Reduced titin phosphorylation
Impaired LV relaxation	Improved by reduction in afterload	Improved relaxation
Systolic dysfunction	Improved by reduction in afterload	Possibly improved by reduction in afterload
Increased aortic stiffness	Reduced Possible specific effect of spironolactone	Minor effects
Increased wave reflection from conduit arteries	Reduced reflection (minor)	Reduced reflection
Microvascular dysfunction	Reduced peripheral resistance	Endothelium-derived NO beneficial
Skeletal muscle dysfunction	Possible effect	Improved mitochondrial respiration

**Table 1** Pathophysiologic mechanisms in heart failure with preserved ejection fraction (HFpEF) and potential benefits of antihypertensive treatments and manipulation of the nitric oxide-cGMP pathway.

**Abbreviations:** cGMP, cyclic guanosine monophosphate; LV, left ventricular; LVH, left ventricular hypertrophy; NO, nitric oxide.

## Summary and future perspective

The effective treatment of HFpEF represents a major unmet clinical need. Accurate diagnosis of the condition is difficult, and the mechanisms underlying the pathophysiology are poorly understood. HFpEF appears to be a highly heterogeneous condition in which different subgroups may require different therapeutic strategies. Although large randomized clinical trials have validated many new therapies for cardiovascular disease and prevention over the last 30 years, including new CHF treatments, they have relied on a simplicity of diagnosis and inclusion criteria that apparently has not worked well for the HFpEF population. We suggest that a more rigorous and detailed clinical phenotyping, diagnosis, and classification of HFpEF into more homogeneous subtypes is required in order to advance basic understanding of the pathophysiology and develop effective personalized therapies. ■

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