

Heart failure with preserved ejection fraction—where is the problem: heart or arteries?

Sebastian Ewen, MD; Michael Böhm, MD

Department of Internal Medicine III, Cardiology, Angiology, and Intensive Care, Saarland University Hospital, Homburg/Saar, Germany

Correspondence: Dr Sebastian Ewen, Department of Internal Medicine III, Cardiology, Angiology, and Intensive Care, Saarland University Hospital, Kirrberger Str., Geb. 40, 66421 Homburg/Saar, Germany
E-mail: Sebastian.Ewen@uks.eu

Abstract

Chronic heart failure is one of the most common chronic syndromes worldwide, with increasing prevalence and incidence. Heart failure with preserved ejection fraction seems to have a different epidemiology and etiology than heart failure with reduced ejection fraction. The present review aims to provide an overview of heart failure with preserved ejection fraction based on the current guidelines of the European Society of Cardiology. First, pathophysiologic concepts will be explained. Second, trials in patients with heart failure with preserved ejection fraction using evidence-based therapies from heart failure with reduced ejection fraction will be presented. Finally, new pharmacological developments, such as angiotensin–neprilysin inhibition and I_f -channel inhibition with ivabradine, will be discussed. ■
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Introduction

Chronic heart failure (CHF) is one of the most common chronic diseases worldwide, and its prevalence and incidence are increasing. CHF with preserved systolic function (HFpEF) accounts for 40% to 50% of all patients with CHF.¹ Approximately half of the patients with acute decompensated heart failure in emergency wards present with a normal ejection fraction (EF) of $\geq 50\%$. However, in contrast to heart failure with reduced EF (HFrEF; EF $<50\%$), there is no therapeutic strategy currently available that prevents cardiovascular death and hospitalization.² Nearly two-thirds of the patients with HFpEF die from cardiovascular causes,³ corresponding to an annual mortality rate between 10% and 30%.⁴ The

postdischarge prognosis for patients with HFpEF seems to be slightly superior to that in patients with HFrEF. However, rates of long-term mortality and hospitalization because of CHF are comparable.^{4,5} HFpEF is distinct from HFrEF, with different pathophysiology and etiology, comorbidities, clinical and demographic characteristics, and response to therapy (Figure 1).^{6,7} Crucial risk factors for developing HFpEF include age, female sex, hypertension, metabolic syndrome, diabetes mellitus, obesity, microalbuminuria, high waist-to-hip ratio, and physical inactivity.¹

HFpEF represents the cumulative expression of the above risk factors and comorbidities, which induce a systemic inflammatory state with increased plasma levels of interleukin (IL)-6, tumor necrosis factor (TNF)- α , soluble ST2 (sST2), and pentraxin 3.

Abbreviations

CHF: chronic heart failure; **CHAMPION:** CardioMEMS Heart sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA class III heart failure patients; **EDIFY:** Preserved Left Ventricular Ejection Fraction Chronic Heart Failure with Ivabradine Study; **HFpEF:** heart failure with preserved ejection fraction; **I-PRESERVE:** Irbesartan patients with heart failure and PRESERVED systolic function; **LV:** left ventricular; **PARAGON-HF:** Efficacy and Safety of LCZ696 Compared to Valsartan on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction; **SENIORS:** Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure; **SOCRATES:** SOLuble guanylate Cyclase stimulator heART failure Studies; **TOPCAT:** Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist Trial

These lead to increased expression of vascular cell adhesion molecule 1 and activate the cardiac endothelium, with a consequent decrease in the production of nitric oxide, an agent known to exert direct antifibrotic effects through the cyclic guanosine monophosphate pathway (Figure 2).^{1,8,9} Diastolic stiffness is attributed to excessive myocardial collagen deposition and cardiomyocyte stiffness, of which the latter is

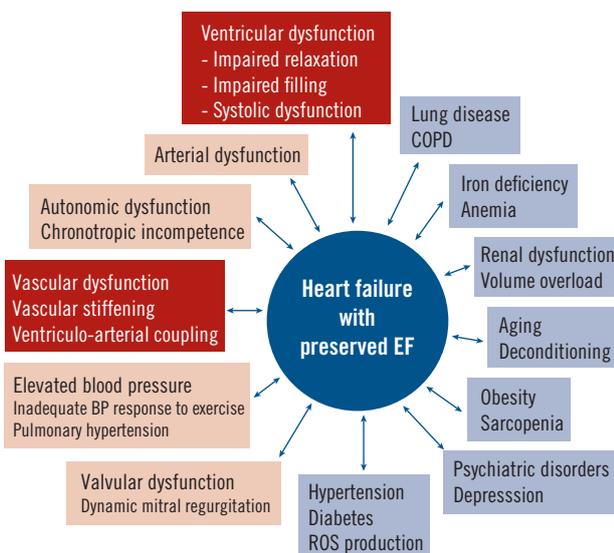


Fig. 1 Heart failure with preserved ejection fraction. Schematic showing potential cardiovascular risk factors, cardiovascular abnormalities, and other comorbidities that may be present.

Abbreviations: BP, blood pressure; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; ROS, reactive oxygen species.

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necessary to induce HFpEF without any involvement of the extracellular matrix.¹⁰ In addition, coronary microvascular disease is involved in the pathophysiology of the development of HFpEF.⁹ This new conceptual paradigm has shifted the emphasis from excess left ventricular overload to coronary microvascular pathology. This hypothesis was supported by findings of an association between microvascular density and left ventricular fibrosis in autopsy specimens from subjects with an antemortem diagnosis of HFpEF.¹¹ Numerous pathophysiologic mechanisms for coronary microvascular dysfunction, including endothelial, smooth muscle, and sympathetic dysfunction; microvascular spasm; extramural rarefaction; and luminal obstruction, have been hypothesized (Figure 3).¹² Further understanding of the underlying pathogenesis of HFpEF is necessary to find novel treatment options and improve the prognosis of these patients.

Clinical trials

The current guideline states that “no treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFpEF.”² The current recommendation is to use diuretics to control sodium and water retention and reduce dyspnea and edema. Furthermore, hypertensive therapy should include

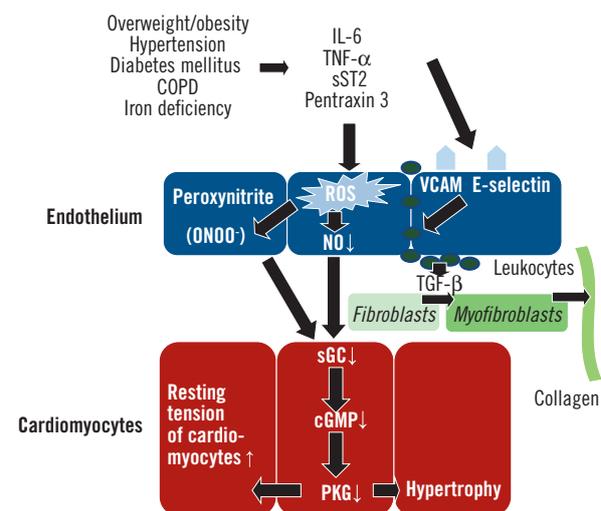


Fig. 2 Myocardial remodeling in heart failure with preserved ejection fraction.

Abbreviations: cGMP, cyclic guanosine monophosphate; COPD, chronic obstructive pulmonary disease; IL-6, interleukin 6; NO, nitric oxide; PKG, protein kinase G; ROS, reactive oxygen species; sGC, soluble guanylate cyclase; sST2, soluble ST2; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; VCAM, vascular cell adhesion molecule.

After reference 9: Paulus and Tschope. J Am Coll Cardiol. 2013;62(4):263-271. © 2013, American College of Cardiology Foundation.

β -blockers and angiotensin-converting enzyme (ACE) inhibitors (or angiotensin II receptor blockers [ARBs]); in case of myocardial ischemia, β -blocker therapy is obligatory; and in case of atrial fibrillation, the heart rate should be controlled in order to improve symptoms. Over the past few years, a number of established treatments for HFpEF have been tested in patients with HFpEF. However, even pharmacological therapies that had a reliable evidence base in HFpEF achieved only neutral results in randomized clinical trials in HFpEF.

β -Blocker trials have failed to provide conclusive results in HFpEF. Subgroup analysis of the results from the SENIORS trial (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure) showed that the efficacy of nebivolol in patients with HFpEF (mean EF, 49%) was similar to its efficacy in those with HFpEF (mean EF, 29%) in reduction of all-cause and cardiovascular mortality.¹³ However, a meta-analysis of 15 observational studies and two randomized controlled trials including more than 27 000 patients reported that whereas β -blockers were beneficial in terms of mortality in observational studies, this was not shown in the randomized controlled trials.¹⁴ Meta-analysis of the observational trial results indicated that β -blocker treatment reduced all-cause mortality, but not hospitalization for CHF. On the other hand, the randomized

controlled trial results indicated no significant effect of the use of β -blocker on either end point. The authors of the meta-analysis concluded that further randomized clinical trials with β -blockers for HFpEF are certainly warranted.

There is also no evidence of any clinical benefit associated with the use of ACE inhibitors, ARBs, endothelin antagonists, or metalloproteinase inhibitors in HFpEF from randomized controlled trials.^{15,16} Even spironolactone, which is known to have a positive effect on left ventricular mass and aortic stiffness,¹⁷ failed to demonstrate a benefit in the TOPCAT study (Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist Trial; NCT00094302).¹⁸ TOPCAT included 3445 patients with HFpEF and compared the effect of spironolactone (15-45 mg/day) with that of placebo. After 72 months, there was no significant difference in the primary end points of cardiovascular death, cardiac arrest, or hospitalization for CHF.¹⁸ Only hospitalization for CHF as an individual component achieved a significant improvement in the spironolactone group ($P=0.04$). The overall neutral results of the trial might be explained by methodological problems, including enrolment based on clinical symptoms and hospitalization or B-type natriuretic peptide (BNP) levels. Another factor may have been the regional variations, since patients from the Americas (USA, Canada, Brazil, and Argentina) appeared to be at a five times higher risk for the primary end points than patients in Russia or Georgia. A post hoc analysis of the TOPCAT data indicated that there were greater potassium and creatinine changes with spironolactone in the patients from the Americas, and this may well translate into greater clinical benefit.¹⁹

Experimental data suggested that the phosphodiesterase-5 inhibitor sildenafil prevents cardiac and myocyte remodeling in advanced hypertrophy²⁰ and would, therefore, be beneficial in the treatment of HFpEF. However, a randomized double-blind, placebo-controlled clinical trial in 216 outpatients with a median left ventricular EF (LVEF) of 60% failed to demonstrate improvements in exercise capacity or clinical status over 24 weeks of treatment.²¹ There are a number of treatments currently under exploration for HFpEF, of which at least some may lead to an evidence-based management strategy for this condition. One avenue for research involves advanced glycation end products, which may play a role in

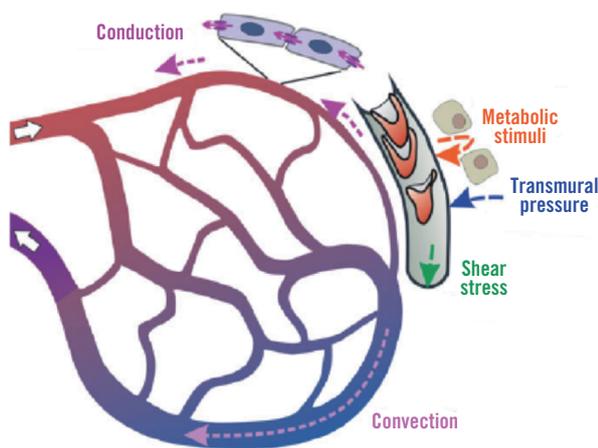


Fig. 3 Model for vascular diameter adaptation in microvascular networks. Such adaptation occurs through the response of microvascular vessels to signals that are transmitted upstream by conduction through gap junctions in the vessel wall, signals transmitted by convection of substances with blood flow downstream, metabolic stimuli, and local hemodynamic signals—such as transmural pressure and wall shear stress.

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the development and progression of CHF and have, therefore, been considered as potential targets in HFpEF.²² Another treatment showing great promise is the angiotensin receptor–neprilysin inhibitor LCZ696, which reduced N-terminal-proBNP in a phase 2 trial in 300 patients with HFpEF (LVEF \geq 45%).²³ LCZ696 is currently being tested on a large scale in the phase 3 trial PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction; NCT01920711). The first results of PARAGON-HF are expected by the start of 2019. Molecules that stimulate the soluble guanylate cyclase pathway are also undergoing phase 2 testing in patients with HFpEF. The agent vericiguat is currently being investigated in the SOCRATES trial (SOluble guanylate Cyclase stimulator heArT failure Studies; NCT01951638), which intends to recruit a mixed population of patients with HFpEF (470 patients to be randomized) and HFrEF (410 patients).²⁴

Another topic of interest is the use of pharmacological heart rate reduction, other than by β -blockers. This is particularly relevant because elevated resting heart rate is known to predict mortality in HFpEF. An analysis in the I-PRESERVE (Irbesartan patients with heart failure and PRESERVED systolic function; NCT0095238) database of patients with HFpEF (LVEF $>$ 45%) showed that every 12-beats-per-minute increase in heart rate was associated with a 13% increase in risk for a composite of cardiovascular death or hospitalization for CHF.²⁵ Preliminary and experimental results with the I_f inhibitor ivabradine indicated potential for heart rate reduction in HFpEF.^{26,27} Ivabradine is currently undergoing further phase 2 testing for HFpEF in the ongoing EDIFY trial (Preserved Left Ventricular Ejection Fraction Chronic Heart Failure with Ivabradine Study; EUCTR2012-002742-20-DE). According to the concept that heart rate reduction might be important in HFpEF, novel devices and treatments with this target, such as vagal and carotid artery stimulation, are under investigation. Another avenue that is being actively explored is wireless pulmonary artery pressure monitoring as a guide for management. In the single-blind, randomized CHAMPION trial (CardioMEMS Heart sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA class III heart failure patients; NCT00531661), microelectromechanical pressure sensors were implanted during right heart catheterization in patients

with HFpEF.²⁸ Participants were then randomly allocated to either receive treatment guided by daily recorded pressures or normal treatment. Over nearly 18 months of follow-up, those in the guided-treatment group were 50% less likely to be hospitalized for HF.²⁸ Further studies of this approach are required. In addition to the formal treatment with pharmacological agents or other interventions, the effect of lifestyle changes on HFpEF is also being explored. A recent trial on endurance exercise training showed positive results in 40 patients with HFpEF, with improvements in peak oxygen consumption and exercise capacity after 4 months.²⁹

Conclusion and perspectives

HFpEF is a complex disorder caused by multifactorial stresses secondary to comorbidities. To date, only the prevention of HFpEF through treatment of risk factors has been effective.³⁰ Finding new multidirectional strategies to abrogate endothelial dysfunction and subsequent cardiac remodeling will be challenging. Further randomized controlled trials are needed to prove the hint of positive results in phase 2 trials and achieve an evidence-based treatment for this difficult-to-treat disease. HFpEF—where is the problem: the heart or the arteries? Probably both! ■

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