European Journal of Heart Failure (2015) **17**, 665–671
doi:10.1002/ejhf.304

REVIEW

Heart failure with preserved ejection fraction: uncertainties and dilemmas

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Received 9 January 2015; revised 10 March 2015; accepted 24 April 2015; online publish-ahead-of-print 16 June 2015

Many uncertainties surround the syndrome of heart failure with preserved ejection fraction (HFpEF), which was the topic reviewed in an Expert Meeting at the University of Ferrara. This concluded that the absence of clear diagnostic clinical criteria was the major barrier to progress. There was general agreement that symptoms or signs of heart failure, normal LVEF despite an elevated plasma concentration of natriuretic peptides, and signs of abnormal LV relaxation, LV filling, LV hypertrophy, or left atrial enlargement, or diastolic dysfunction supported the diagnosis. However, HFpEF, like all heart failure syndromes, is heterogeneous in aetiology and pathophysiology, rather than being a single disease. HFpEF may account for about half of all patients with heart failure. The classical risk factors for developing HFpEF include age and co-morbidities, notably hypertension, atrial fibrillation, and the metabolic syndrome. When complicated by increasing congestion requiring hospital admission, the prognosis is poor; 30% or more of patients will die within 1 year (nearly two-thirds die from cardiovascular causes). Patients with chronic stable symptoms have a much better prognosis. Despite many clinical trials, there is no solid evidence that any treatment alters the natural history of HFpEF. Several treatments have shown promising early results and are now being tested in substantial randomized clinical trials. Further basic research is required to better characterize the disease and accelerate progress. Our review highlights the many difficulties encountered in performing randomized clinical trials in HFpEF, often due to difficulties in characterizing HFpEF itself.

Keywords Heart failure • Preserved ejection fraction

Introduction

The scientific community was, for years, puzzled by the recognition that patients could present classical signs and symptoms of congestive heart failure (HF) despite having a normal LVEF. In 2001, a short paper in the *New England Journal of Medicine* set to overturn the field of HF. In a relatively small-scale study in just 38 patients, Gandhi *et al.*[1] showed that patients with hypertensive acute pulmonary oedema and HF had the same LVEF during the acute phase as after successful treatment when the signs of HF were no longer present. This report constituted the first definitive observation that it was possible to have the clinical symptoms of HF without having reduced LVEF. Since that time, uncertainties have reigned surrounding the characteristics and the management of patients with heart failure with preserved ejection fraction (HFpEF). This short review is a summary of a closed Expert Meeting organized at the University of Ferrara on HFpEF to discuss this complex and still unrevealed field.

The scepticism and the wording

To differentiate from systolic HF (characterized by a markedly reduced LVEF, i.e. HFrEF), the condition was initially referred to as 'diastolic heart failure', a notion that led to much scepticism and many long discussions over wording in the cardiology community. There were two factions of cardiologists, divided according

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to whether they were for or against a clear separation between systole and diastole (which is, of course, physiologically impossible). It was then suggested that the size of the ventricle could differ between the two conditions—even though it would have been difficult to refer to 'small heart failure' vs. 'large heart failure'! Another proposed alternative is heart failure with normal ejection fraction (HFNEF).[2] Eventually, the European Society of Cardiology (ESC) Guidelines settled on the wording used in this paper, 'heart failure with preserved ejection fraction', or 'HFpEF',[3] which is a clearer compromise since it depends on objective measurement of LVEF, a parameter that cardiologists love and understand.

This dominance of LVEF may seem strange in an era in which cardiologists tend to promote the use of biological indices for diagnosis, such as B-type natriuretic peptide (BNP) (or its precursor N terminal-proBNP (NT-BNP)), which is typically elevated in classical HFrEF. On the other hand, most patients with HFpEF have significantly lower NT-proBNP levels than their HFrEF counterparts.[4,5] This can be explained in terms of end-diastolic wall stress, which is a trigger for BNP production and release, and has been found to be lower in HFpEF.[4] However, insofar as almost a third of HFpEF patients have normal levels of BNP, then BNP cannot be used to exclude a diagnosis of HFpEF, and LVEF remains the best option to distinguish between the two conditions.[6] However, the BNP issue is not trivial. In strict terms, patients with normal BNP and normal EF are not likely to suffer from HF, and yet they may have been randomized in some of the trials, adding to uncertainties on the syndrome of HFpEF. The availability of an objective parameter is essential to diagnosis because HF is a highly subjective condition. Indeed, the results of a recent study of 405 elderly patients in long-term care found that a majority of HF cases (90%) were undiagnosed and—equally alarmingly—that 76% of previous HF diagnoses were actually misdiagnoses.[7] This illustrates the poor diagnostic reliability of the common signs and symptoms of HF.

It follows that the diagnostic criteria for HFpEF are currently signs or symptoms of heart failure, normal LVEF, and signs of abnormal LV relaxation, LV filling, LV hypertrophy, or left atrial enlargement, or diastolic dysfunction.[3,8] To complicate matters further, we should note that measuring diastolic function is difficult and that BNP patients with normal diastolic function can be erroneously targeted as HF patients. Moreover, in patients with HFpEF, right ventricular systolic and diastolic dysfunction are common and could contribute to the symptomatology of patients and predict poorer outcomes. This may even constitute an important target for treatment.[9,10] As such, HFpEF remains a difficult diagnosis and one largely based on exclusion. Furthermore, patients may have co-existent abnormalities in systolic function or even normal diastolic function. For example, echocardiographic analyses of randomized controlled trials in HFpEF suggest that >30% may have normal diastolic function, which could also be related to fortuitous LV unloading because of prior administration of diuretics.[11] Finally, the predictors of HFpEF are neither specific nor sensitive. Indeed, there is a need for an update of the guidelines to clarify the diagnostic criteria for HFpEF.

Common and not benign, and yet unclear

Heart failure with preserved ejection fraction accounts for 40–50% of all HF. About half of acute HF patients have preserved systolic function or just mild dysfunction. This may be one of the reasons behind the disappointing results for pharmacological treatment of acute HF: the trials included unselected patients, with both reduced or preserved EF, and these patients—as we shall see later—have a totally different pathology. Patients with HFpEF have poor outcomes generally, though whether they fare worse, similarly to, or better than HFrEF patients remains unclear.[12–16] The immediate post-discharge prognosis appears to be slightly better in HFpEF, though rates of long-term mortality or readmission are similar,[13,17] and prior HF hospitalization identifies HFpEF patients at the highest risk.[18] Evidence for the utility of BNP in determining prognosis is mixed. Results from the 10-year Copenhagen Heart Failure Study showed that use of a diagnosis requiring elevated NT-proBNP resulted in a lower measured prevalence of HFpEF and a similar rate of survival to HFrEF.[19] In contrast, when NT-proBNP is not considered in the diagnosis, then HFpEF is associated with a lower rate of mortality than HFrEF.

Annual mortality in HFpEF ranges from 10% to 30%.[13] Nearly two-thirds (60%) of HFpEF patients die from cardiovascular causes, mostly sudden death and heart failure death.[20,21] Data on cause of death are highly variable, with rates of cardiovascular death of 70% in clinical trials vs. 51–60% in epidemiological studies.[22,23] Non-cardiovascular deaths constitute a higher proportion of deaths in HFpEF than in HFrEF, with fewer deaths due to coronary artery disease (CAD). Key mortality risk factors include age, gender, body mass index, co-morbidity burden, and CAD.

Uncertainty and patient profiles

All the evidence suggests that HFpEF is a separate syndrome from HFrEF. To underline the differences, the two differ in terms of pathophysiology and aetiology, co-morbidities, clinical and demographic characteristics, time to overt disease, structural and functional remodelling (with a smaller ventricle with concentric LV hypertrophy in HFpEF and eccentric dilated remodelling in HFrEF), neurocrine activation and biochemical parameters, and response to therapy.[22,24–28] The transition from HFpEF to HFrEF appears to occur principally in patients with intercurrent myocardial infarction.[29]

As regards patient profiles, compared with HFrEF, patients with HFpEF are generally older, more likely to be female, and have higher body mass index; they also have higher rates of iron deficiency, hypertension, and atrial fibrillation (AF), and have less CAD or valvular disease.[13,14,30]

Pathophysiology and dilemmas

Independently of whether it is correct or not, considering HFpEF and HFrEF as two separate entities can aid our understanding of the pathophysiology of the disease. Indeed, HFrEF can be regarded

as a cardiac syndrome, driven by myocardial cell loss and fibrosis, with an important systemic (neurohormonal) component, which is eventually responsible for the symptoms and constitutes a key target for antineurohormonal therapy. On the other hand, and quite to the contrary, HFpEF seems to be a systemic syndrome driven by accumulated risk factors and co-morbidities, which, in vulnerable subjects, causes the symptoms of HF, probably due to loss of compliance and adaptability of both heart and vessels. Therefore, schematically, we might say that there are two syndromes: one starting from the heart and leading to the periphery, HFrEF; and one starting from the periphery and leading to the heart, HFpEF.[31]

The classical risk factors for developing HFpEF include age, female gender, hypertension, metabolic syndrome, diabetes, obesity, renal dysfunction, waist-to-hip ratio, and physical inactivity,[32,33] such that 85% of HFpEF patients have metabolic syndrome. Consequently, like the metabolic syndrome, HFpEF is widely regarded as an inflammatory disease, for which there are two hypotheses. In one of these, HFpEF reflects the cumulative expression of the above risk factors and co-morbidities, which leads to a systemic proinflammatory state, activating the endothelium, with a consequent decrease in nitric oxide (NO) production. The presence of free radicals leads to cardiomyocyte dysfunction and hypertrophy, particularly related to diastolic function.[31] The alternative hypothesis is that all the risk factors and co-morbidities are united by a common thread consisting again of a systemic inflammatory state, leading to endothelial dysfunction and driving the clinical syndrome. In accordance with this, the prevalence of diastolic dysfunction increases with age in the general population, and HFpEF is classically a disease of the elderly.[33]

A number of studies have been performed over the last 10 years in HFpEF, mainly on biopsied tissue from patients, exploring differences in myocardial structure, cardiomyocyte function, and intramyocardial signalling in patients with HFpEF or HFrEF.[31] A study in 12 HFpEF patients with LVEF of $71 \pm 11\%$ showed that they had more hypertrophied and stiffer cardiomyocytes than controls.[34] Another study reported that LV myocardial structure and function differed in HFpEF and HFrEF, notably showing that myofibrillar density is normal in HFpEF.[35] Indeed, there is an increased resting tension in the myocytes when LVEF is at normal levels, and an increase in adhesion molecules (i.e. activation of the endothelium).[36] Recent studies in patients with hypertension with or without HFpEF suggested that the development of HFpEF depends on changes in both cardiomyocyte dysfunction (titin homeostasis) and interstitial components (collagen homeostasis).[37] Inflammation has been demonstrated to play a role in HFpEF by triggering extracellular remodelling and fibrosis.[38] Finally, there is also evidence that HFpEF patients have increased oxidative stress, most probably due to the prevalence of metabolic co-morbidities.[39] Age-related changes in body mass correlate positively with changes in end-systolic elastance and stiffness,[40] supporting the notion that HFpEF is related to the metabolic syndrome. Further support for these findings in patients comes from preliminary animal studies suggesting that myocardial microvascular inflammation and oxidative stress (particularly in the endothelium) play an important role in HFpEF (C. Franssen *et al.*, unpublished data). All together, these results suggest that HFpEF is essentially due to endothelial dysfunction, while HFrEF is due to cardiomyocyte dysfunction. Of course, it is important to have animal models resembling the course of events leading to HFpEF. Unfortunately, at the present time, such models do not exist. The major difficulty is reproducing all of the co-morbidities in aged animals, whereas laboratory animals are usually young and healthy. This is probably the reason why we know more about the pathophysiology of HFrEF (where some animal models exist) than HFpEF.

Trials and tribulations in heart failure with preserved ejection fraction

Although many treatments have been tested in HFpEF, the European guidelines are categorical:[3] 'No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFpEF'. They go on to recommend diuretics to control sodium and water retention, and relieve breathlessness and oedema. It is also recommended to manage any hypertension with beta-blockers, ACE inhibitors, or ARBs, myocardial ischaemia with beta-blockers, and control heart rate in the case of AF to improve symptoms. Most of the drugs that should be avoided in HFrEF should also be avoided in HFpEF; exceptions include verapamil and diltiazem, which are not recommended in HFrEF but can be used in HFpEF.

Treatments with neutral trials

A number of treatments have returned neutral results in randomized clinical trials in HFpEF. Experimental data suggested that the phosphodiesterase-5 inhibitor sildenafil prevents cardiac and myocyte remodelling in advanced hypertrophy,[41] and would therefore be of promise in HFpEF. However, a randomized double-blind, placebo-controlled clinical trial in 216 stable outpatients with HFpEF (median LVEF 60%) failed to detect any improvement in exercise capacity or clinical status over 24 weeks of treatment.[42] There is also no randomized controlled trial evidence for any clinical benefit associated with use of ACE inhibitors, ARBs, endothelin antagonists, or metalloproteinase inhibitors in HFpEF.[3,43–45]

Treatments with inconclusive trials

Even though spironolactone has a positive effect on LV mass and aortic stiffness,[46] the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial) trial failed to demonstrate a benefit.[47] TOPCAT assigned 3445 patients with HFpEF (LVEF $\geq$45%) to spironolactone (15–45 mg/day) or placebo for 3 years. There was no difference in the primary endpoint of cardiovascular death, cardiac arrest, or hospitalization for HF [hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.77–1.04, $P = 0.14$].[47] The overall neutral results of the trial may have been related to methodological problems, including enrolment on the basis of either clinical symptoms and hospitalization or BNP criteria, and the trial should be repeated.[48] Another factor may have been regional variations, since the patients from Russia

or Georgia appeared to be at four times lower risk for the primary endpoint than the patients from the Americas (USA, Canada, Brazil, and Argentina). 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 that this may well translate into greater clinical benefits.[49] The authors traced these differences to variations in the clinical diagnostic criteria used in the two regions.

The beta-blocker trials have also failed to provide conclusive results in HFpEF. A small-scale trial with carvedilol suggested that long-term therapy with a beta-blocker could improve diastolic function, with prevention or partial restoration of LV dilatation.[50] Analysis of data from the SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure) trial reported that nevibolol had a similar efficacy in a subgroup of patients with HFpEF (mean LVEF 49.2%) compared with those with HFrEF (mean LVEF 28.7%) in terms of prevention of all-cause and cardiovascular mortality.[51] Pooled data from three randomized controlled trials are suggestive of a positive impact on outcomes, with a trend towards a significant reduction in all-cause mortality [odds ratio (OR) 0.75, 95% CI 0.54–1.03],[52] but this remains to be confirmed.

A recent meta-analysis of 15 observational studies and 2 randomized controlled trials in >27 000 patients deduced that there were mortality benefits of beta-blockers in observational studies, but not in randomized controlled trials.[53] Meta-analysis of the observational trial results indicated that treatment with a beta-blocker reduced all-cause mortality [relative risk (RR) 0.81, 95% CI 0.72–0.90], but not hospitalization for HF (RR 0.79, 95% CI 0.57–1.10). On the other hand, the trial data indicated no significant effect of the use of beta-blocker on either endpoint (RR 0.94, 95% CI 0.67–1.32, and RR 0.90, 95% CI 0.54–1.49, respectively). As the authors of that meta-analysis conclude, further randomized clinical trials are certainly warranted with beta-blockers in HFpEF.

Treatments with promise

There are a number of treatments currently in exploration for HFpEF, some of which may lead to an evidence-based management strategy for this condition. One avenue for research concerns advanced glycation end-products (AGEs), which have been surmised to play a role in the development and progression of HF and have therefore been considered as potential targets in HFpEF.[54] Small-scale studies with AGE cross-link breakers have had mixed success. In one open-label study with 23 HF patients (LVEF >50%), 16 weeks of treatment with the AGE breaker alagebrium resulted in improvements in LV mass and LV diastolic filling, along with improvements in quality of life on the Minnesota Living with Heart Failure score.[55] Even though a later proof of concept study in patients with HFrEF (LVEF ≤45%) failed to find a beneficial effect for alagebrium,[56] these concepts still merit further exploration.

Data from the 4S trial in coronary heart disease suggested a possible use for statins in preventing the occurrence of HF in patients without previous evidence for congestive HF.[57] These are also supported by experimental studies indicating that statins prevent the development of cardiac hypertrophy and reduce fibrosis.[58,59] Preliminary clinical trial results in 137 patients with HFpEF (LVEF ≥50%) were positive for statins, with a substantial improvement in all-cause mortality over 21 months vs. patients without statins (RR for death 0.2, 95% CI 0.07–0.64, $P = 0.006$).[60] Interestingly, the same analysis failed to find similar effects for beta-blockade, an ACE inhibitor or ARB, or a calcium channel blocker.[60] The case for statins has also found support in registry data. A report from the EuroHeart Failure Survey analysed just over 6800 HF patients, nearly half of whom (46%) had HFpEF.[61] The patients who were receiving statins did substantially better in terms of all-cause mortality over 12 weeks. A recent meta-analysis of nearly 18 000 patients in 11 studies clearly supported the hypothesis that the use of statins may improve survival of HFpEF patients,[62] calling for further randomized controlled trials of statins in this patient population. It is relevant to recall that statins failed to improve outcomes in two mega-trials in patients with HFrEF.[63,64] If benefits of statins in HFpEF were to be confirmed in properly randomized controlled studies, this would further emphasize the different pathophysiological background of the two conditions.

Another treatment showing great promise is the angiotensin receptor–neprilysin inhibitor LCZ696, which has been demonstrated to reduce NT-proBNP in a phase II trial in 300 patients with HFpEF (LVEF ≥45%).[65] LCZ696 is currently being tested on a large scale in the phase III trial PARAGON-HF (Efficacy and Safety of LCZ696 compared to Valsartan on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction study) (NCT01920711).

Molecules that stimulate the soluble guanylate cyclase pathway are also undergoing testing in phase II in patients with HFpEF. The agent verciguat 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 both HFpEF (470 patients to be randomized) and HFrEF (410 patients).[66]

A number of other agents and classes are of promise, but require further investigation. For example, antifibrotic, antihypertrophic, and anti-inflammatory agents have shown positive results in HFpEF in registries. Another candidate compound is ranolazine. There are experimental data for I_{Na},[67–69] and a proof of concept study in 20 patients with HFpEF recently reported that ranolazine improved haemodynamic parameters but not relaxation.[70] Full-scale clinical trials with ranolazine in HFpEF have not yet been initiated.

Another interesting avenue is the use of pharmacological (and not only) heart rate reduction, especially as elevated resting heart rate is known to predict mortality in HFpEF.[71,72] An analysis in the I-PRESERVE (Irbesartan Patients with Heart Failure and Preserved Systolic Function) database in patients with HFpEF (LVEF >45%) showed that every 12.4 b.p.m. (standard deviation) increase in heart rate was associated with a 13% increase in risk for a composite of cardiovascular death or hospitalization for HF.[72] Preliminary and experimental results with the I_f inhibitor ivabradine indicated potential for heart rate reduction in HFpEF.[73–75] Ivabradine is currently undergoing further phase II testing in HFpEF in the ongoing EDIFY (Preserved Left Ventricular Ejection Fraction Chronic Heart Failure with Ivabradine Study) trial (EUCTR2012-002742-20-DE). According to the concept that heart rate reduction might be

important in HFpEF, novel devices and treatments with this target are under investigation, such as vagal and carotid artery simulation.

Another avenue that is being actively explored is wireless pulmonary artery pressure monitoring to guide management. In the single-blind randomized CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial, 119 HFpEF patients were implanted with a microelectromechanical pressure sensor during right heart catheterization.[76] The participants were then randomly allocated to treatment guided by the daily recorded pressures or normal treatment. Over nearly 18 months follow-up, those in the guided treatment group were 50% less likely to be hospitalized for HF.[76] Clearly, further studies of this approach are warranted.

Finally, beyond formal treatment with pharmacological agents or other interventions, the effect of lifestyle changes in HFpEF is also being explored. A recent trial of constant exercise training reported positive results in 40 patients with HFpEF,[77] with improvements in peak oxygen consumption and exercise capacity after 4 months. Should we ignore pharmacological treatment and concentrate simply on a healthy lifestyle?

Conclusion

This was an Expert Meeting of just 1 day. The experts discussed and enjoyed the topic. However, apart from a general agreement that HFpEF exists, the only real consensus was that it is difficult from existing data to provide clear avenues for future research. We need to be clearer on the patients involved in the clinical trials, as well as the protocols of the animal studies. It is also becoming important to have a clear definition for registries to ensure proper epidemiological evaluation of the scale of the problem. It is fundamental to fulfil these still unmet needs in order to find the right road to beat this clinically important dilemma. Only then can we hope to find a promising treatment that can transform into a reality for patients. We are convinced that this goal will be achieved with teamwork and brainstorming activities such as the University Meeting held in Ferrara.

Funding

This work was supported by a grant from Fondazione Anna Maria Sechi per il Cuore (FASC), Italy. The funders had no role in the study design, data collection and analysis, decision to publish, or the preparation of the manuscript.

Conflicts of interest: R.F. reported that he received honoraria from Servier for steering committee membership, consulting, and speaking, and support for travel to study meetings. In addition, he received personal fees from Boehringer-Ingelheim, Novartis, Merck Serono, and Irbtech. M.B. reported that he was a member of the following Advisory Boards: Astra Zeneca, Bayer AG, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, Sanofi-Aventis, and Servier; and of the Bureau for: Astra Zeneca, AWD Dresden, Bayer AG, Boehringer Ingelheim, Berlin-Chemie, Daiichi-Sankyo, MSD, Novartis, Pfizer, Sanofi-Aventis, Servier, and Medtronic. He also received study support from: Astra Zeneca, Bayer AG, Boehringer Ingelheim, Novartis, Pfizer, Sanofi-Aventis, Servier, and Adrian-Medtronic. J.G.C. reported that he received honoraria and research funding from Servier and Novartis and participates in studies of ivabradine (EDIFY) and LCZ696 (PARAGON) in patients with HFpEF. He has also received research support from Roche, which manufactures NT-proBNP that has an important diagnostic role in this context. W.J.P. is supported by the FP7 programme (Health 2010; MEDIA; 261409). He received honoraria from Servier and Amgen. B.P. is member of speakers' bureau and/or steering committee for Bayer Healthcare, Novartis, Stealth Peptides, and CVRx. C.R. has no conflict of interest to report. L.T. is a trial committee member and member of the speaker's bureau for Servier, and trial committee member for Boston Scientific, Medtronic, Cardiorentis, CVIE Therapeutics, ZS Pharma, and St Jude Medical.

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