Novel insights into heart failure with preserved ejection fraction

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Chapter 5

Clinical implications for patients with heart failure with preserved ejection fraction

5.1. Heart failure with preserved ejection fraction: a clinical dilemma.

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is now recognized as a major and growing public health problem worldwide. Yet significant uncertainties still surround its pathophysiology and treatment, leaving clinicians in a dilemma regarding its optimal management. Whether HFpEF and Heart Failure with Reduced Ejection Fraction (HFrEF) are two distinct entities or two ends of a common spectrum remains a matter of debate. In particular, the lack of benefit observed with renin angiotensin system blockers has raised questions regarding our understanding of the pathophysiology of HFpEF. New paradigms including a prominent role of comorbidities, inflammation, endothelial dysfunction and pro-hypertrophic signalling pathways have been proposed. Recent proof of concept trials using a phosphodiesterase inhibitor, a mineralocorticoid receptor antagonist, an angiotensin receptor / neprilysin inhibitor, a soluble guanylate cyclase stimulator or a sino atrial If current blocker provide important insight for the development of novel therapeutic strategies in HFpEF.

INTRODUCTION

Historically, clinical trials in heart failure (HF) required a low left ventricular ejection fraction (LVEF), a rather crude measurement of cardiac function, as an inclusion criterion. Indeed, these clinical trials in HF with reduced EF (HFrEF) were highly successful in identifying effective therapies which improved survival in HFrEF. However, large epidemiologic studies subsequently demonstrated that HF could occur in the presence of a normal LVEF, and in fact, patients with so-called HF with preserved ejection fraction (HFpEF) may represent up to half of the HF population. In contrast to HFrEF, outcomes in HFpEF have not improved over the last decades, underscoring our continued lack of effective therapies for this important syndrome.2,3

The purpose of this review is to provide a global perspective on HFpEF, to discuss the controversies surrounding the disease syndrome, to analyse the reasons for failure of clinical trials to improve outcomes, and to gain insight from recent proof of concept trials.

IS HFpEF A SPECIFIC SYNDROME?

Does the syndrome of HFpEF exist?

The concept that HFpEF existed as an entity was challenged until two decades ago, as reflected in the statement from the 1995 European Society of Cardiology (ESC) Guidelines for the diagnosis of HF4 that "Conclusive evidence that most elderly patients with a diagnostic label of HF but with normal systolic function at rest do indeed have HF is lacking." ESC current guidelines now fully acknowledge HFpEF as an important HF syndrome, in line with robust evidence that (i) HFpEF comprises almost half the HF population in epidemiologic studies;5 (ii) classic hemodynamic changes of HF are present in HFpEF (elevated left ventricular filling pressures and abnormal vasorelaxation in both the systemic and pulmonary circulations);6-9 and (iii) neurohormonal activation characteristic of HF (renin-angiotensin-aldosterone axis, sympathetic nervous system) also occurs in HFpEF.10-11

Is HFpEF just a transitory stage in the HF spectrum or is it a distinct disease phenotype?

The dilemma of whether to consider HFpEF as part of the same disease process as "conventional" HFrEF, as opposed to a distinct

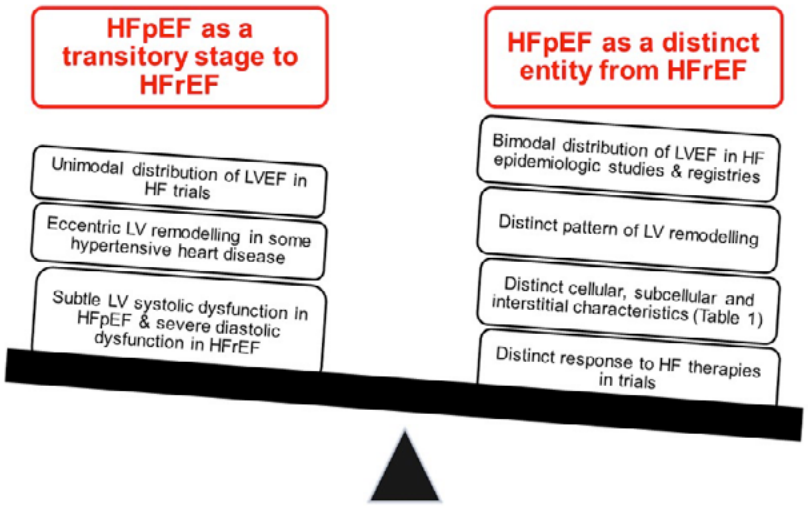


Figure 1: Arguments for HFpEF as a transitory stage to HFrEF (left) versus HFpEF as a distinct entity from HFrEF (right)
LV: left ventricular, EF: ejection fraction

disease entity in itself, remains unresolved (Figure 1).12-13 The demonstration of a unimodal distribution of LVEF in patients with HF from the CHARM Programme14 and the IMPROVEMENT of Heart Failure Programme;15 the existence of subtle left ventricular systolic dysfunction in HFpEF and of diastolic dysfunction in HFrEF;16-19 as well as the progression to eccentric left ventricular remodelling and HFrEF in hypertensive heart disease20;all argue for HFpEF and HFrEF being overlapping syndromes or stages in the same disease process. However, a bimodal distribution of LVEF was revealed after accounting for the larger proportion of patients with low ejection fraction enrolled in the CHARM Programme21 and after stratification by sex in prior registries.22 Two independent studies of patients with chronic HF with a wide range of ejection fraction; the OPTIMIZE Registry of patients with acute HF23, as well as the community-based study from Olmsted County,13 have also confirmed the bimodal distribution of ejection fraction among large numbers of patients with HF, thus providing strong argument for two separate diseases. In addition, the evolution of preserved to reduced ejection fraction in hypertensive heart disease has been shown to be a rare occurrence, and to be largely attributable to an interim myocardial infarction in these uncommon cases.24-25

Finally, despite overlapping systolic and diastolic abnormalities, there are fundamental differences in the pattern of left ventricular remodelling at the chamber and ultra-structural levels, and the response to therapeutic interventions, between HFpEF and HFrEF. Left ventricular chamber dilation (eccentric remodelling) is a specific characteristic of HFrEF, whereas in HFpEF chamber size is normal or near normal with increased wall thickness relative to chamber dimension (concentric remodelling).6,10,26-30 These distinct structural changes in HFrEF versus HFpEF are also associated with distinct functional consequences involving in particular the left ventricular end-systolic pressure-volume relationship.18,26,31,32 The slope of the end-systolic pressure-volume relationship, or end-systolic elastance, is markedly reduced in HFrEF but elevated in HFpEF (Figure 2A). As a result, patients with HFrEF respond favorably to arterial vasodilators, with minimal drop in blood pressure and substantial improvement in stroke volume.32 In contrast, the steeper end-systolic pressure-volume relationship in HFpEF implies a marked sensitivity to volume changes

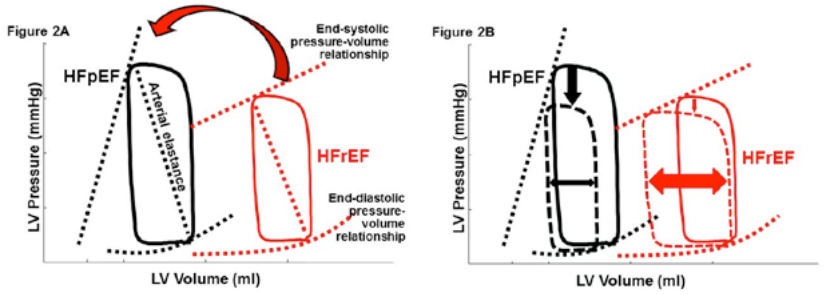
Table 1. Cellular, subcellular and interstitial differences between HFpEF and HFrEF

	HFpEF	HFrEF
Cardiomyocyte diameter	↑	↓
Myofibrillar density	↑	↓
Passive cardiomyocyte resting tension	↑↑	↑
Cardiomyocyte calcium sensitivity	↑↑	↑
Abnormal phosphorylation of sarcomeric proteins	↑↑	↑
Titin isoform N2BA/N2B ratio	↓	↑
Myocardial protein kinase G activity	↓	↑
Myocardial oxidative stress	↑	↔
Myocardial cyclic guanosine monophosphate concentration	↓	↑
Myocardial pro-B-type natriuretic peptide-108 expression	↔/↑	↑↑
Mysial collagen volume fraction	↑	↓
Perivascular collagen volume fraction	↑	↑↑
Scar-related collagen volume fraction	↑	↑↑
Endomyocardial MMP-1:TIMP-1 ratio	↔	↑↑
Myocardial advanced glycation end products in diabetic HF	↑	↑↑

References: 30, 36 - 41

and more exaggerated drops in blood pressure with vasodilator therapy (Figure 2B). These differences in ventricular-vascular function may partially explain the failure of vasodilators to improve outcomes in clinical trials for HFpEF33-35 unlike what was observed in HFrEF.

Differences between HFpEF and HFrEF extend to the tissue and to the cellular level (Table 1): cardiomyocytes are narrow and elongated in HFrEF, with reduced myofibrillar density, whereas myocyte diameter and resting tension are both increased in HFpEF. At the subcellular level, there is an increased ratio of the stiffer isoform of the macromolecule titin in HFpEF compared with HFrEF, which may contribute to higher resting tension and the larger drop in tension in response to phosphorylation. Finally, at the level of the interstitium, matrix collagen turnover differs between HFrEF and HFpEF, where changes in matrix metalloproteinases and their inhibitors favouring



Figures 2A and 2B: Pressure volume loop characteristics in HFpEF (black) and HFrEF (red) in baseline conditions (2A), and in response to vasodilators (2B)
2A: Curved arrow depicts the steeper end-systolic pressure-volume relationship in HFpEF compared to HFrEF. **2B:** Pressure-volume loops before (solid) and after (dotted) administration of vasodilators. Arrows contrast the drop in blood pressure and changes in stroke volume between HFpEF and HFrEF in response to vasodilators. In HFrEF, administration of arterial vasodilators results in minimal drop in blood pressure and substantial improvement in stroke volume. In contrast, the steeper end-systolic pressure-volume relationship in HFpEF results in more exaggerated drops in blood pressure with vasodilator therapy, with potential reduction in stroke volume.

increased extracellular matrix degradation appear to predominate in HFrEF.30,36-41

Does HFpEF simply represent a collection of comorbidities rather than a pathophysiologically distinct entity?

Since HFpEF is a disease of the elderly, it is not surprising that age-related comorbidities are highly prevalent among HFpEF patients, including cardiovascular (e.g. atrial fibrillation) and non-cardiovascular (e.g. renal impairment, chronic lung diseases, anemia, obesity, cancer, liver disease, peptic ulcer disease, and hypothyroidism) comorbidities.5 Indeed, the Charlson index, a weighted prognostic score of comorbidity, was ≥3 in 70% of community-based HFpEF patients27 indicating a high comorbidity burden. Comorbidities herald the onset of symptomatic decompensation in HFpEF, contribute to ventricular-vascular dysfunction, influence functional status and impact prognosis.42-45

The recognition of the importance of comorbidities in HFpEF has led some to question if HFpEF simply represents a collection of comorbidities in elderly breathless patients, rather than a distinct disease entity.46 However, a comparison of mortality in patients from HFpEF

trials to patients with similar age, gender and comorbidity distribution in other cardiovascular trials of hypertension, coronary heart disease, and diabetes mellitus shows striking differences47 : a much higher mortality was observed in HFpEF trials despite a lower comorbidity burden compared to non-HFpEF trial patients. Similarly, cardiovascular parameters were compared among HFpEF patients, age-/gender-matched healthy controls and hypertensive patients without HF from the Olmsted County.43 Adjusting for covariates, comorbidities (obesity, anemia, diabetes and renal dysfunction) impacted ventricular-vascular profile and survival, but could not fully account for the more severe cardiovascular abnormalities in HFpEF compared to healthy controls and hypertensive controls without HF. Thus, the worse prognosis and more severe cardiovascular dysfunction in HFpEF compared to patients with cardiovascular risk factors but without HF, suggest that HFpEF is not merely about old age and comorbidities but that it is an independent entity.

Is HFpEF a uniform syndrome?

The term “diastolic HF” was first coined to reflect the leading pathophysiologic factor believed to cause the syndrome – left ventricular diastolic dysfunction. In a landmark study,6 abnormalities in left ventricular relaxation and compliance were uniformly demonstrated in 47 cases of HF despite a normal ejection fraction. However, population-based studies also showed that left ventricular diastolic dysfunction

Table 2: Heterogeneity of HFpEF

Pathophysiologic mechanisms	Clinical phenotypes
LV diastolic dysfunction	“Pure” diastolic heart failure
Systolic LV-arterial stiffening Abnormal LV-arterial coupling	“Common” HFpEF (associated with hypertension, obesity, diabetes)
Myocardial contractile dysfunction	Coronary artery disease- associated
Impaired exercise reserve Chronotropic incompetence	Early HFpEF (with exercise-induced diastolic dysfunction)
Left atrial dysfunction	Atrial fibrillation- predominant
Pulmonary hypertension	Pulmonary hypertension and/or right heart failure
Volume overload Endothelial dysfunction	Non-cardiac cause – related volume overload (such as chronic kidney disease or anemia)

was present in a large proportion of community-based adults without HF,48 and that patients with “systolic HF” were even more likely to have moderate/severe diastolic dysfunction compared to patients with so-called “diastolic HF”27 Nonetheless, progression of left ventricular diastolic dysfunction was found to be a major mechanism distinguishing HFpEF from age-, sex- and body size-matched healthy controls and hypertensive individuals without HF in the general community.26

Other mechanistic studies challenged the concept that HFpEF was a uniform syndrome of “diastolic HF”. These studies described various abnormalities beyond diastolic dysfunction, including abnormal ventricular-arterial coupling with exercise,28,31 impaired systemic vasodilator reserve,7,28 chronotropic incompetence,7,49 myocardial contractile dysfunction despite a normal ejection fraction,18,50 left atrial dysfunction,51 pulmonary hypertension with intrinsic pulmonary vascular disease,9,52 endothelial dysfunction,28,53 and volume overload (related to extra-cardiac causes such as obesity, chronic kidney disease, or anemia).54 It is possible that each of these mechanistic studies selected a specific subset of patients with HFpEF: only 2% of hospitalized patients with HFpEF were eligible in a study of static and dynamic left ventricular diastolic function.55 This, in turn, suggests that HFpEF is not a single homogeneous syndrome, but is rather a heterogeneous condition consisting of several pathophysiological sub-types.56 It has in particular been proposed that three subtypes of HFpEF patients exist: those with exercise induced diastolic dysfunction, those with chronic volume overload and those with associated right HF and/or pulmonary hypertension. The phenotype heterogeneity of HFpEF is probably more complex as illustrated in Table 2. The use of novel analytic strategies such as “phenomapping” where dense multidimensional data are used to distinguish different phenotypes might be helpful in this respect.

The importance of recognizing the heterogeneity of the pathophysiology in HFpEF is highlighted by the fact that a “one size fits all” approach for clinical trials in HFpEF has been disappointing and that treatments directed at HFpEF as a large undifferentiated group have failed to improve outcomes. Understanding the heterogeneity of HFpEF and improved phenotypic characterization of mechanistic sub-

types might therefore allow the design of more targeted HFpEF clinical trials.

HOW IS THE DIAGNOSIS OF HFpEF ESTABLISHED?

The accurate diagnosis of HFpEF remains a challenging and controversial topic. Several diagnostic criteria have been proposed.58-61 The original criteria58 were criticized for a lack of sensitivity, since the definitive diagnosis mandated determination of ejection fraction within 72h of presentation and invasive demonstration of left ventricular diastolic dysfunction -a situation which is rarely performed or even available to clinicians. The stipulation that ejection fraction had to be measured during periods of acute decompensation was deemed unnecessary in later guidelines, since these acute measurements were shown to be similar to those performed after in-hospital stabilization.62

The need for invasive demonstration of left ventricular diastolic abnormalities was also questioned, since these were shown to be uniformly present in patients with clinical HF and a normal ejection fraction, suggesting that the diagnosis could rely on the presence of clinical HF and a normal ejection fraction alone.6

However, given the lack of specificity of symptoms of HF, as well as the co-existence of age-related comorbidities that could explain the symptoms, some form of demonstration of left ventricular diastolic dysfunction is deemed necessary : the ESC consensus provided practical recommendations on the evaluation of diastolic dysfunction using echocardiography (both Doppler-based as well as structural assessments of LV mass and left atrial size), measurement of natriuretic peptides, and the presence of atrial fibrillation, in addition to cardiac catheterization.60 The most recent version of the ESC Heart Failure guidelines further expanded these criteria and includes “relevant structural heart disease (left ventricular hypertrophy/ left atrial enlargement)” in addition to, or as an alternative to, the demonstration of diastolic dysfunction.1

In general, all proposed diagnostic criteria to date share three features in common (Figure 3): (1) clinical signs or symptoms of HF; (2) evidence of preserved ejection fraction; and (3) evidence of abnormal left ventricular structure and/or diastolic dysfunction. Some

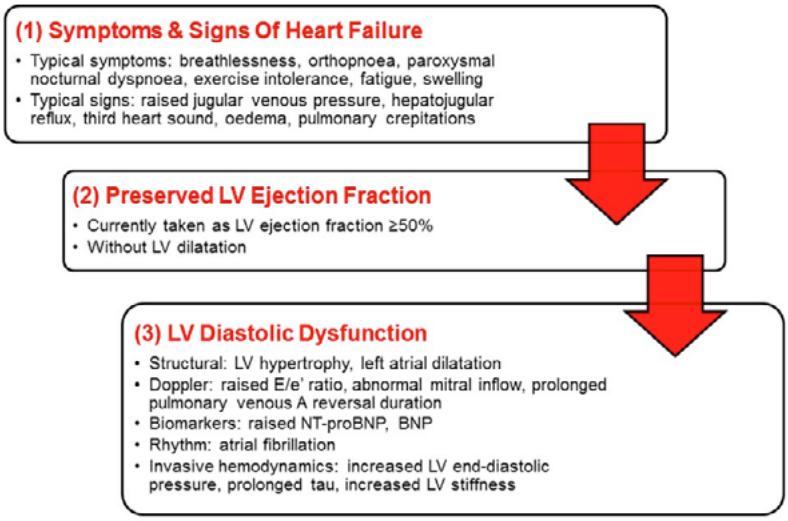


Figure 3: Scheme for diagnosis of HFpEF. In general, all proposed diagnostic criteria to date share three features in common: (1) symptoms and signs of heart failure; (2) evidence of preserved left ventricular (LV) ejection fraction; and (3) evidence of LV diastolic dysfunction, which may include structural, Doppler echocardiographic, biomarker, rhythm or invasive hemodynamic criteria.

issues are not fully addressed in the available guidelines: (1) the lack of sensitivity in patients who have increased filling pressures only during exercise (but not at rest); (2) the phenotypic diversity of HFpEF and the identification of pathophysiologically distinct subsets; (3) the impact and significance of important comorbidities on diagnostic thresholds. Other areas of continued controversy include the optimal cut-off to define “preserved” or “normal” ejection fraction, and how to classify patients who are in the “gray zone” (40-50%) or those who transition between ejection fraction zones.63 Furthermore, none of the published criteria have been prospectively tested for their diagnostic utility in large cohorts of unselected patients.

HOW DO PATIENTS WITH HFpEF DIE?

Since multiple age-related comorbidities may co-exist in patients with HFpEF, knowledge of cause-specific mortality, and not just all-cause mortality alone, is important to discern the risk related to the comorbidity versus the risk associated with HFpEF itself.

Numerous studies have now shown that the mortality burden

of HFpEF is substantial, ranging from 10-30% annually, and is higher in epidemiologic studies than clinical trials.64 The pooled death rate in HFpEF was 121 (95% confidence interval [CI]: 117, 126) deaths per 1000 patient-years in a meta-analysis of 31 studies.65 Mortality rates are clearly elevated compared to age- and comorbidity-matched controls without HF,48 and may be as high as in HFrEF.2,3 The majority of deaths in HFpEF are cardiovascular deaths, 51-60% of deaths in epidemiologic studies,66 and ~70% in clinical trials. Among cardiovascular deaths, sudden death and HF death are the leading cardiac modes of death in HFpEF clinical trials.67,68 However, compared to HFrEF, the proportions of cardiovascular deaths, sudden death and HF deaths are lower in HFpEF and conversely, non-cardiovascular deaths constitute a higher proportion of deaths in HFpEF than HFrEF, particularly in epidemiologic studies.65

A greater non-cardiac comorbidity burden in HFpEF offers a potentially simple explanation for the mortality differences between epidemiologic studies and clinical trials, or between HFpEF and HFrEF. However, the extent to which non-cardiac comorbidities predict death in HFPEF remains unclear, and non-cardiac comorbidities alone do not explain mortality differences between different HF cohorts. For example, in the Olmsted County studies, the burden of non-cardiac comorbidities was similar between HFpEF and HFrEF groups, yet the proportion of non-cardiovascular deaths was higher in the former.3 The extent of coronary artery disease appears to be inversely related to non-cardiovascular deaths in both the Olmsted County community-based cohort and in the clinical trial population from TIME-CHF69: a lower baseline proportion of coronary artery disease was related to a higher proportion of non-cardiovascular deaths in HFpEF versus HFrEF. A potential explanation for these observations is that patients with HFpEF “escape” death related to coronary artery disease and subsequently die from their non-cardiac comorbidities. Alternatively, patients with coronary artery disease may have been more likely to “transition” to HFrEF following a myocardial infarction, thus enriching the HFrEF population eventually with more coronary heart deaths.

HOW ARE PATIENTS WITH HFpEF TREATED?

Current international guidelines acknowledge a lack of evidence in the management of HFpEF. The ESC recommends the use of diuretic agents to relieve breathlessness and oedema, an optimal management of hypertension or myocardial ischaemia, and to control heart rate since elevated heart rate is usually poorly tolerated in these patients with stiff left ventricle.1

The pattern of HF medications prescriptions differs significantly between HFpEF and HFrEF. In the large OPTIMIZE HF registry, a lower rate of prescription of ACE inhibitors, aldosterone antagonists, betablockers, loop diuretics, digoxin and a higher rate of use of amlodipine were observed in patients with HFpEF than in those with HFrEF both at admission and discharge. This trend also existed comparing patients with EF > 50% and those with 40% £ EF £ 50%.23 The international meta-analysis MAGGIC using individual data from randomized clinical trials, from observational studies and from management strategy controlled trials found a similar pattern of prescription results in 10.347 HFpEF patients compared to 31.625 HFrEF patients.65

Betablockers and calcium channel blockers.

Slowing the heart rate should result in an increase in the diastolic filling period in an abnormally stiff left ventricle with prolonged relaxation. However, slowing the heart rate in the absence of increased heart rate tends to prolong diastasis where transmitral flow plays a minor role.70 In addition, there is a high prevalence of chronotropic incompetence in HFpEF which is associated to exercise limitation, and chronotropic reserve might be a key factor to increase cardiac output during exercise.28,71

In this context, the role of betablockers remains uncertain. Nebivolol, a third generation betablocker, was tested in 2.128 patients > 70 years with a history of HF or known ejection fraction < 35% in the SENIOR trial.72 There was a 14% reduction in the primary composite outcome (all cause mortality or cardiovascular admission). A similar benefit was observed in those patients with an EF > 35% (approximately 1/3 of the total number)73 or <35%. Since the threshold of EF used

Table 3 : Outcome trials in HFpEF

	PEP CHF	CHARM PRESERVED	I-PRESERVE	TOP CAT
Reference	35	33	34	100
N patients	850	3.023	4.128	3.445
Drug tested	Perindopril	Candesartan	Irbesartan	Spironolactone
Target dose (mg/day)	4	32	300	30/45
Mean follow-up (months)	26.2	36.6	49.5	42 estimate
Age at inclusion (years)	≥ 70	≥ 18	≥ 60	≥ 50
Mean age (years)	76	67	72	68.6
Men / Women %	45 / 55	60 / 40	40 / 60	48 / 52
HF aetiology				
Ischaemic	26*	57	25	59
Hypertensive	79*	23	64	91**
EF% at inclusion	LV WMI* 1.4 – 1.6	> 40	≥ 45	≥ 45
BNP/NT proBNP at inclusion (pg/ml)	-	-	-	> 360 (NT proBNp) > 100 (BNP)
NT proBNP/BNP Median value at baseline (pg/ml)	453(Pbo)/335(Active)	-	320(Pbo)/360(Active)	950(NT proBNP)/234(BNP)
BMI (kg/m²)	27.5	29	30	32
6 minute walk test (m)	297(Pbo)/290(Perindopril)	N/A	N/A	N/A
Primary composite endpoint	All cause mortality / HF hospitalization	CV death / HF hospitalization	All cause death / CV hospitalization	CV death / HF hospitalization / aborted cardiac arrest
Hazard ratio	0.92 (0.70-1.21)	0.89 (0.77-1.03)	0.95 (0.86-1.05)	N/A
P Value	0.54	0.12	0.35	-

* Prior hypertension / prior myocardial infarction for PEP CHF ; ** Hypertension history TOP CAT

was very low (35%), no definite conclusion can be drawn from this subgroup of patients about the applicability of results to patient with HFpEF where EF≥50%. In addition, an echocardiographic substudy did not show any effect of Nebivolol on parameters of systolic or diastolic dysfunction.74

In another study, ELANDD, Nebivolol did not influence symptoms or exercise capacity in HFpEF; however there was a direct correlation between the decrease of peak heart rate and the decrease of peak oxygen consumption in the Nebivolol group.75 In the OPTIMIZE HF registry, a risk and propensity adjusted model was used which showed no significant relationship between discharge use of betablockers and mortality and/or rehospitalisation rate at 60 to 90 days.23 Finally, in the COHERE registry (Carvedilol Heart Failure Registry), the benefit of Carvedilol on mortality, clinical status and need for hospitalisations76 was lower in patients with EF > 40%. Conversely, prescription of betablockers was associated with a marked mortality reduction in a cohort of HFpEF patients followed-up for 25 months.77

Data regarding the heart rate lowering calcium channel blocker Verapamil are scarce. A small size study suggested some improvement of symptoms and of exercise capacity in these patients.78

There is therefore no conclusive evidence for the benefit (or lack of benefit) of beta-blockers or verapamil in HFpEF.

ACE-inhibitors and angiotensin receptor blockers.

Three outcome trials have been conducted in HFpEF with ACE inhibitors or angiotensin receptor blockers (Table 3). The rationale in the use of a renin angiotensin system antagonist (RAS) is to block the pro-hypertrophic and pro-fibrotic effects of Angiotensin-II.

The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM Preserved) trial included 3.023 patients with an ejection fraction > 40%.33 In the active arm, Candesartan was uptitrated to 32 mg/day. This trial failed to demonstrate a significant benefit on cardiovascular mortality whereas a reduction in HF hospitalisations was observed.

The Perindopril for Elderly People with Chronic Heart Failure trial (PEP CHF) enrolled elderly patients with EF > 40% and with

echocardiographic evidence of diastolic dysfunction.35 No reduction in the occurrence of the primary composite endpoint (all cause mortality or HF hospitalisation) was observed in the Perindopril arm titrated to 4 mg/day. A long recruitment period with, as a result, a number of crossovers together with the limited sample size (n = 850) might explain the neutral result of this trial. A post hoc analysis performed after one year of follow-up, suggested indeed a favourable trend in the Perindopril arm.

The large Irbesartan in HF with Preserved Systolic Function trial (I-PRESERVE) enrolled 4.128 elderly HF patients with EF > 45% who were randomly assigned to Irbesartan or placebo.34 No reduction in the composite outcome (all cause mortality or cardiovascular hospitalisation) or in any secondary outcome was observed after nearly 50 months of follow-up.

These disappointing results with ACE-inhibitors / ARBs contrast with the benefit observed in HFrEF. However, in a large prospective cohort of unselected HFpEF patients form Sweden, the use of a renin

Table 4: Recent proof of concept studies

	Aldo DHF	**PARAMOUNT**	**RELAX**
Reference	99	96	93
N patients	422	266	216
Drug	Spironolactone	Angiotensin Receptor Neprylisin inhibitor (LCZ 696) vs Valsartan	Sildenafil
Men / Women (%)	48/52	43/57	52/48
Mean age (years)	67	71	69
Baseline E/E'	12.7	12.4 / 13	16
6mn walk test (m)	-	N/A	305(Pbo)/308 (Sildenafil)
Target dose (mg/ day)	25	400 (ARNi)/320 (Valsartan)	60 -12 weeks 180 -12 weeks
EF at inclusion (%)	≥ 50	≥ 45	≥ 50
NT proBNP at inclusion (pg/ml)	-	≥ 400	≥ 400 <400 if elevated LV filling pressure
NT proBNP baseline geometric mean (pg/ml)	-	794(ARNi)/870 (Valsartan)	-
Median (pg/ml)	148(Pbo)/179 (Spironolactone)	828(ARNi)/939 (Valsartan)	648(Pbo)/757 (Sildenafil)
Primary endpoint	E/E' /peak VO^2	Change NT proBNP	Change Peak VO^2
Duration	12 months	12 weeks	24 weeks

angiotensin system antagonist was associated with a lower all cause mortality.79

Digoxin

In the Digitalis Interaction Group trial (DIG), a subgroup of 988 patients with EF > 45% was randomized to placebo or to Digoxin. No difference was observed in all cause, HF or cardiovascular mortality, or in the composite outcomes of HF death or hospitalisation, or all cause mortality or cause specific mortality after 37 months of follow-up.80 However, a trend towards a reduction of HF hospitalization was observed together with a trend for increased hospitalization for unstable angina.

WHY DID THE PRIOR TRIALS FAIL?

A. Patient factorsp

The identification of patients with HFpEF is particularly challenging since: (i) signs and symptoms of HF are not specific and may be observed in other conditions such as obesity, anemia, renal dysfunction or pulmonary disease -- all conditions which are frequently associated with HFpEF ; (ii) there is no real consensus on the definition of “normal” ejection fraction: The ESC guidelines recommend a threshold of 50% but randomized clinical trials conducted in HFpEF have used lower values (>40% CHARM Preserved, >45% I-PRESERVE) which might indicate an already significantly altered systolic performance and, hence a clinical profile closer to that observed in HFrEF ; (iii) invasive confirmation of the presence of left ventricular diastolic dysfunction is not feasible in daily practice and non-invasive markers are therefore needed: A central place has been given to the Echo-Doppler E/E’ ratio but there is increasing use of surrogate markers including left atrial enlargement, left ventricular hypertrophy or raised natriuretic peptide plasma levels. The only randomized clinical trial using comprehensive echo parameters of diastolic dysfunction was PEP CHF.35 The concern therefore remains that the patients recruited in the neutral trials above did not have HFpEF but had left ventricular hypertrophy with a non-cardiac reason for dyspnea such as obesity. Nonetheless, the fact remains that the rate of cardiovascular mortality or HF hospitalizations is much higher in HFpEF trials than that observed in clinical trials on

hypertension with or without left ventricular hypertrophy, suggesting that patients enrolled in these HFpEF trials indeed had HF.47

B. Disease factors

An analysis of the inclusion criteria of the outcome trials as well as that of recent proof of concept studies including Aldo-DHF, PARAMOUNT or RELAX reveals notable heterogeneity with regards to age or level of neurohormonal stimulation as assessed by BNP/NT proBNP plasma level (Table 4). This suggests differences in the stage of disease of patients enrolled in these trials. Elderly HFpEF patients with a long standing history of hypertension and significant accumulation of cardiac extracellular matrix may be poor responders to any pharmacological intervention ("too sick to benefit")

For instance, a post-hoc analysis of I-PRESERVE showed that Irbesartan improved clinical outcomes in those patients with below the median values of NT proBNP but not in those with higher levels.81 It is therefore possible that a pharmacological intervention using an ARB would benefit at an earlier stage of the disease.

On the other hand, it was argued that spironolactone was not ideally tested in Aldo-DHF since patients were "too well" and had only mild cardiac dysfunction based on E/E' value, NT proBNP plasma levels and exercise capacity. This explanation was put forward to explain the lack of improvement of exercise capacity in patients with early stage HFpEF.82 Yet, in the Exercise Training in Diastolic Heart Failure–Pilot (Ex-DHF-Pilot) Study, exercise training was effective at increasing peak VO2 in patients with similarly early stage HFpEF83. Furthermore, half of the patients in Aldo-DHF had disease that was advanced enough to fulfil ESC criteria of HFpEF, and the effects of spironolactone on E/e' and peak VO2 in these patients were similar in those who did not fulfil the ESC criteria. It would therefore appear that pharmacological and non-pharmacological therapeutic approaches in HFpEF vary in their effects on exercise capacity at different stages of the disease.

C. Trial factors

The outcome trials PEP CHF and I-PRESERVE were associated with a prolonged recruitment period. This is likely attributable to the inherent difficulties in confirming the clinical diagnosis of HFpEF and the need for cardiac imaging expertise. As a result of the trial prolongation, a high rate of drop-out was observed together with a significant number of randomized patients receiving an open label RAS antagonist during the course of the trials. In I-PRESERVE, approximately 1/5 of patients randomized to Irbesartan were prescribed an ACE inhibitor during the follow-up period and 1/3 dropped out of the active arm. Similarly in PEP CHF, 40% of the patients randomized to Perindopril and 36% of those randomized to placebo stopped the study treatment and 1/3 received an open label ACE inhibitor.

As discussed above, cardiovascular mortality and morbidity are the most prevalent outcomes in HFpEF.67,68 However, the proportion of patients dying of non cardiovascular causes increases with ejection fraction.14 Cardiovascular drugs such as RAS antagonists might therefore have a limited effect in a condition where the non cardiovascular mode of death is more prevalent and sudden cardiac death or HF death less prevalent than in HFrEF.

D. Drug factors

Both ACE inhibitors and ARBs are associated with a significant reduction in morbidity and mortality in HFrEF.

The final pathway of these two classes is to inhibit the synthesis or the action of Angiotensin II and Aldosterone which promote cardiac fibrosis and hypertrophy. In addition, ARBs have been shown to be more efficient on left ventricular hypertrophy than beta-blockers in hypertension.84 There is therefore no clear explanation why blockade of the RAS system failed to bring benefit in HFpEF. In particular it is unknown whether the different pattern of remodelling may explain this finding.

A lower level of neurohormonal stimulation assessed by NT proBNP / BNP has been reported in HFpEF than in HFrEF and up to 1/3 of patients show plasma levels within the normal range.85 However, in HFpEF, NT proBNP elevation remains a very powerful predictor of poor outcome.86

Also, increased plasma levels of peripheral collagen turnover markers were not influenced by Irbesartan in I-PRESERVE although fibrosis and increased extracellular matrix are believed to be key factors in HFpEF.87

It is therefore possible that a differential pattern of neurohormonal activation and its downstream consequences plays a role in the lack of response reported so far in HFpEF with RAS antagonists.

Overall, the lack of benefit of traditional HF therapies in HFpEF underscores our lack of understanding of the pathophysiology of this syndrome, emphasizes that a uniform “blanket rule” approach does not work in HFpEF, and supports the view that HFpEF is indeed a distinct syndrome from HFrEF. A paradigm shift in our understanding of the mechanisms that may be targeted in HFpEF, and the patients most likely to benefit from these targeted approaches, is urgently needed.

NEW PARADIGM IN HFpEF

A new paradigm based on observation of specific myocardial structural and functional changes observed in HFpEF has been put forward88. This paradigm emphasizes the role of a pro-inflammatory state with widespread endothelial dysfunction, leading to reduced nitric oxide (NO) bioavailability in cardiomyocytes, reduced myocardial cyclic guanosine 3’, 5’-monophosphate (cGMP) content and low protein kinase-G activity (PKG).

The central role of the NO-cGMP-PKG pathway is described in this paradigm (Figure 4): Endothelial dysfunction has been shown to be highly prevalent and independently predictive of survival in HFpEF, suggesting that it plays a major role in the pathophysiology of HFpEF89-90. Endothelial dysfunction occurs in diabetes and hypertension, both important risk factors for HFpEF, and causes oxidative stress with high levels of reactive oxygen species which interfere with NO production in endothelial cells. This leads to reduced NO bioavailability to adjacent cells such as cardiomyocytes. cGMP is the second messenger that plays a role in various key physiologic pathways, including cardiovascular homeostasis, cellular growth and contractility, and inflammation. Guanylate cyclases are enzymes that catalyze the conversion of guanosine-5’-triphosphate to cGMP.

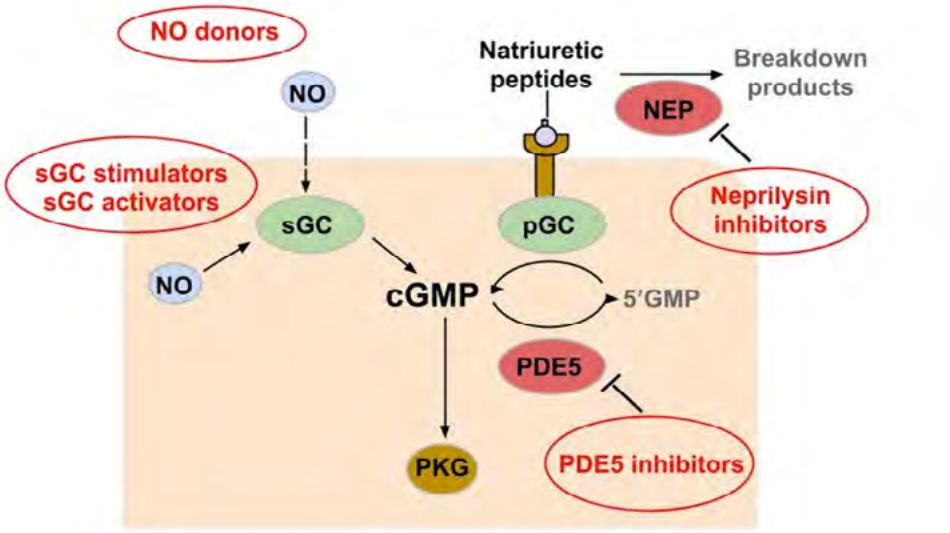


Figure 4: Role of nitric oxide (NO) - cyclic guanosine 3', 5'-monophosphate (cGMP) - protein kinase-G activity (PKG) pathway in HFpEF. NO: nitric oxide ; sGC: soluble guanylate cyclase ; NEP: neutral endopeptidase ; pGC: particular guanylate cyclase ; PKG: protein kinase G ; PDE5: phosphodiesterase-5 ; cGMP: cyclic guanylate monophosphate

Membrane-bound particulate guanylate cyclase (pGC) serves as a receptor for natriuretic peptides, whereas soluble guanylate cyclase (sGC) acts as a receptor for NO. Subsequently, cGMP effectors include cGMP-dependent protein kinases, such as PKG. The disruption of the NO–cGMP-PKG signalling pathway can therefore explain the development of concentric LV remodelling, increased stiffness of the cardiomyocyte through hypo-phosphorylation of titin, and increased collagen deposition in HFpEF (Figure 4).

LESSONS FROM RECENT PROOF OF CONCEPT STUDIES.

(Table 4)

Until now, attempts to target the NO-cGMP-PKG pathway in HFpEF have been unsuccessful. Administration of exogenous nitrates or NO donors is dependent on biotransformation to the active, nitric oxide-containing compound and is limited by tolerance in the long term or can even paradoxically cause endothelial dysfunction, oxidative stress, and release of endothelin-1.91

1°) Phosphodiesterase-5 inhibitors

Since cGMP is inactivated by Phosphodiesterase-5 (PDE-5), blockade of cGMP degradation by inhibition of PDE-5 could have beneficial effects such as improvement in cardiac relaxation and left ventricular reverse remodelling.

Experimental data suggest that PDE-5 over-expression induces cardiac cardiomyocyte hypertrophy and that this is reversed by the selective PDE-5 inhibitor Sildenafil.92

A small clinical study showed that Sildenafil improved left ventricular diastolic function, hypertrophy and reduced pulmonary pressures after twelve months of exposure in HFpEF patients with pulmonary hypertension.93

However, these beneficial effects were not confirmed by the RELAX trial including 216 elderly HFpEF patients.94 After 24 weeks of treatment, no effect on maximal exercise capacity, on six minutes walk distance, on clinical status, quality of life, left ventricular remodelling or diastolic function was observed.

Several explanations have been put forward in order to explain these neutral results: absence of pulmonary hypertension, high prevalence of chronotropic incompetence, insufficient duration of the trial. Basal plasma levels of NT proBNP were also markedly elevated, suggesting that these patients were in an advanced stage of the disease and, therefore, less likely to benefit from this pharmacological intervention. Furthermore, it is postulated that impaired cGMP production, rather than increased degradation, may be the predominant pathophysiologic mechanism in HFpEF. This may explain the relative lack of effectiveness of therapies targeting inhibition of cGMP degradation, and suggest that stimulation of cGMP production may be an important therapeutic strategy in HFpEF.

2) Soluble guanylate cyclase stimulators

Small molecules can directly stimulate the sGC pathway with a dual mode of action: the sensitization of sGC to endogenous NO by stabilizing the NO-sGC binding and direct stimulation of sGC via an NO independent binding site.

The Phase IIa Acute hemoDynamic effects of rIociguat in

patients with puLmonary hypertension Associated with diasTolic heart failurE (DILATE-1) study characterized the hemodynamic effects, safety, and pharmacokinetics of three different single doses of riociguat, a sGC stimulator, in patients with HFpEF and pulmonary hypertension.95 There was no significant change in the primary endpoint of peak change in mPAP from baseline to 6 hours in the riociguat 2 mg arm vs placebo. Riociguat significantly increased stroke volume and decreased systolic blood pressure without significantly changing pulmonary vascular resistance, transpulmonary pressure gradient, or heart rate. Importantly, riociguat was well tolerated, and increased flow did not result in increased left ventricular filling pressures.

These results will need to be compared to the Soluble Guanylate Cyclase stimulator Heart Failure Studies (SOCRATES)-Preserved trial is a placebo-controlled double-blind dose-finding phase IIb study in which a new oral sGC stimulator BAY1021189 will be tested in patients with worsening chronic HFpEF requiring hospitalization (clinicaltrials.gov identifier NCT01951638

3°) Neprilysin inhibitors

LCZ 696 is a complex molecule (angiotensin receptor Neprilysin inhibitor) which combines an inhibitory effect of Neprilysin (endopeptidase 24-11) together with an angiotensin receptor blocker. Neprilysin is the enzyme responsible for the degradation of biologically active natriuretic peptides. The blockade of Neprilysin increases intracellular cGMP and improves relaxation and hypertrophy.96 This new compound was tested against Valsartan in 301 HFpEF patients treated for 36 weeks in the PARAMOUNT trial.97

The primary endpoint was the change in NT proBNP, a marker of wall stress, from baseline to 12 weeks. LCZ 696 significantly reduced the plasma level of NT proBNP compared to Valsartan but the difference was no longer significant at 36 weeks. Left atrial volume and dimension were also favourably influenced at the end of the trial whereas there was no change in other echocardiographic parameters, including diastolic function.

These encouraging results deserve confirmation and a large outcome study is planned to determine if this new class might be

beneficial in HFpEF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON-HF], ClinicalTrials.gov Identifier: NCT01920711).

4°) Mineralocorticoid Receptor Antagonists.

Activation of the mineralocorticoid receptor by Aldosterone results in sodium retention, cardiac fibrosis, endothelial dysfunction and cardiac hypertrophy.98 Small studies suggest that mineralocorticoid receptor antagonists (MRAs) might be beneficial in diastolic HF.99 In the Aldosterone receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial, 422 HFpEF patients were randomized to Spironolactone 25 mg/day or placebo and followed-up for 12 months.100

Diastolic function assessed primarily by the e/e' ratio on Doppler-Echocardiography was significantly but modestly improved by Spironolactone, along with reduction in left ventricular mass and NT-proBNP; whereas no change was observed in maximal exercise capacity, patient symptoms or quality of life.

An explanation put forward to explain the lack of change in exercise capacity was the fact that patients enrolled in this trial had only mild cardiac dysfunction and modest symptom limitation at baseline. Of note, even in HFrEF where mineralocorticoid receptor antagonists are considered a Class I therapy, spironolactone had only a marginal effect on functional capacity in HFrEF patients101 despite significant effects on left ventricular remodelling.

It therefore remains possible that mineralocorticoid antagonism in HFpEF may, in spite of limited impact on symptoms, lead to outcome benefits in mortality and morbidity. The large outcome trial TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) has just been completed. It compares Spironolactone uptitrated to 45 mg/day vs placebo on a composite outcome of cardiovascular mortality, aborted cardiac arrest or HF hospitalization in an elderly population of 3.445 patients.100 The results are expected shortly.

5°) Ranolazine

Ranolazine is a selective inhibitor of the late sodium (INa+)current which is activated in HF and leads to Ca2+ overload, impaired relaxation and pro-arrhythmic after depolarizations.102

The RALI DHF trial was a small trial including 20 patients which suggested that Ranolazine administered intravenously for 24 hours modestly improved hemodynamic parameters but had no effect on relaxation.103

The acute phase was followed by 13 days of oral administration which did not result in any change of echocardiographic parameters, NT proBNP or exercise performance.

The ERIPE study (EUDRA CT n° 2011-000805-27) is currently evaluating the effect of Ranolazine on six minutes walking distance and on Echo-Doppler parameters in 120 patients treated for 26 weeks.

6°) Ivabradine

Ivabradine is an inhibitor of the sino atrial node If current and reduces elevated heart rates. It has shown benefit in HFrEF in sinus rhythm and with elevated heart rate.104 Selective heart rate reduction improves diastolic filling by prolonging the diastole without significant lusitropic or inotropic effects.105

In a mouse model of diabetes with diastolic dysfunction, Ivabradine reduced effective arterial elastance, increased aortic distensibility and decreased left ventricular end-systolic elastance106. In addition, a favourable effect was observed on the activity of SERCA 2a, a key player in the uptake of calcium by the sarcoplasmic reticulum. Recently, 61 patients with HFpEF and an increased baseline heart rate were assigned to Ivabradine 5mg bid or placebo for seven days.107 A significant increase was observed in exercise capacity with a contribution from left ventricular improved filling pressure response to exercise as reflected by e/e' ratio. These results are short term and need confirmation. The EDIFY study (EUDRA CT n° 2012 002742-20) will enroll 400 HFpEF patients and will assess the effect of Ivabradine uptitrated to 10 mg bid on e/e' ratio as well as on other echocardiographic parameters, on six minutes walking distance and on NT proBNP plasma levels after 8 months of follow-up.

7°) Advanced glycation end products cross link breakers.

Increased diastolic left ventricular stiffness is a marker of left ventricular dysfunction induced by diabetes mellitus, a major comorbidity in HFpEF. This has been related to myocardial deposition of advanced glycation end products (AGEs) which are formed by oxidative or non-oxidative reactions between proteins and carbohydrates and form cross links in the extracellular matrix.108

AGEs cross link breakers such as alagebrium chloride have been tested in experimental models and in a small open label clinical study enrolling 23 elderly patients with diastolic HF.109 After 16 weeks of follow-up, an improvement in diastolic function was observed. Whether this class might have beneficial effects in patients with HFpEF and diabetes needs to be evaluated in a properly designed large-scale and longer-term clinical trial.

8°) Other potential perspectives

Statins

By blocking the activity of several Guanosine Triphosphate binding proteins, statins suppress left ventricular hypertrophy and decrease collagen synthesis in experimental models.110,111. However, in the clinical area, only one small study suggested a beneficial effect of statins on mortality in HFpEF patients112 whereas in the GISSI HF trial, no benefit was observed with Rosuvastatin in the 10% of patients enrolled with relatively preserved ejection fraction.113

Calcium cycling modulators

Ryanodine receptors which trigger calcium release from the intracellular stores, the sarcoplasmic reticulum, are dysfunctional in HF and lead to Ca2+ leakage, impaired relaxation and after depolarizations.114 A Ryanodine receptor stabilizer, K 201, has been tested in vitro with favourable effects115 but there are as yet no data on the clinical effects of this compound. Down regulation of the sarcoplasmic reticulum Ca2+ ATPase 2a isoform (SERCA2), which is responsible for the reuptake of calcium in the sarcoplasmic reticulum, is observed in HF and leads to impaired relaxation. A non-pharmacological approach using SERCA2 gene treatments by an adenovirus has been tested with some promising results in HFrEF.116 Whether this approach could be beneficial in HFpEF deserves consideration.

Micro RNAs

In the last 5 years, evidence has rapidly accumulated indicating a pivotal role for micro RNAs (miRNAs), a class of small non-coding RNAs, in cardiovascular development and response to injury.117,118 Precursor “primary” miRNAs undergo processing to the mature form which binds with complementary sequences on target messenger RNA and prevents translation and /or accelerates degradation of message RNA. MicroRNAs may also return to the nucleus and act upon DNA as transcription factors. MiRNAs have been shown to be differentially expressed in the failing myocardium and to play an important role in progression of HF by targeting genes that govern diverse functions in LV remodelling.119 The strategy of replacement of miRNAs of interest or of blockade of potentially harmful miRNAs (anti-MIRs) is currently being tested in preclinical studies. Whether the use of anti-hypertrophic anti-MIRs could be used in the clinical setting needs to be evaluated.

Exercise

Exercise training in chronic HF may improve symptoms and quality of life, via beneficial effects on endothelial function, central hemodynamics, inflammatory markers, neurohormonal activation, as well as skeletal muscle structure and function. The safety and efficacy of exercise training has been investigated in chronic HFrEF.120 In HFpEF, the Exercise Training in Diastolic Heart Failure–Pilot (Ex-DHF-Pilot) Study121 randomized 64 patients with HFpEF to supervised endurance/resistance training in addition to usual care or to usual care alone. The primary endpoint was the change in peak VO2 after 3 months. Peak VO2 increased with exercise training and remained unchanged with usual care alone. Exercise training was also associated with improvements in the physical functioning score (36-Item Short-Form Health Survey), atrial reverse remodelling and improved left ventricular diastolic function in HFpEF. A larger study examining the effects of exercise training in HFpEF is in progress (http://www.controlled-trials.com/ ISRCTN86879094).

Sodium restriction

Dietary sodium restriction improves ventricular-vascular stiffness and function in hypertensive heart disease. In hypertensive HFPEF patients, a 21-day trial of the sodium-restricted Dietary Approaches to Stop Hypertension (DASH) diet was associated with favourable changes in LV diastolic function, arterial elastance, and LV-arterial coupling in a small clinical study (N=13).122 (Clinical Trial Registration-URL: http://www.clinicaltrials.gov. Unique identifier: NCT00939640).

CONCLUSION

The accurate diagnosis and optimal pharmacological treatment of HFpEF remain challenging. Progress has been made in the understanding of the pathophysiology of this condition, and there is increasing emphasis on therapeutic strategies aimed at altering specific signalling pathways. It is critical for future clinical trials to ensure a proper characterization of the phenotype of patients to be tested. Several novel approaches appear promising in pre-clinical or early clinical studies, but need to be tested in properly designed clinical trials.

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