Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction

A Multiorgan Roadmap

ABSTRACT: Heart failure (HF) with preserved ejection fraction (EF; HFpEF) accounts for 50% of HF cases, and its prevalence relative to HF with reduced EF continues to rise. In contrast to HF with reduced EF, large trials testing neurohumoral inhibition in HFpEF failed to reach a positive outcome. This failure was recently attributed to distinct systemic and myocardial signaling in HFpEF and to diversity of HFpEF phenotypes. In this review, an HFpEF treatment strategy is proposed that addresses HFpEF-specific signaling and phenotypic diversity. In HFpEF, extracardiac comorbidities such as metabolic risk, arterial hypertension, and renal insufficiency drive left ventricular remodeling and dysfunction through systemic inflammation and coronary microvascular endothelial dysfunction. The latter affects left ventricular diastolic dysfunction through macrophage infiltration, resulting in interstitial fibrosis, and through altered paracrine signaling to cardiomyocytes, which become hypertrophied and stiff because of low nitric oxide and cyclic guanosine monophosphate. Systemic inflammation also affects other organs such as lungs, skeletal muscle, and kidneys, leading, respectively, to pulmonary hypertension, muscle weakness, and sodium retention. Individual steps of these signaling cascades can be targeted by specific interventions: metabolic risk by caloric restriction, systemic inflammation by statins, pulmonary hypertension by phosphodiesterase 5 inhibitors, muscle weakness by exercise training, sodium retention by diuretics and monitoring devices, myocardial nitric oxide bioavailability by inorganic nitrate-nitrite, myocardial cyclic guanosine monophosphate content by neprilysin or phosphodiesterase 9 inhibition, and myocardial fibrosis by spironolactone. Because of phenotypic diversity in HFpEF, personalized therapeutic strategies are proposed, which are configured in a matrix with HFpEF presentations in the abscissa and HFpEF predispositions in the ordinate.

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Heart failure (HF) with preserved ejection fraction (EF; HFpEF) currently accounts for >50% of all heart failure cases and its prevalence relative to HF with reduced EF (HFrEF) continues to rise at an alarming rate of 1% per year.[1] In the past 3 decades, HFrEF evolved to a distinct therapeutic entity partly because large outcome trials demonstrated the efficacy of neurohumoral inhibition. No similar evolution has occurred in HFpEF, where large trials testing neurohumoral inhibition consistently failed to reach a positive primary outcome either individually[2] or on meta-analysis.[3] In trials testing angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), or mineralocorticoid receptor antagonists, a modest positive trend was sometimes observed but only for secondary outcomes[4] or retrospectively defined subgroups.[5,6] The failure of neurohumoral inhibition in the large HFpEF outcome trials led some investigators to challenge HFpEF as a distinct HF phenotype.[7–9] More recent views attributed this failure to different systemic and myocardial signaling in HFpEF and HFrEF[10] or to diverse phenotypes within the HFpEF patient population.[11–14] In line with these views, the current HFpEF treatment roadmap first addresses HFpEF-specific systemic and myocardial signaling, subsequently configures HFpEF phenotypes in a matrix of predispositions and presentations, and finally discusses therapeutic inroads that fit into the phenotypic framework.

SYSTEMIC AND MYOCARDIAL SIGNALING

Large outcome trials and registries all revealed HFpEF patients to be of advanced age and predominantly women and to have multiple comorbidities such as overweight/obesity (84%),[15] arterial hypertension (60%–80%),[16] type 2 diabetes mellitus (20%–45%),[16] renal insufficiency, and sleep apnea. Aging and the aforementioned comorbidities may initiate chronic systemic inflammation as manifest from biomarker profiles which revealed high plasma levels of soluble interleukin 1 receptor-like 1, C-reactive protein, and growth differentiation factor 15 in HFpEF.[17–20] Initial studies revealed plasma levels to be similarly elevated in HFpEF and HFrEF,[17] but recent studies observed them to be higher in HFpEF[19] and therefore suggested a larger involvement of systemic inflammation in HFpEF. Systemic inflammation may affect myocardial remodeling and dysfunction in HFpEF through a signaling cascade, which begins with coronary microvascular endothelial dysfunction (Figure 1).[10,21] It subsequently involves myocardial infiltration by activated macrophages,

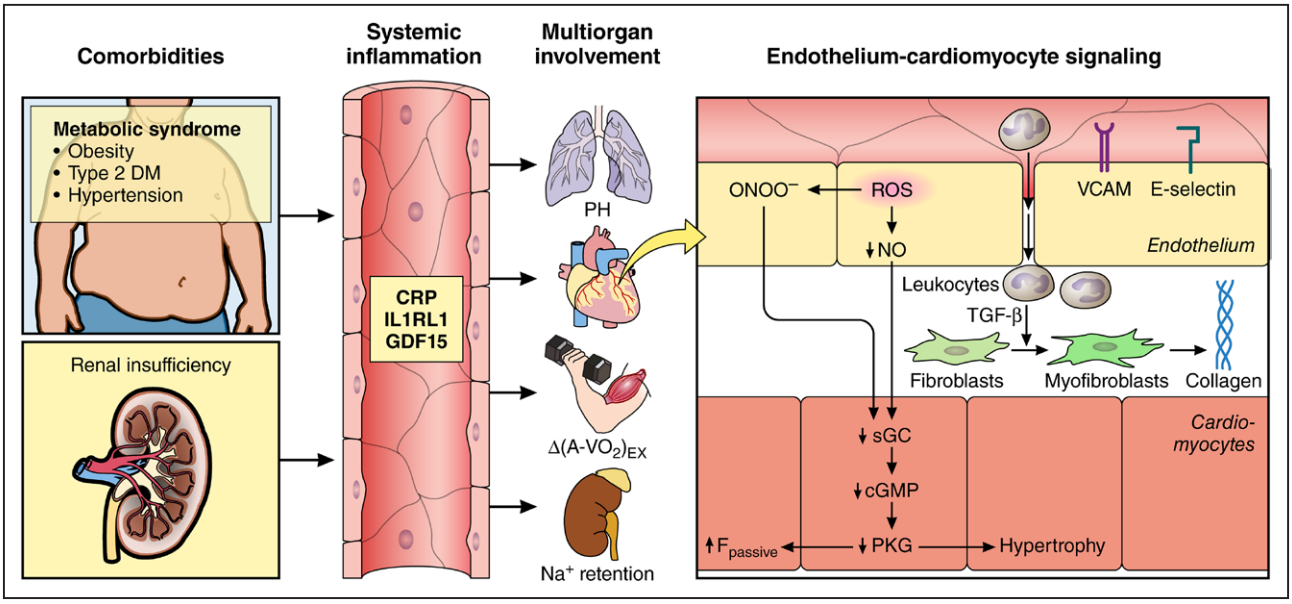

Figure 1. Systemic and myocardial signaling in HFPEF.
Comorbidities induce systemic inflammation, evident from elevated plasma levels of inflammatory biomarkers such as soluble interleukin 1 receptor-like 1 (IL1RL1), C-reactive protein (CRP), and growth differentiation factor 15 (GDF15). Chronic inflammation affects the lungs, myocardium, skeletal muscle, and kidneys leading to diverse HFpEF phenotypes with variable involvement of pulmonary hypertension (PH), myocardial remodeling, deficient skeletal muscle oxygen extraction ($\Delta A\text{-}Vo_2$) during exercise (Ex), and renal Na^+ retention. Myocardial remodeling and dysfunction begins with coronary endothelial microvascular inflammation manifest from endothelial expression of adhesion molecules such as vascular cell adhesion molecule (VCAM) and E-Selectin. Expression of adhesion molecules attracts infiltrating leukocytes secreting transforming growth factor β (TGF-β), which converts fibroblasts to myofibroblasts with enhanced interstitial collagen deposition. Endothelial inflammation also results in the presence of reactive oxygen species (ROS), reduced nitric oxide (NO) bioavailability, and production of peroxynitrite ($ONOO^-$). This reduces soluble guanylate cyclase (sGC) activity, cyclic guanosine monophosphate (cGMP) content, and the favorable effects of protein kinase G (PKG) on cardiomyocyte stiffness and hypertrophy. HFpEF indicates heart failure with preserved ejection fraction.

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Table. Unequal Structural, Functional, and Ultrastructural LV Characteristics in HFpEF and HFrEF

	HFpEF	HFrEF
LV structure/function		
End-diastolic volume	↔	↑
End-systolic volume	↔	↑
Wall thickness	↑	↔
Mass	↑	↑
Mass/volume ratio	↑	↓
Remodeling	Concentric	Eccentric
Ejection fraction	↔	↓
Stroke work	↔	↓
End-systolic elastance	↔	↓
End-diastolic stiffness	↑	↓
LV ultrastructure		
Myocyte diameter	↑	↔
Myocyte length	↔	↑
Myocyte remodeling	Concentric	Eccentric
Fibrosis	Interstitial/reactive	Focal/ replacement

HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and LV, left ventricular.

which induce reactive interstitial fibrosis[22] and altered paracrine communication between endothelial cells and surrounding cardiomyocytes.[21] The latter deprives cardiomyocytes of nitric oxide (NO) and of cyclic guanosine monophosphate (cGMP), which renders them hypertrophied and stiff.[23] High cardiomyocyte stiffness is caused by diminished distensibility of the giant cytoskeletal protein titin, whose elastic properties are dynamically modulated by isoform shifts, phosphorylation, and oxidation.[24,25] Strong support for an extramyocardial origin of HFpEF came from parabiosis experiments in which hearts of young animals acquired HFpEF-like features when exposed to blood from old animals and vice versa, because hearts of old animals reversed HFpEF-like features when exposed to blood of young animals.[26]

The extramyocardial origin of HFpEF differs from the intramyocardial origin of HFrEF, where remodeling is driven by cardiomyocyte cell death because of ischemia, infection, or toxicity.[27] Distinct origins of HFpEF and HFrEF are mirrored by unequal left ventricular (LV) structural and ultrastructural remodeling (Table). Biomarker profiles in HFpEF and HFrEF are consistent with the distinct origins of both HF phenotypes because they show lower markers of myocardial injury (high-sensitivity troponin T) or of myocardial stress (N-terminal pro brain natriuretic peptide [N-terminal pro-BNP]) in HFpEF.[17–20,28–30] Lower high-sensitivity troponin T is explained by less cardiomyocyte damage as a result of limited upregulation in HFpEF myocardium of nicotinamide adenine dinucleotide phosphate oxidase 2 evident in infiltrating macrophages or endothelial cells but not in cardiomyocytes.[21] Lower N-terminal pro-BNP is explained by concentric LV remodeling/hypertrophy in HFpEF in contrast to eccentric LV remodeling/hypertrophy in HFrEF[31] and by visceral distribution of adipose tissue in the mostly overweight or obese HFpEF patients,[32] which is associated with decreased production and increased clearance of natriuretic peptides (NPs).

In HFpEF, chronic systemic inflammation affects not only the myocardium, but also other organs such as lungs, skeletal muscles, and kidneys (Figure 1). Although HFpEF patients may stop exercising because of a rapid and brisk rise in LV filling pressures,[33–38] in a substantial subset of patients, effort tolerance is limited by inappropriate pulmonary vasoconstriction evident from pulmonary hypertension, or by inadequate peripheral skeletal muscle vasodilation, perfusion, and oxygen use evident from absent widening of arteriovenous oxygen difference.[39–43] Systemic inflammation also affects the renal microcirculation and the ability of the kidneys to excrete a sodium load.[44] Inability to excrete a sodium load contributes to the progressive volume expansion observed during transition from chronic compensated to acute decompensated HFpEF[45,46] and explains the efficacy of diuretics because they restore the pressure-natriuresis relationship.

PHENOTYPIC FRAMEWORK

HFpEF clinically presents as a diverse syndrome initiated by a variety of comorbidities and inflammatory mediators with extracardiac manifestations and cardiac abnormalities.[13,47–49] Despite the diversity of the HFpEF syndrome, the treatment strategy thus far has focused on a one-size-fits-all approach that has worked relatively well for chronic HFrEF. However, virtually all clinical syndromes benefit from more tailored, personalized therapy, and this may also be true of HFpEF. Successfully addressing the diversity of HFpEF is an active area of investigation, and solutions for the problem range from simple (eg, stratifying based on type of clinical presentation[47]) to sophisticated (eg, machine-learning techniques to perform data reduction to classify patients based on intrinsic patterns in dense phenotypic data[49]). Although the field of machine learning is not new,[50] its application to clinical medicine is still relatively novel, and these techniques will require iterative testing and application to clinical trials before they can be applied clinically on a routine basis.

In the absence of compelling outcome data to support individual therapies, we propose a matrix configuration combining predisposition phenotypes with clinical presentation phenotypes as a starting point to guide current clinical care and future prospective research (Figure 2). Rare etiologies such as constrictive pericarditis, valvular heart disease, high-output failure, or infiltrative cardiomyopathies are presumed to be excluded beforehand. Fig-

HFpEF Predisposition Phenotypes	HFpEF Clinical Presentation Phenotypes: Lung Congestion	+Chronotropic Incompetence	+Pulmonary Hypertension (CpcPH)	+Skeletal muscle weakness	+Atrial Fibrillation
Overweight/obesity/ metabolic syndrome/ type 2 DM	• **Diuretics (loop diuretic in DM)** • **Caloric restriction** • Statins • Inorganic nitrite/nitrate • Sacubitril • Spironolactone	+Rate adaptive atrial pacing	+Pulmonary vasodilators (e.g. PDE5I)	**+Exercise training program**	+Cardioversion + Rate Control **+Anticoagulation**
+Arterial hypertension	+ACEI/ARB	+ACEI/ARB +Rate adaptive atrial pacing	+ACEI/ARB +Pulmonary vasodilators (e.g. PDE5I)	+ACEI/ARB **+Exercise training program**	+ACEI/ARB +Cardioversion + Rate Control **+Anticoagulation**
+Renal dysfunction	+Ultrafiltration if needed	+Ultrafiltration if needed +Rate adaptive atrial pacing	+Ultrafiltration if needed +Pulmonary vasodilators (e.g. PDE5I)	+Ultrafiltration if needed **+Exercise training program**	+Ultrafiltration if needed +Cardioversion + Rate Control **+Anticoagulation**
+CAD	+ACEI +Revascularization	+ACEI +Revascularization +Rate adaptive atrial pacing	+ACEI +Revascularization +Pulmonary vasodilators (e.g. PDE5I)	+ACEI +Revascularization **+Exercise training program**	+ACEI +Revascularization +Cardioversion + Rate Control **+Anticoagulation**

Figure 2. Phenotype-specific HFpEF treatment strategy using a matrix of predisposition phenotypes and clinical presentation phenotypes.
A stepwise approach is proposed that begins in the left hand upper corner of the matrix with general treatment recommendations, presumed to be beneficial to the vast majority of HFpEF patients as they address the presentation phenotype of lung congestion and the predisposition phenotype of overweight/obesity present in >80% of HFpEF patients. Subsequently, supplementary (+) recommendations are suggested for additional predisposition-related phenotypic features when moving downward in the matrix and for additional presentation-related phenotypic features when moving rightward in the matrix. Arterial hypertension, renal dysfunction, and coronary artery disease are proposed as additional predisposition phenotypes. Additional clinical presentation phenotypes, in which specific therapeutic interventions could be meaningful, include chronotropic incompetence, pulmonary hypertension (especially combined precapillary and postcapillary pulmonary hypertension [CpcPH]), skeletal muscle weakness, and atrial fibrillation. Only therapeutic measures indicated in bold are currently established. All other therapeutic measures require further testing in specific phenotypes. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CAD, coronary artery disease; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; and PDE5I, phosphodiesterase 5 inhibitor.

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PHENOTYPIC TREATMENT STRATEGY

Numerous steps of the HFpEF signaling cascade, which range from systemic inflammation to myocardial titin elasticity, are valid treatment targets either for the vast majority of the HFpEF population (ie, the lung congestion/metabolic risk phenotype in the upper left hand corner of Figure 2) or for specific presentation/predisposition HFpEF phenotypes (Figure 2).

Lung Congestion/Metabolic Risk Phenotype

The lung congestion/metabolic risk phenotype is considered the garden variety of HFpEF, because, by definition,

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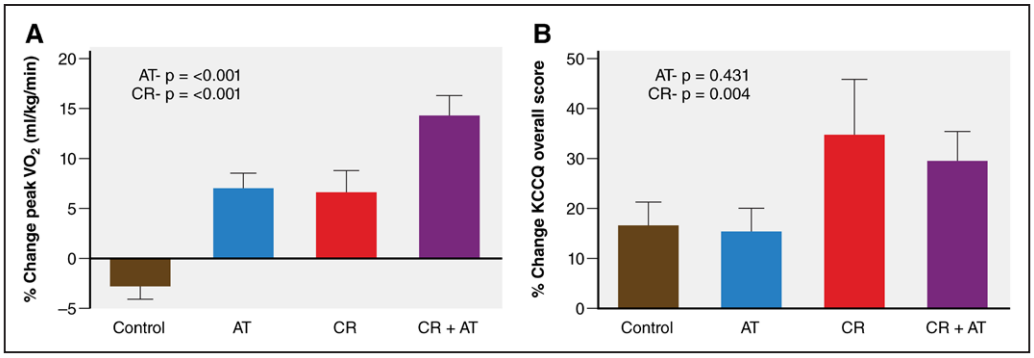

Figure 3. Effects of a 20-week caloric restriction diet on exercise capacity and quality of life in HFpEF.
The graph displays percent changes ± standard errors at the 20-week follow-up relative to baseline by randomized group for peak Vo_2 (mL·kg^{-1}·min^{-1}, **A**), and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score (Quality of Life Score; **B**). P values represent effects for AT and CR. AT indicates aerobic exercise training; and CR, caloric restriction diet.

HF patients have evidence of lung congestion at rest or during exercise and because overweight/obesity (body mass index >25 kg/m^2) is highly prevalent in HFpEF (>80%)[15] and increasingly recognized to drive HFpEF development. The latter was evident from recent longitudinal noninvasive studies, which revealed close correlations over a 4-year time interval between diastolic LV stiffness and body mass index and concluded that central adiposity predisposed to HFpEF.[51,52] Similar evidence was already provided by the ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial), which enrolled patients with arterial hypertension and 1 additional cardiovascular risk factor, and observed a high body mass index at enrolment to be the strongest predictor of HFpEF development.[53]

Diuretics

Lowering of LV filling pressures with diuretics is of paramount importance for HFpEF patients to achieve symptomatic benefit, to reduce pulmonary artery pressures, and to improve right ventricular (RV) loading.[54] Their efficacy relates to a restored pressure-natriuresis relationship in the presence of renal microvascular inflammation.[55] Administration of diuretics can be guided by the use of implantable hemodynamic monitors that either directly and continuously measure diastolic LV pressures or provide surrogates of pressure.[45] Studies evaluating hemodynamic monitoring have demonstrated that, even in HFpEF patients considered by expert HF clinicians to be compensated, diastolic LV pressures are elevated and these elevations have important prognostic implications.[56] When transition to decompensated HF occurs, diastolic LV pressures progressively increase over weeks. During this time interval, hemodynamic monitoring allows for early uptitration of diuretics, which improves outcome as demonstrated in the CHAMPION trial (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients). In this study, treatment guided by implantable hemodynamic monitoring significantly decreased cardiovascular death and HF hospitalizations in HFPEF patients.[57,58]

Caloric Restriction

Because increased body adiposity promotes inflammation and impairs cardiac, arterial, renal, and skeletal muscle function, weight loss should be considered in a treatment strategy for the vast majority of HFpEF patients. Kitzman et al[59] recently reported that a 20-week caloric restriction diet was feasible and appeared safe in older, obese HFpEF patients, and significantly improved their symptoms, peak oxygen consumption (Vo_2), and quality-of-life scores (Figure 3). The quality-of-life improvement was significantly greater with diet than exercise. The combination of diet with endurance exercise training was additive and produced a large (2.5 mL·kg^{-1}·min^{-1}) increase in peak Vo_2 (Figure 3), similar to or larger than what most drug or other treatments produced in HFrEF patients. The validity of the increase in peak Vo_2 was supported by significant increases in 5 other measures of physical performance that are independent of body mass: Vo_2 reserve, exercise time to exhaustion, workload, 6-minute walk distance, and leg power. The increase in peak Vo_2 was strongly correlated with reduced body fat mass, increased percent lean body mass, higher thigh muscle/intermuscular fat ratio, and lower biomarkers of inflammation all of which support the hypothesis that overweight/obesity contributes to exercise intolerance in HFpEF through systemic inflammation.[59]

Statins

The presence of systemic inflammation supports the use of statins in HFpEF. Statins improve endothelial redox balance and restore NO bioavailability, independently of low-density lipoprotein lowering.[60,61] Analysis of endomyocardial biopsy material revealed statin-treated HFpEF patients to have less myocardial nitrotyrosine, higher myocardial protein kinase G (PKG) activity, less cardiomyocyte hypertrophy, and lower cardiomyocyte resting tension.[10] In an observational study, statin-treated HFpEF patients were also less prone to develop atrial fibrillation.[62] These findings support the positive outcome of small phase 2 trials and HF registries that showed statin use to improve

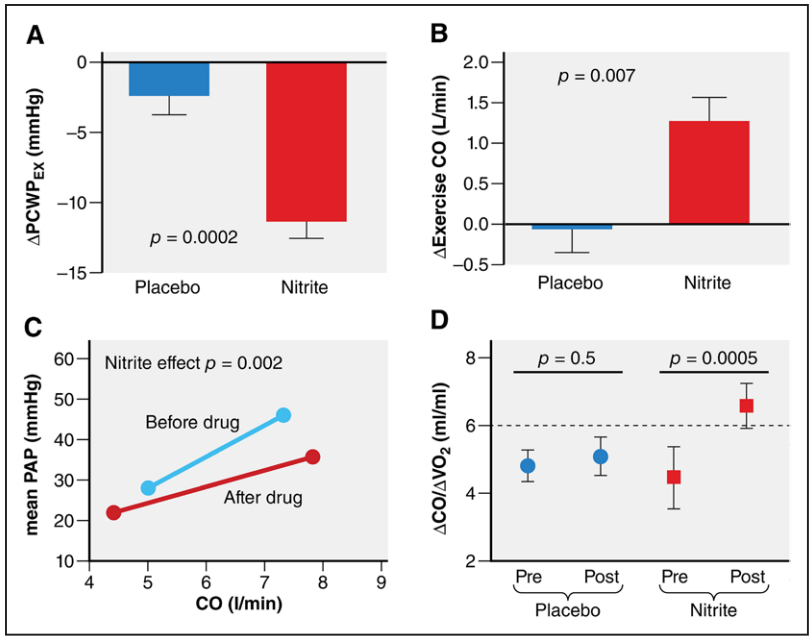

Figure 4. Effects of acute infusion of inorganic nitrite on exercise hemodynamics in HFpEF.
$\Delta PCWP_{EX}$ indicates change in exercise-induced pulmonary capillary wedge pressure (**A**); ΔExerciseCO, increase in exercise induced cardiac output (**B**); mean PAP, mean pulmonary artery pressure (**C**); and $\Delta CO/\Delta V_{O_2}$, ratio of exercise-induced increase in cardiac output over exercise-induced increase in oxygen consumption (**D**).

outcome of HFpEF patients.[63–65] It remains to be explored whether other novel approaches to treat systemic inflammation might be effective in HFpEF.[66]

Inorganic Nitrite/Nitrate

In the HFpEF signaling cascade, cardiomyocytes are deprived of NO and cGMP because of altered paracrine communication between inflamed microvascular endothelial cells and cardiomyocytes (Figure 1). Organic NO donors were therefore suggested to be potentially useful in HFpEF because they could restore myocardial NO content and concomitantly correct the elevated arterial load. Recently however, Redfield et al[67] demonstrated in patients with HFpEF that the organic nitrate isosorbide mononitrate tended to reduce chronic activity levels measured by accelerometry, with no improvement in submaximal exercise capacity. This result might be interpreted as disproving the NO hypothesis in HFpEF, but there are some important caveats to consider. Organic nitrates may produce greater than expected hypotensive effects in people with HFpEF or potentially impair cardiac output because of excessive preload reduction.[68] Organic nitrates tonically increase local NO levels and require bioactivation in the tissues. The latter can cause pharmacological tolerance, whereas the former can chronically lower renal perfusion pressure, which, as alluded to before, is countered by renal sodium retention. This may override any beneficial reduction in filling pressures, a phenomenon known as pseudotolerance. Perhaps more importantly, organic nitrates such as isosorbide mononitrate have also been shown to cause endothelial dysfunction[69,70] which plays a central role in the HFpEF signaling cascade.

In contrast to organic nitrates, the inorganic nitrate-nitrite pathway represents an important alternative route to restore NO signaling in HFpEF.[71] Formerly considered as an inert byproduct of NO metabolism, nitrite is now known to function as an important in vivo NO reservoir. Importantly, nitrite is preferentially reduced to NO in the presence of hypoxia and acidosis, which occurs during physical exercise, thus delivering NO at the time and locations (ie, skeletal and cardiac muscles) of greatest need. Nitrate-nitrite preparations have been shown to improve conduit artery stiffness in healthy volunteers and improve systemic vasodilation during exercise in patients with HFpEF.[72,73] More recently, acute infusion of sodium nitrite was shown in a placebo-controlled trial of patients with HFpEF to preferentially reduce diastolic LV pressures and pulmonary artery pressures during exercise while restoring cardiac output reserve toward normal (Figure 4).[74] Part of this benefit was mediated by vasodilation, but evidence for a direct myocardial benefit, such as increased stroke work, was also observed. Another recent study found that inorganic nitrate, delivered as 1 week of once-daily beetroot juice consumption, improved submaximal exercise endurance.[75]

Sacubitril and Other PKG-Stimulating Drugs

A substantial number of HFpEF patients have pathological ventricular hypertrophy, with interstitial fibrosis and diastolic chamber stiffening. This has encouraged efforts to block key activators and to stimulate intrinsic suppressors of these changes. Among the attractive pathways representing the latter approach are those coupled to cGMP and its cognate kinase, PKG. PKG stimulation has potent antifibrotic and antihypertrophic effects in cultured myocytes and fibroblasts,[76–79] and has been protective in a wide array of experimental cardiac disease models including pressure-overload hypertrophy.[80–82] Moreover, there are multiple therapeutic approaches to stimulate PKG already in clinical use or under active investigation, which increases the potential translational relevance of this pathway.

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Stimulation of PKG requires cGMP, which is either synthesized by soluble guanylate cyclase (sGC) activated by NO or by receptor guanylate cyclase linked to the NP receptor.[83–85] This is, in turn, counterbalanced by hydrolysis of cGMP back to GMP by select members of the phosphodiesterase (PDE) superfamily, and their inhibition, which leads to increased cGMP, can also increase PKG activity (Figure 5). cGMP also controls cAMP levels by feedback modulation of PDE2 and PDE3. At low levels of cGMP, proinotropic effects via cAMP have been observed, whereas, at higher levels and with cAMP costimulation, cGMP induces an antiadrenergic effect. Four members of the PDE superfamily (PDE1, PDE2, PDE5, and PDE9 of which both PDE5 and PDE9 are selective for cGMP) regulate cGMP in the heart. PDE5 and PDE9 are not redundant, but target different intracellular pools, with PDE5 largely impacting NO-sGC–derived cGMP, whereas PDE9 regulates NP- receptor guanylate cyclase –derived pools.[80] These local pools impact different intracellular compartments of PKG, as detected by differences in net phosphokinomes and effects on transcriptional regulation.[80]

Recent studies have defined multiple targets relevant to the lusitropic, antihypertrophic, and antifibrotic impact of PKG. HFpEF cardiomyocytes display greater passive diastolic stiffness that have been linked to changes in titin phosphorylation at PEVK-region residues (so named because it contains primarily proline [P], glutamate [E], valine [V] and lysine [K] residues) modulated by PKA and PKG.[23,86–88] The latter is a particularly potent regulator of titin stiffness, which in turn impacts cardiac muscle stiffness.[23] Antihypertrophic and antifibrotic mechanisms include PKG suppression of transforming growth factor-β signaling by phosphorylation of Smad proteins that blocks their nuclear translocation and signaling.[89]

Data regarding myocardial cGMP/PKG signaling in HFpEF remain fairly limited, but several studies have revealed critical features in this disease that could ultimately dictate how a successful therapy would need to work. Most pertinently, human LV biopsy analysis from HFpEF has reported very low levels of cGMP and associated PKG activity, particularly compared with patients who have HFrEF and aortic stenosis.[23] This may help explain reduced titin phosphorylation and muscle stiffening, and contributory signaling to hypertrophy and fibrosis (ie, the brake has been removed). It also raises questions regarding the initiating mechanism. Myocardial oxidative stress coupled with a proinflammatory microvascular environment has been proposed[10] and was recently supported by comparative analysis of HFpEF, HFrEF, and aortic stenosis samples, which in HFpEF revealed higher microvascular expression of adhesion molecules and nicotinamide adenine dinucleotide phosphate oxidase 2 with higher hydrogen peroxide and lower nitrite/nitrate content.[21]

Administration of sGC activators or stimulators could provide downstream correction for the low myocardial NO bioavailability in HFpEF. Use of the sGC activator cinaciguat in HFrEF was hampered by hypotension.[90] The oral sGC stimulator riociguat improved exercise tolerance or quality of life in pulmonary arterial hypertension (PATENT [Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial]),[91] in chronic thromboembolic pulmonary hypertension (CHEST [Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial]),[92] and in pulmonary hypertension attributable to HFrEF (LEPHT [Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial]).[93] In these 3 studies, arterial blood pressure also decreased by up to 9 mm Hg and this is especially worrisome for HFpEF patients because of their limited ability to increase LV stroke volume.[68] The use of vericiguat, another sGC stimulator, was well tolerated in HFrEF but failed to lower NP except at the highest dose.[94] It is currently being tested in HFpEF in the SOCRATES-PRESERVED trial (Phase IIb Safety and Efficacy Study of Four Dose Regimens of BAY1021189 in Patients With Heart Failure and Preserved Ejection Fraction Suffering From Worsening Chronic Heart Failure).

Because of concentric LV remodeling, NP stimulation is less marked in HFpEF than HFrEF, a finding that may limit counter stimulation via this pathway. NPs are

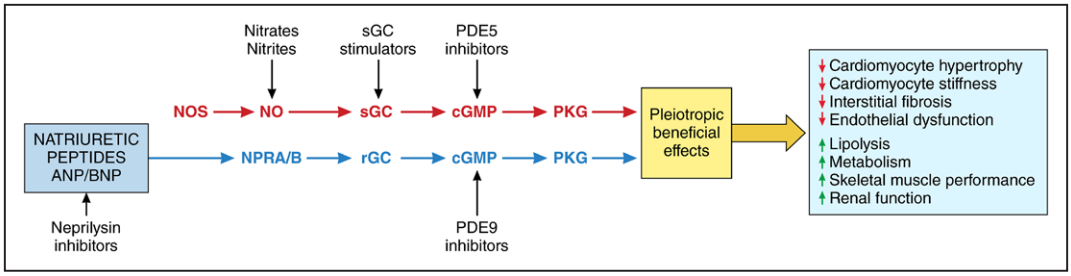

Figure 5. Myocardial cGMP signaling and pharmacological interventions in HFpEF.
Nitric oxide (NO) produced by NO synthases (NOS) stimulates soluble guanylate cyclase (sGC) to produce cyclic guanosine monophosphate (cGMP), which activates protein kinase G (PKG). Inorganic nitrate/nitrite, sGC stimulators and phosphodiesterase (PDE) 5 inhibitors target this pathway. The natriuretic peptides ANP and BNP attach to the natriuretic peptide receptors A/B (NPRA/NPRB). This stimulates receptor guanylate cyclase (rGC) to produce cGMP, which again activates PKG. Neprilysin inhibitors such as sacubitril and PDE9 inhibitors act through this pathway. ANP indicates atrial natriuretic peptide; and BNP, brain natriuretic peptide.

degraded by circulating neprilysin. Inhibition of this peptidase could augment deficient NP-receptor guanylate cyclase signaling and therefore be beneficial in HFpEF, as suggested by the decrease in NP following administration of valsartan/sacubitril in the phase 2 (PARAMOUNT study [Prospective Comparison of ARNI with ARB on Management of Heart Failure With Preserved Ejection Fraction]).[95] Use of valsartan/sacubitril is currently being tested in the multicenter PARAGON-HF trial (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction).

Another approach is to block PDEs to increase cGMP levels and hence PKG activity. PDE5 upregulation in HFrEF was reported by multiple[96,97] but not all[98] laboratories. Data in HFpEF did not support a similar elevation,[23] and 2 PDE5-inhibitor trials in HFpEF yielded a neutral outcome.[99,100] An alternative may therefore be inhibiting PDE9. A recent study found marked upregulation of PDE9 protein in human LV biopsies from HFpEF patients and from HFrEF and aortic stenosis patients, as well.[80] This suggests the low cGMP levels might be related to enhanced expression of PDE9, and if so, inhibiting this PDE should have beneficial effects. In mice subjected to sustained pressure overload, blocking PDE9 by gene deletion or selective pharmacological inhibition suppressed hypertrophy, fibrosis, and chamber dysfunction.[80] PDE9 inhibition has been previously examined clinically for its potential to alter cognition[101] but these new data may trigger interest in HFpEF and other forms of heart failure.

Spironolactone and E-Matrix Modification

The extracellular matrix is composed of fibrillary proteins (such as collagen and elastin), nonfibrillary proteins (such as aminoglycans, fibronectin, laminin), and bioactive proteins (such as transforming growth factor-β, matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases , and matricellular proteins). The homeostatic control of collagen is especially important for abnormal diastolic function in HF.[102] Important differences in geometry, composition, and homeostatic mechanisms are seen in HFpEF versus HFrEF. HFpEF is more often associated with interstitial, reactive fibrosis and HFrEF with focal, replacement fibrosis (Table). The extent of collagen cross-linking tends to be higher in HFpEF,[103] and homeostasis in HFpEF is profibrotic while fibrinolytic in HFrEF.

Resident myocardial fibroblasts control collagen homeostasis in normal hearts. Whether resident fibroblasts remain responsible for increased collagen production or whether recruitment of fibroblasts occurs from a different source, such as bone marrow or microvascular endothelium, remains uncertain. In murine HFpEF models, resident fibroblasts and not bone marrow–derived cells or endothelial-mesenchymal transition were primarily responsible for myocardial collagen production following transverse aortic constriction.[105,106] Recruited cells could still be involved through the secretion of cytokines or matricellular proteins, however. Myofibroblasts have also been implicated in collagen deposition in HFpEF because they are closely associated with fibrotic collagen deposition and scar contracture. In HFpEF, fibroblasts are presumed to convert to myofibroblasts because of exposure to transforming growth factor-β as a result of monocyte/macrophage myocardial infiltration.[22]

Collagen metabolism requires sequential, highly orchestrated and regulated steps: (1) procollagen synthesis and secretion, (2) procollagen postsynthetic processing, (3) collagen posttranslational modification, and (4) collagen degradation. Each of these steps is altered in HFpEF, contributes either individually or in aggregate to LV diastolic dysfunction, is mirrored in plasma biomarkers, and serves as a unique treatment target (Figure 6). Procollagen I and III are synthesized in myocardial fibroblasts and secreted as a soluble molecule with NH2 (N)-terminal and COOH (C)-terminal propeptides attached. These are removed to create insoluble collagen[107] and appear in plasma as procollagen I C-terminal peptide, procollagen III C-terminal peptide, procollagen I N-terminal peptide, and procollagen III N-terminal peptide, all of which reflect the rate of collagen synthesis. Subsequent formation of insoluble collagen requires enzymatic formation of cross-links by lysyl- or hydroxylysy-

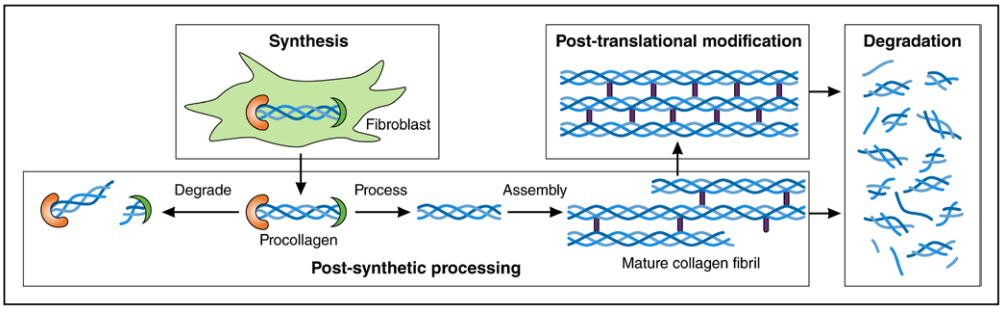

Figure 6. Sequential steps of collagen metabolism.
Collagen metabolism involves sequential steps consisting of procollagen synthesis, procollagen processing to collagen fibrils, posttranslational modification of collagen fibrils and collagen degradation.

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loxidase. Nonenzymatic cross-links can also be formed by advanced glycation end products, which can activate profibrotic pathways through binding with the receptor for advanced glycation end products. Insoluble collagen formation is promoted by matricellular proteins (SPARC [secreted protein acidic and rich in cysteine], thrombospondin, osteopontin). To maintain collagen homeostasis, insoluble collagen is continuously degraded by matrix metalloproteinases, which are in turn regulated by tissue inhibitors of matrix metalloproteinases.[108] Collagen degradation results in formation of collagen telopeptides (C-telopeptide for type I collagen, C-telopeptide for type III collagen). Matrix metalloproteinases, C-telopeptide for type I collagen, and C-telopeptide for type III collagen can be measured in plasma and, in combination with procollagen I C-terminal peptide, procollagen I N-terminal peptide, procollagen III C-terminal peptide, and procollagen III N-terminal peptide allow for an integrated multibiomarker assessment of collagen homeostasis.[103] In HFpEF, such an assessment revealed collagen synthesis to be increased and collagen degradation to be decreased resulting in a net increase in collagen content.[109] Additional biomarkers that are useful estimates of myocardial collagen content are galectin-3 and solubleST2. The former is secreted by infiltrating macrophages and stimulates fibroblasts, whereas the latter is a member of the interleukin-1 receptor family which is also profibrotic, because it acts as a decoy for interleukin-33, which inhibits profibrotic signaling.

To date, 3 pharmaceutical agents that affect the extracellular matrix have been tested in HFpEF: spironolactone in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), valsartan/sacubitril in PARAMOUNT, and torasemide. In TOPCAT, spironolactone (a mineralocorticoid receptor antagonist) failed to reduce the composite primary end point in the overall trial population[110] but not in patients with elevated BNP, which was a marker of enrollment in the Americas (P=0.003).[111] The neutral outcome in the overall population may have been related to aberrant patient enrollment in Russia/Republic of Georgia rather than to inefficacy of spironolactone. In PARAMOUNT, salutary effects of valsartan/sacubitril consisting of a significant decrease in Nterminal pro-BNP and left atrial volume were observed in HFpEF patients.[95] These effects support fibrosis-specific therapy for HFpEF patients with advanced extracellular matrix modification.[112] The loop diuretic torasemide affects collagen cross-linking, and its use has been shown to improve diastolic LV dysfunction in patients with hypertensive heart disease.[113] Finally, use of mesenchymal stem cells has been examined in Dahl salt-sensitive rats with promising results. In this model, a single intracoronary dose of allogeneic mesenchymal stem cells reduced myocardial collagen volume fraction and normalized diastolic LV function without effect on cardiomyocyte hypertrophy.[114]

Arterial Hypertension

Arterial hypertension is found in ≥80% of HFpEF patients. Treatment of arterial hypertension in older people without HF reduces incident HF.[53] In acutely decompensated HFpEF patients with elevated blood pressure, symptoms may improve markedly with blood pressure lowering alone even before diuresis is achieved. However, in chronic stable HFpEF patients, there is uncertainty about whether adding blood pressure–lowering medications provides additional benefit. A discordance was indeed present between substantial blood pressure lowering and outcome in large trials testing neurohumoral inhibition in HFpEF.[2] This was even more surprising, because, along with blood pressure lowering, there were numerous other mechanisms whereby neurohumoral inhibition was expected to benefit HFpEF, including improvements in myocardial hypertrophy, myocardial fibrosis, and vascular stiffness. However, treating arterial hypertension for non-HF–related macrovascular indications (eg, stroke, myocardial infarction) also remains an important goal in HFpEF patients. In this regard, it is worth noting that large outcome trials confirmed ACEIs and ARBs to be safe and well tolerated as antihypertensive medications.[2,4] Diuretics, spironolactone, and ACEIs/ARBs are therefore reasonable first choices to control blood pressure based on the currently available data. Although it is true that previously tested ACEIs and ARBs did not reduce mortality, increasing the quality of life may be the better strategy in HFpEF patients because they are often elderly and debilitated. Some previously completed trials of ACEIs/ARBs showed relevant symptomatic benefits, such as reduced HF hospitalization, in these patient populations.[2,4]

Arterial hypertension can affect myocardial remodeling and dysfunction in HFpEF through myocardial overload[115] or systemic inflammation.[116] The importance of overload is unclear because, in a concentrically remodeled LV with normal EF, a favorable late-systolic Laplace relation protects LV myocardium from loading increments provoked by large reflected arterial pressure waves. However, in the presence of a minor LV shortening deficit, hypertensive HFpEF patients may develop late-peaking systolic LV wall stress. This may explain the favorable effects in HFpEF patients of nitrate-rich beetroot juice, which reduces the magnitude of reflected arterial pressure waves,[75] or of the sodium-restricted DASH (Dietary Approaches to Stop Hypertension) diet, which improves ventricular-arterial coupling.[117]

Renal Dysfunction

HFpEF and renal dysfunction are mutually promoting (Figure 1).[118] HFpEF promotes renal dysfunction by (1) an elevated central venous pressure, which results from pulmonary hypertension and RV dysfunction; (2) inability to increase cardiac output following arterial vasodilation

because of chronotropic incompetence and fixed LV stroke volume[119]; (3) systemic inflammation, endothelial dysfunction, and low NO bioavailability, which reduces renal blood flow[55,120] and sodium excretion.[44] Renal dysfunction promotes HFpEF by worsening systemic inflammation, endothelial dysfunction, and NO bioavailability, in part, because of renal-specific mediators such as high levels of fibroblast growth factor 23, phosphorus, parathyroid hormone or uremic toxins, and low levels of vitamin D or erythropoietin.[118] Limited tolerability of systemic vasodilation and impaired sodium excretion are of therapeutic importance.[68] Impaired sodium excretion implies the arterial pressure-natriuresis relationship to be shifted to the right. Under these conditions, a fall in arterial pressure because of systemic vasodilation without cardiac output increase is especially deleterious because it leads to additional sodium retention and extracellular volume expansion, which wipes out any direct beneficial effect of vasodilation on LV filling pressures.[68] This mechanism could partially account for the neutral outcome of the RELAX trial (PhosphodiesteRasE-5 Inhibition to Improve CLinical Status And EXercise Capacity in Diastolic Heart Failure),[99] where sildenafil lowered arterial pressure, raised plasma creatinine and urea levels, and failed to improve exercise tolerance.

HFpEF in the presence of renal dysfunction recently emerged as a distinct phenotype with more LV hypertrophy, a larger LV systolic functional deficit, impaired left atrial mechanics, RV dysfunction, and poor prognosis.[121,122] The latter relates to exaggerated reactive pulmonary hypertension and RV dysfunction. Because of RV dysfunction, renal venous congestion importantly contributes to renal dysfunction in HFpEF. Vigorous diuresis (and ultrafiltration if necessary) is therefore important in HFpEF patients with renal dysfunction.

Coronary Artery Disease

The presence of coronary artery disease also identifies a distinct HFpEF phenotype with a larger LV systolic functional deficit, poor prognosis,[123,124] and a high incidence of sudden death.[125] Use of ACEIs is recommended for prevention of new cardiovascular events. In HFpEF patients with coronary artery disease, observational data suggest that complete revascularization is associated with better preservation of LV systolic function and an improved prognosis, although prospective trial data are still lacking.[123]

Chronotropic Incompetence

Many patients with HFpEF display marked impairments in cardiac output reserve during exercise, despite normal resting values.[126] Impaired cardiac output reserve in HFpEF is related not only to decreased stroke volume augmentation, but also to chronotropic incompetence.[127–129]

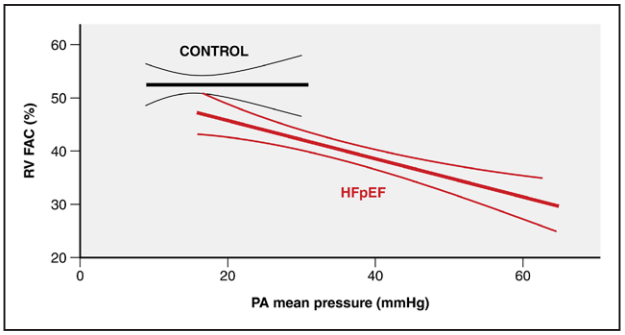

Figure 7. Heightened afterload sensitivity of the right ventricle in HFpEF.
The relation between echocardiographic right ventricular (RV) fractional area change (FAC) and mean pulmonary artery (PA) pressure is flat in controls but steep in HFpEF patients. HFpEF indicates heart failure with preserved ejection fraction.

One study actually indicated that chronotropic incompetence was the major contributor to reduced cardiac output reserve in HFpEF.[42] The importance of chronotropic incompetence is further supported by the worsened exercise capacity when heart rate was slowed by the I_f blocker ivabradine.[130] Chronotropic incompetence was previously shown to be related to endothelial dysfunction and systemic inflammation[131] and therefore fits well into the multiorgan signaling cascade that appears to drive HFpEF development. Because there is a direct relationship between heart rate response to activity and aerobic capacity,[128] a clinical trial is currently testing whether rate-adaptive atrial pacing can improve exercise capacity in patients with HFpEF (NCT02145351).

Pulmonary Hypertension

Recent evidence stressed the importance in HFpEF of pathophysiologic targets beyond the heart (Figure 1).[54] Pulmonary hypertension is frequently present at rest[132] and patients can also develop an exaggerated pulmonary hypertensive response to exercise.[36,37,39] In HFpEF, pulmonary pressures can be augmented by increased left atrial pressure and by pulmonary vasoconstriction. When both mechanisms prevail, combined precapillary and postcapillary pulmonary hypertension is present.

Because of pulmonary hypertension and shared predisposing mechanisms, RV dysfunction is common in HFpEF and is associated with increased morbidity and mortality.[133–135] The RV in HFpEF displays heightened afterload sensitivity, suggesting favorable potential for benefit from reduction in pulmonary pressures (Figure 7).[133] An early single-center trial recruiting mainly combined precapillary and postcapillary pulmonary hypertension patients indeed reported salutary effects on hemodynamics and RV function following treatment with the PDE5 inhibitor sildenafil.[136] However, 2 subsequent larger trials in patients with isolated postcapillary pulmonary hypertension and combined

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precapillary and postcapillary pulmonary hypertension failed to corroborate this finding.[99,100] A recent trial reported significant improvement in pulmonary vascular function in response to dobutamine in HFpEF patients, greatly exceeding the pulmonary vasodilatory response seen in non-HF controls.[137] Improved right ventricular-pulmonary artery coupling in this study was achieved predominantly through reduction in afterload rather than enhanced RV function, highlighting the importance of management of pulmonary hypertension in HFpEF. A number of trials have or are currently testing the effects of pulmonary vasodilators targeting cGMP,[138] endothelin,[139] and NO (NCT02713126; NCT02262078) in patients with HFpEF.

In contrast to the pulmonary vasculature, changes in the lung parenchyma are less characterized in HFpEF but likely also play an important role. Impairments in pulmonary function predict incident development of HFpEF independent of cardiac function.[140] Patients with HFpEF display gas exchange abnormalities manifest by reduced alveolar capillary membrane conductance.[141,142] These impairments become more dramatic during exercise because of high LV filling pressures during stress.[141] HFpEF patients with increased interstitial pulmonary edema display greater pulmonary vascular abnormalities and RV dysfunction, supporting aggressive therapies to reduce left heart filling pressures chronically in patients with HFpEF.[142]

Skeletal Muscle Weakness

Exercise intolerance can be objectively measured as peak Vo_2. By the Fick equation, Vo_2 is the product of cardiac output and arteriovenous oxygen difference ($\Delta A\text{-}Vo_2$). Multiple studies indicate that peak exercise $\Delta A\text{-}Vo_2$ is significantly reduced in HFpEF and accounts for ≥50% of their severely reduced peak Vo_2.[40,143] What are the causes of the reduced peak $\Delta A\text{-}Vo_2$ in HFpEF patients? HFpEF patients have abnormalities in skeletal muscle mass, composition, capillary density, and oxidative metabolism. Haykowsky et al[43] showed that, in comparison with age-matched healthy controls, older HFpEF patients have a significantly reduced percentage of total lean body mass and of leg lean mass. When peak Vo_2 was indexed to total lean body mass or leg lean mass, it remained significantly reduced. Thus, HFpEF patients have abnormal O_2 use that is independent of and in addition to their reduced muscle mass. HFpEF patients also have abnormal skeletal muscle composition with infiltration of adipose tissue, which is directly related to their reduced peak Vo_2.[144] Increased intramuscular fat reduces capillary density, thereby increasing the distance O_2 must traverse from the capillaries to the muscle fibers. In HFpEF patients, the reduced thigh muscle capillary density is associated with their reduced peak Vo_2 (Figure 8).[145] Multiple studies indicate that HFpEF patients also have impaired skeletal muscle oxidative metabolism. Kitzman et al[145] showed that, in comparison with healthy age-matched controls, HFpEF patients have a shift in skeletal muscle fiber type distribution from oxidative, slow type 1 fibers to glycolytic, fast type 2 fibers, which results in a lower type 1/type 2 fiber ratio. Similar to capillary density, these alterations are also associated with their severely reduced peak exercise Vo_2 (Figure 8). A consequence of this fiber type shift is reduced skeletal muscle oxidative metabolism during exercise, which was evident after cessation of exercise from the delayed regeneration of quadriceps muscle phosphocreatine stores by using phosphorus magnetic resonance spectroscopy.[146]

What are the implications of these extensive skeletal muscle abnormalities in HFpEF? First, they confirm that HFpEF is a systemic disorder involving not only the heart, but also other organ systems and that skeletal muscle and cardiac abnormalities are incited by common, circulating factors such as proinflammatory cytokines originating from multiple comorbidities.[147] Second, they suggest opportunities for novel interventions. Unlike the myocardium, which is terminally differentiated and has minimal capacity for regeneration, skeletal muscle has robust capacity for rapid repair, regeneration, and growth, which can be exploited by participation in an exercise training program.[148] Exercise training, shown in

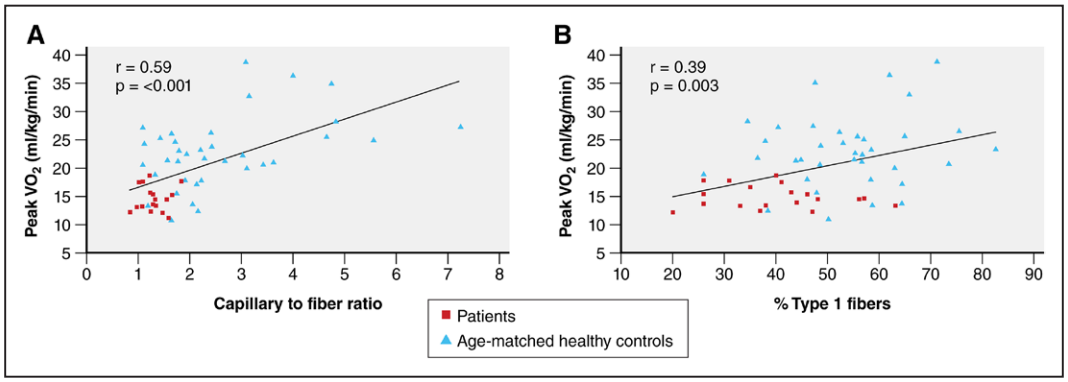

Figure 8. Peak Vo_2 and skeletal muscle histology in HFpEF.
Relationship of capillary to fiber ratio (**A**) and percent type 1 muscle fibers (**B**) with peak Vo_2 in older HFpEF patients (squares) and age-matched healthy controls (triangles). HFpEF indicates heart failure with preserved ejection fraction.

multiple studies to significantly improve peak Vo_2 in HFpEF,[148–151] achieves this primarily by improving skeletal muscle mitochondrial mass or function.[148] Most studies to date have used endurance training; high-intensity and strength training might produce even larger improvements but have not been examined systematically.[148]

Atrial Fibrillation

Prevalent atrial fibrillation in HFpEF goes along with a more advanced stage of cardiac remodeling evident from a larger left atrium and uniformly carries a worse prognosis.[62,152,153] Incident atrial fibrillation in HFpEF also accompanies worse LV diastolic dysfunction and was inversely related to statin use.[62] Prevalent atrial fibrillation was shown to be associated with incident HFpEF and prevalent HFpEF with incident atrial fibrillation.[154] These interactions suggest atrial fibrillation to beget HFpEF and vice versa and suggest efforts to restore sinus rhythm could be included in a HFpEF treatment strategy. Similar to HFpEF, atrial fibrillation reacts favorably to exercise training and weight loss.[155] To restore sinus rhythm, only cardioversion is recommended because catheter ablation of atrial fibrillation had limited long-term success in HFpEF with single- and multiple-procedure drug-free success rates of 27% and 45%, respectively.[156] If cardioversion is unsuccessful, rate control and permanent anticoagulation become mandatory.

CONCLUSIONS

HFpEF, the most common form of HF, is increasing out of proportion to HFrEF, and is associated with significant morbidity and mortality. Medication trials to date have been largely neutral on their primary outcomes and, so far, only exercise training and weight loss appear to improve exercise intolerance and quality of life. Recent insights provide an understanding of the fundamental basis of LV dysfunction in HFpEF, which involves systemic inflammation, coronary microcirculatory disturbances, cardiomyocyte stiffening, and myocardial fibrosis. These insights also provide a more expanded view on HFpEF that includes involvement of the pulmonary circulation, RV failure, skeletal muscle weakness, and renal dysfunction. These new perspectives on HFpEF open an array of novel therapeutic targets either in the garden-variety phenotype of lung congestion/metabolic risk or in specific phenotypes that may propel future advances in treatment and prevention of this important disorder.

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FOOTNOTES

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Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap

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Carolyn Lam: Welcome to Circulation on the Run, your weekly podcast summary and backstage pass to the journal and its editors. I'm doctor Carolyn Lam, Associate Editor from the National Heart Center and Duke National University of Singapore.

I am excited to be joined today by 2 guests and we will be discussing the feature paper on phenotype specific treatment of heart failure with preserve ejection fraction but first here are the highlights from 5 original papers in this week's issue. The first paper by first author doctor Haas, corresponding author Dr. Bidinger and colleagues from Boston Children's Hospital aim to investigate the role of PCSK9 in nephrotic syndrome associated hypercholesterolemia. The authors did this by first looking at 50 patients with nephrotic syndrome and showing that resolution of nephrotic syndrome was associated with a decrease in their plasma cholesterol, as well as a decrease in their plasma PCSK9 levels. They then looked at two mouse models of nephrotic syndrome. One using nephrotoxic serum to induce immune mediated damage of the kidney podocytes. The second, a model of genetic ablation of the kidney podocyte.

In both these models nephrotic syndrome produced hypercholesterolemia and a 7 to 24 fold induction of plasma PCSK9 levels. The authors then went on to look at the effect of knocking out PCSK9 both in the whole body as well as specifically in the liver in these mice. They showed that mice lacking PCSK9 no longer showed the increase in LDL cholesterol with nephrotic syndrome induced by nephrotoxic serum. Thus in summary, podocyte damage triggered mocked inductions in plasma PCSK9 and conversely knocking out PCSK9 in ameliorated this lepodimia in a mouse model of nephrotic syndrome. The cool thing about this data is that they now opened the door to the consideration of PCSK9 inhibitors in patients with nephrotic syndromes associated hypercholesterolemia.

The second paper by Dr. Fortis and colleagues from Duke Clinical Research Institute aimed to address an important knowledge gap that has not yet been addressed in the pivotal noac trials or large registries. Which is whether outcomes differ among atrial fibrillation papers with worsening renal function compared with those with stable renal function while taking a noac versus warfarin. The authors looked a this by studying more than 12,600 patients who were treated with rivaroxaban compared to warfarin in the ROCKET AF trial. On treatment worsening renal function was defined as a decrease of more than 20% from screening creatinine clearance measurement any time point during the study.

The main finding was that among patients with on treatment worsening renal function, rivaroxaban was associated with lower rates of stroke and systemic embolism compared with warfarin without an increase in the composite leading end point. This is really encouraging to all of us who treat these patients, knowing that it is possible to safely anti-coagulate patients with worsening renal function without excessive bleeding and to know that rivaroxaban may be an alternative to warfarin in these patients. This paper is accompanied by a beautiful editorial on the multifaceted dilemma of renal function and atrial fibrillation by doctors Hijazi and Wellington.

The third paper by doctor [inaudible 00:04:32] and colleagues from Massachusetts Journal Hospital describes a randomized controlled trial of an advanced care planing video decision support tool in 246 patients with advanced heart failure. Patients were randomized to an intervention arm which consisted of a six minute video as well as an advanced care planning checklist or to a control arm where patients received only a verbal description of the goals of care. This video began by first introducing to the patient the concept of advanced care planning and then using images to depict the three part goals of care namely, life prolonging care, limited medical care and comfort care. Patients in the intervention arm who were showed the video, were more likely to be informed, to select a focus on comfort and less likely to desire CPR and intubation compared to patients receiving the verbal information only. The clinical application of this finding is that advanced care planning video decision needs can stimulate and supplement patient decision communication. Indeed we need such tools to enhance patients understanding of their goals of care options and to ensure that our patients get care that reflects their well-informed wishes.

The fourth paper is by first author Dr. [inaudible 00:06:12] and corresponding author Dr. Lloyd Jones and colleagues from the Northwestern University Feinburg school of medicine in Chicago. These authors provided the first prospective evaluation of atherosclerotic cardiovascular disease outcomes in adults with heterozygous familial hypercholesterolemia in the US population. They did this by using individual pool data from 6 epidemiologic cohorts including more than 68,500 baseline person exams and 1.2 million person years of follow up. They confirmed substantially elevated long term, meaning up to 30 year risks of coronary heart disease and total atherosclerotic cardiovascular disease including stroke in US adults with a familial hypercholesterolemia phenotype defined as LDL cholesterol above 190 milligrams per deciliter. This was associated with an acceleration of coronary heart disease risk by up to 20 to 30 years. These findings were independent of other risk factors and were consistent using various definitions of the familial hypercholesterolemia phenotype.

What are the clinical implications of these findings? This was discussed by Dr. Rodriguez and Dr. [inaudible 00:07:47] in an editorial, the take home message is that there is likely an important long term burden of atherosclerotic cardiovascular disease in phenotypic but unrecognized familial hypercholesterolemia patients in the United States. Current efforts to identify patterns and gaps in the diagnosis and management are well justified. The findings also have implications for risk communication to patients.

Finally, the fifth paper is by Dr. [inaudible 00:08:25] and colleagues of the TIMI study group from Brigham and Women's Hospital. These authors looked at the impact of renal function on outcomes with edoxaban and oral factor 10 A inhibitor with 50% renal clearance compared to warfarin in the ENGAGE AF-TIMI 48 trial. In the pre-specified subgroups of granting clearance 30 to 50 and more than 50 ml per minute. The higher dose edoxaban regiment was comparable to warfarin for

preventing stroke or systemic embolism and resulted in significantly less major bleeding. In further exploratory analysis, there was a suggestion of lower relative efficacy for prevention of stroke or systemic embolism with the high dose edoxaban regiment, compared to warfarin in the upper range of creatinine clearance beyond 95 ml per minute. Due to lower rates of major bleeding, the net clinical benefit was more favorable with the higher dose edoxaban regiment across the range of creatinine clearance.

In summary, edoxaban demonstrated superior safety and comparable efficacy to warfarin for the prevention of thromboembolic events in many patients with atrial fibrillation. However the authors were careful to note that there was insufficient evidence to allow definitive conclusions to be drawn in patients with normal renal clearance above 95 ml per minute. The authors called for further investigation of optimal dosing of edoxaban in the higher range of creatinine clearance.

Those were our highlights now for our feature paper of the week. Phenotype specific treatment of heart failure with preserved ejection fraction, a multi-organ road map. The first author is Dr. [inaudible 00:10:31] from Northwestern University Feinberg School of Medicine in Chicago and colleagues. To discuss this very special paper today I have two guests, one is a corresponding author, Dr. Walter Paulus from the VU, University medical center in Amsterdam as well as Dr. Jarett Berry, associate editor from UT Southwestern. Welcome Walter and Jarett.

Jarett Berry: Thanks Carolyn.

Walter Paulus: Thank you very much Carolyn.

Carolyn Lam: To start us off this is an in depth review paper and it is a really very special type of paper that it's new to *Circulation*. Jarett could you tell us a little bit about these reviews and how this paper came to be?

Jarett Berry: As we think about the new *Circulation* and our goals to really make the content of *Circulation* as clinically relevant as possible, as we think of the different circumstances and clinically challenges faced by practicing physicians, many different topics come to mind and one in particular, therapeutic area heart failure with preserved ejection fraction is one particular type of cardiovascular disorder that has been very difficult to find novel treatments for. As we all know there has been a number of large scale clinical trials that have failed to improve clinical outcomes in these patients, in situations like this what we really need is wisdom and a guide from those with expertise in this area so we can take that wisdom and that perspective and incorporate it into our approach to caring for these patients in a way that can provide a road map moving forward.

This particular review addressing heart failure with preserved ejection fraction was timely in that sense and the choice of author, of course, Walter and his colleagues are leaders in the field in terms of the research and our understanding of HFpEF. With that goal, we're really trying to reach out to these types of investigators for

these types of reviews to provide us with a framework to help us think about charging our way forward and we couldn't think of a more appropriate choice to lead that effort other than Walter Paulus.

Carolyn Lam: Thank you so much Jarett, that's so well put and I couldn't agree more. I mean HFpEF is one of those disease syndromes were guidelines haven't changed in years and basically the first sentence is that we don't have outcome improving treatments available. Walter this must have been particularly challenging and I really congratulate you because one of the central figures that I'm so impressed with in this review is actually a clinical application figure and I'm referring to figure 2. Do you think you could tell the readers a little bit more about this?

Walter Paulus: I would like to thank first the editors of *Circulation* for having given us the opportunity to write this in-depth review. I must admit before answering Carolyn's question that I really enjoy this [inaudible 00:13:37]. We have a very challenging team of co-authors and the most difficult part of the enterprise was to have all the noses directed in the same direction. You have to align very many ideas and it has been a very challenging in-depth but I think it will be teamed out with a, not a compromise but something, a paper where everybody is still happy with its content. This is somehow also reflected in the figure 2 to which Carolyn is alluding.

When we start speaking about the phenotypic diversity, it's very difficult to [inaudible 00:14:13] with a conceptual theme on how we're going to organize therapy when there are many different phenotypes around. I think this is what this figure is all about, it tries to organize the phenotypic diversity and come up with a type of personalized medicine for each phenotype in a very comprehensive way. This figure, in fact, orders the phenotypes, presentation phenotypes and pre-disposition phenotypes with presentation phenotypes on the abscissa and the pre-disposition phenotypes on the ordinate. Then you get a matrix configuration, you start out in the matrix in the left hand corner for the most common phenotype which is metabolic risk combined with [inaudible 00:14:59] congestion. Then you go on and you see that you can have [inaudible 00:15:04] hypertension, then you have additional measures that need to be taken. You can go downwards in the graph and then you'll find out that it might be renal dysfunction and then you find specific measures that have to be taken when renal dysfunction is present.

By combining the ordinate and the abscissa in the matrix, you find a very personalized type of therapy for the individual phenotype. I think this to me what makes the figure that feeling is that it's structured, it's organized, it's something very complex in something which is easily comprehensible.

Carolyn Lam: Walter, I have not seen a figure like this that it's so novel and I know that clinicians will really welcome this because as Jarett so nicely put, it's wisdom and some sort of simplification and yet with in-depth understanding that we so need in the management of this syndrome. Another thing that I thought was very special about your paper is that you tackled head on the divergent results of several recent trials. You described the low nitric oxide, low cyclic guanosine monophosphate cycle

that's present in HFpEF but also try to put into context the need trial, the relax trial, top cat and even mention Socrates preserved in all of this. Do you have any quick top line comments, not to give the whole story away because I'm sure readers are now encouraged to look at the paper but on how all of this actually falls into place in your schema.

Walter Paulus: I think how everything falls into place is illustrated in the figure 1. Figure 1 shows a very broad perspective on the problems of HFpEF as it shows HFpEF to be the result of systemic inflammatory state but so far we have focused only on the project manifestations of the systemic inflammatory state [inaudible 00:17:08] cardiac manifestations, which is the stiffness of the myocardium, and the [inaudible 00:17:12] of the myocardium. There are also things going in the pulmonary [inaudible 00:17:16], there are things going on in the skeletal muscle and there are things going on in the kidney. I think that if you do not take these other organs into perspective, then the image you will have from the results of your trials is getting blurred. For instance, we have so many trials about look at the exercise [inaudible 00:17:35] in terms of elevation of [inaudible 00:17:37].

It's my feeling that many patients with HFpEF just get treated diabetic. You see them afterwards again in your [inaudible 00:17:46] patient clinic and they have symptoms of nasal fatigue. They no longer being hindered by the elevation of [inaudible 00:17:52] probably because of the administration of the diabetic but they're still highly symptomatic and they have moved over to another board and that limits the [inaudible 00:18:01] mainly the skeletal muscle. It's of course nicely illustrated already for years by the work of Dalane Kitzman which is one of the co-authors, but still these issues, the same goes for the hypertension, a field in which Carolyn has been very active. There are some patients who are persistent [inaudible 00:18:18] hypertension, I'm intrigued by our classification.

It's clear that these patients have moved to a [three catalyst 00:18:24] type of hypertension and we should pay attention to this and we should try to treat it in a very specific way. Again [inaudible 00:18:33] the failure of our trials is also comprehensible. He have two, [inaudible 00:18:38] focus on the myocardium and we should try to keep a very broad perspective and look at [inaudible 00:18:43] in major broader way. Just to support this point is the result of the Socrates reserve trial which I was very intrigued by it, just listen to the results couple of days ago at the European Heart Failure Society meeting in Florence. Turns out if you give this very [inaudible 00:19:01] patients that there is no change in nature at [inaudible 00:19:05], no change in left atrial dimension, there's no single argument that something is changing in the myocardium. Nevertheless the effort tolerance of the patients was greatly increased and the question is in quality of life, how that has drastically improved? What I think is going on, is that maybe on the dose of the [inaudible 00:19:23] you are using this very [inaudible 00:19:24].

The main effect might be going on the [inaudible 00:19:27] and you just took the wrong end point, you are again focusing very narrowly on the myocardium. I think most of the patients have entered such a trial are relatively stable. You're not going

to put in a trial a patient who is unstable, they must be all be treated with diabetics and you shift symptoms from the myocardium to the other organs. I think that the index review which we provide, I think has 2 main issues, that you should have a broad perspective on HFpEF with inclusion of the other organs and secondly, that we provide a matrix configuration for phenotypes specific treatment.

Carolyn Lam: Walter that is beautifully put and Jarett I think I'm speaking on behalf of you too that this paper has really accomplished what our in-depth reviews were aiming to do, which is to provide a clinical perspective and really insightful comments regarding the syndrome. Is there anything else you'd like to add Jarett?

Jarett Berry: Yeah, I just wanted to echo your congratulations and just to really highlight the importance of this figure 2. I think it is an important step for us to begin to take the concept of the heterogeneity the phenotype, whether it's something happening centrally or peripherally and take that heterogeneity and try to incorporate that into our practice pattern. I think that's obviously been discussed in length in literature before but has not been put together in a practical way for practicing clinicians. I just want to echo your comments that Walter and his coauthors have done an important service for all of us as we think about how to take care of our patients with HFpEF.

Carolyn Lam: That's awesome, I think anyone listening is really going to want to take hold of that journal and have a look at both figures, 1 and 2 and read this beautiful paper. Thank you very much Jarett and Walter for your time, today.

Jarett Berry: Thanks Carolyn.

Walter Paulus: Thank you very much Carolyn, [good night 00:21:20].

Carolyn Lam: You've been listening to Circulation on the Run, thank you for listening and don't forget to join us next week for more highlights.