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Unmet Needs in Cardiovascular Science and Medicine:

Heart Failure with Preserved Ejection Fraction: Mechanisms, Clinical Features, and Therapies

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Abstract

The clinical syndrome comprised of heart failure symptoms but with a left ventricular ejection fraction that is not diminished, e.g. heart failure with a preserved ejection fraction (HFpEF), is increasingly the predominant form of HF in the developed world, and soon to reach epidemic proportions. It remains among the most challenging of clinical syndromes for the practicing clinician and scientist alike, with a multitude of proposed mechanisms involving the heart and other organs and complex interplay with common co-morbidities. Importantly, its morbidity and mortality is on par with heart failure and a reduced ejection fraction, and as the list of failed treatments continues to grow, HFpEF clearly represents a major unmet medical need. The field is greatly in need of a more unified approach to its definition and view of the syndrome that engages integrative and reserve pathophysiology beyond that related to the heart alone. We need to reflect on prior treatment failures and the message this is providing, and re-direct our approaches likely with a paradigm shift in how the disease is viewed. Success will require interactions between clinicians, translational researchers, and basic physiologists. Here, we review recent translational and clinical research into HFpEF, give perspectives on its evolving demographics and epidemiology, the role of multi-organ deficiencies, potential mechanisms that involve the heart and other organs, clinical trials, and future directions.

Keywords

heart failure; hypertension; hypertrophy; clinical ccardiology; therapy

Introduction

Heart failure(HF) is a clinical syndrome characterized by breathlessness (dyspnea) at normal or low-level exertion, fatigue, and fluid retention. As it's name implies, HF centrally involves impaired heart function and the percent of blood volume ejected with each beat, or ejection fraction, has traditionally served as an indicator of pump dysfunction, being low in dilated hearts with depressed systolic performance. However, nearly half of all patients with HF symptoms have an EF that is preserved (exceeding 50%), or HFpEF).[1] Importantly, the prevalence of HFpEF is rising, with morbidity, mortality, and healthcare costs on par with

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HF with a reduced ejection fraction (HFrEF).[2-5] This syndrome has proven particularly challenging on virtually every front: A) consensus-based diagnostic criteria results in an very heterogeneous population that has proven very challenging for clinical studies and trials; B) multiple mechanisms have been proposed but many remain hypothetical due to limited access to live human heart tissue; C) good experimental models do not really exist, as many capture components of the human disease but do not reflect its integrative complexity; and D) patients suffer from multiple common comorbidities such as hypertension, diabetes, vasculopathy, renal disease, atrial fibrillation, metabolic syndrome, etc., that have an major impact on the syndrome and mortality. Given this, it is perhaps not surprising that we have yet to find an evidence-based HFpEF therapy beyond diuretics for fluid overload, and conventional treatments for co-morbidities.

In this article, we provide an overview of HFpEF for both the clinical and basic research scientist that includes a brief examination of its diagnostic criteria and evolving epidemiology, a summary of proposed mechanisms involving the heart and other organs, a discussion of our valiant but unsuccessful prior efforts to develop an effective therapy, and a review of newer potential approaches. The literature refers to HFpEF by several names including diastolic heart failure (DHF) and heart failure with normal ejection fraction (HFnlEF). HFpEF is currently the accepted form and we stick to that here. The companion review in this issue by Loffredo et al.[6] focuses on the basic science underlying age-related cardiac disease, most notably diastolic dysfunction. Many of these changes are thought to be relevant to HFpEF, though direct evidence remains limited for most of them. In this presentation, we focus on the major human data findings.

HFpEF: What's in a name?

Until fairly recently, patients with clinical HF yet with a normal-range EF and evidence of slow chamber relaxation were given a diagnosis of DHF.[7-9] However, subsequent studies of such patients revealed minimal diastolic dysfunction in many[10-12] or similar abnormalities in elderly patients with hypertensive heart disease but no HF,[13,14] as well as key non-diastolic features such as limited systolic reserve, abnormal volume regulation, and maladaptive ventricular-arterial interaction.[12, 15-17] In other words, a normal-range EF did not imply normal systolic function. As these and other non-cardiac features were recognized, the disease was re-named HFnlEF, though as of only 8 years ago, there was sufficient debate that DHF and HFnlEF were suggested to be used interchangeably.[18] As more studies questioned whether systole is truly normal,[19-21] the name changed to HFpEF[22, 23] which is now the accepted standard.

Making the Diagnosis of HFpEF

To an extent, the diagnostic criteria for HFpEF have evolved along with its name. By the late 1990's, this included signs and symptoms of HF with an objective measurement of exercise intolerance; "normal left ventricular (LV) function" defined as LVEF > 45%; and abnormal LV relaxation, filling, diastolic distensibility, or diastolic stiffness.[24] Several embellishments were made involving morphological changes in the heart (e.g. hypertrophy, atrial enlargement, diastolic dysfunction),[25] but these have gradually been removed as many

patients often lacked a particular diastolic or structural defect, yet had all the hallmarks of a HF syndrome. Recent guidelines from the 2013 American College of Cardiology/American Heart Association consensus statement reconfirm that in practice, the diagnosis of HFpEF is based on typical symptoms and signs of HF in a patient with a normal LVEF and no significant valvular abnormalities by echocardiography.[26] Diastolic abnormalties are mentioned but nothing specific. The European Society of Cardiology requires normal or mildly abnormal LV function and evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness.[27] We agree that while patients with clinical HF and preserved EF often have diastolic dysfunction, this should not be required for the diagnosis. In cases where dyspnea of unknown cause is present and EF is >50%, then objective evidence of cardiac dysfunction at rest or more likely with exertion would be important to demonstrate to assign a HF diagnosis. It is important for experimental biologists to appreciate that many humans have abnormal diastolic function with a normal EF – and this combination per se does not mean they have HF. Too often one sees animal models presented as HFpEF where diastolic pressures are elevated or relaxation delayed and EF is in the normal range. This may be a model of diastolic abnormalities, but it is not a priori HFpEF.

Epidemiology of HFpEF

Cross-sectional studies from westernized countries have established a view of HFpEF as elderly, predominantly female patients, and small hypertrophied hearts and a high prevalence of hypertension, diabetes, and atrial fibrillation.[3, 4,28-30] Those reporting race have found a Caucasian predominance.[29, 30] However, growing evidence suggests HFpEF patients are far more diverse (Table 1). Melenovsky et al. studied HFpEF in an urban population, finding a somewhat younger, predominantly African American (AA, 76%) population with very high rates of hypertension, marked ventricular hypertrophy, and obesity.[13] Similar findings were reported by the New York Heart Failure Registry, with the addition of worse renal function in AA-HFpEF patients.[31] These differences as recently reviewed by Shah[32] likely impact therapy responses and net outcome. Increasingly, epidemiologic data report a much more balanced sex distribution,[33] and this is seen in most clinical trials.[34-36] The National Ambulatory Cohort of Veterans study examined nearly all men with HF; 30% had HFpEF.[37] Compared to HFrEF, they were older, more likely Caucasian, had higher systolic blood pressure, and a higher prevalence of co-morbidities (diabetes, hypertension, anemia, chronic obstructive pulmonary disease, cancer, and psychiatric disorders). Internationally, HFpEF can be more common than HFrEF, as in Hong Kong where it accounts for 67% of HF admissions,[38] occurring in men and women equally with high rates of hypertension. In Germany, HF is more common in elderly women, largely due to HFpEF.[39] These data reveal HFpEF spans sex, race, and ethnicity, and is affecting increasingly younger patients. The traditional concept that hypertension and hypertrophy are dominant features conflicts with clinical studies finding this in a minority of recruited patients[33-35], but may apply to some populations such as AA. This impacts our understanding of the disease and patient selection for clinical trials.

The clinical outcomes of HFpEF are similar to those with HFrEF, including in-hospital morbidity and hospital readmission rates.[4, 29,30] While in-hospital mortality may be slightly

higher in HFrEF, 30-day to 1-year mortality post discharge is similar between groups.[4, 29,30] Patients with either HF syndrome suffer from comparable functional limitations and poor quality of life.[40, 41] Risk factors for mortality in HFpEF include advanced age, renal impairment, and hemodynamic instability (hypotension, tachycardia).[30] There are differences in the etiology of morbidity and mortality between the groups, with morbidity in HFpEF being often driven more by non-HF cardiovascular conditions,[37, 42, 43] and ~40% of deaths being linked to non-cardiac causes.[44, 45]

Mechanisms of Disease

Given the multi-faceted constellation of comorbidities that are almost invariably present in HFpEF patients, its underlying pathophysiology remains subject to debate. Among the leading contenders are diastolic dysfunction, impaired systolic reserve and perhaps even resting dysfunction, abnormal ventricular-arterial coupling, inflammation and endothelial dysfunction, depressed heart rate response (chronotropic incompetence), altered myocardial energetics and peripheral skeletal muscle metabolism and perfusion, pulmonary hypertension, and renal insufficiency. Several of these mechanisms are non-cardiac. A major challenge to the field is that truly representative experimental models of HFpEF do not exist, yet human data particularly direct myocardial analysis remains very limited. There are no data from beating muscle or cells from human hearts. Animal models usually focus on one or two features common to HFpEF such as pressure-overload (aortic banding or hypertension), obesity, diabetes, renal disease, aging, or ischemic heart disease without infarction. For practical reasons, however, multiple defects are rarely combined, and in this sense, existing animal models fall short of capturing the complexity of the human disease. Finally, there has long been a debate that HFrEF and HFpEF differ only in the letters *r* and *p*; that they are part of a continuum sharing key mechanisms. As attractive as this seems, we believe that mechanistic data and trial experience to date would suggest otherwise. In this section, we will address current cellular/tissue and integrative mechanisms, relying principally on data obtained in humans. These mechanisms are summarized in two cartoons, shown in Figures 1 and 2.

Myocardial Abnormalities

Diastolic Relaxation—HFpEF often presents with diastolic abnormalities including delayed early relaxation, myocardial and myocyte stiffening, and associated changes in filling dynamics. Slow relaxation has been documented in patients by means of invasive pressure recordings or echo-Doppler imaging parameters.[11, 13, 15, 46-49] The magnitude of delay is such that its impact on resting diastolic pressures, particularly in mid to late diastole, is slight, but at faster heart rates,[46] and/or conditions of increased vascular loading,[15] this delay can become a more prominent contributor to elevated pressures. Most of the reported data compares relaxation rates to that of age-matched normotensive subjects or hypertensive patients without LV hypertrophy (LVH); however, the combination of LVH and hypertension without HF generates similar delay.[13]

The mechanisms for slowed chamber relaxation in HFrEF include reduction in the expression and regulation of proteins involved with calcium cycling into and out of the sarcoplasmic reticulum,[50] depression of β-adrenergic signaling, oxidative stress targeting

calcium handling proteins,[51] and reduced recoil of elastic elements compressed during systole.[52] Many of the same abnormalities are suspected in HFpEF, though direct proof remains limited given the lack of live tissue for human myocardial analysis. Clinical studies have found β-adrenergic responsiveness to be depressed.[53] In an interesting study of biopsy samples from HFpEF and HFrEF patients, Hamdani et al.[54] found the expression of calcium handling proteins and phosphorylation of myofilament proteins were very similar between the groups (there were no normal controls).β1-adrenergic receptor expression was somewhat reduced in HFpEF; however, GRK2 and GRK5 expression that can suppress stimulatory adrenergic signaling, were far more elevated in HFrEF. Relaxation is also controlled by passive recoil of elastic elements, notably titin, compressed during systole.[52] With the termination of active force generation, these molecular springs uncoil quickly and re-extension contributes to the kinetics of force decline. Dilated hearts have depressed recoil,[55] as the heart does not contract sufficiently to compress the elastic elements. However, as HFpEF volumes are generally normal, recoil may be less impacted.

Myocardial and Myocyte Stiffening—Passive myocardial stiffness is often observed in HFpEF and is considered an important contributor to disease manifestations. Chamber level analysis has consisted of invasively measured steady-state pressure-volume relations,[46, 56] as well as simplified non-invasive estimates[57] including the end-diastolic volume at a pressure of 20 mmHg.[33] The causes for myocardial stiffening are divided into factors influencing the extracellular space such as fibrosis and infiltrative processes, and those intrinsic to the myocyte itself (Figure 1).

Myocardial fibrosis is a well-established feature of HFrEF and total collagen volume is similarly increased in HFpEF endomyocardial biopsy tissue.[58-60] Both collagen type 1 and type III expression and tissue staining are elevated in HFpEF and are coupled to reduced collagenase, metalloproteinase-1, but increased tissue inhibitor of MMP-1 expression, which may further enhance fibrosis.[61, 62] In addition to altering matrix turnover, cross-linking of collagen including the formation of advanced glycation end products contribute to fibrosis and stiffening.[63, 64] Potential mechanisms for the altered matrix structure include inflammation, diabetes, and neurohumoral stimuli such as the renin-angiotensin-aldosterone system (RAAS). Markers of inflammatory cells are found in HFpEF tissue[62] and have been proposed to play an important role in the disease.[65, 66] The high prevalence of diabetes in HFpEF suggests a mechanism for fibrosis as well as AGE deposition. However, biopsy studies have found such correlations in HFrEF but not HFpEF.[63] RAAS activation stimulates pathological fibrosis in many animal models and has long been presumed a major factor in HFpEF. However, the failure of multiple anti-RAAS clinical HFpEF trials suggests either that other factors and/or mechanisms are more important, or that fibrosis is not as central as assumed. An alternative is myocardial infiltration by amyloid proteins such as transthyretin (wtTTR). This liver synthesized protein is a common form of amyloid whose genetic variations cause hereditary amyloidosis. Recent autopsy data of HF hearts with an EF>40% at time of diagnosis found moderate to severe wtTTR deposition in 5%, with evidence of amyloid deposition in 19%.[67] Whether TTR polymorphisms associated with disease[68] play a role in HFpEF remains unknown.

While extracellular matrix abnormalities are generally similar between HFrEF and HFpEF, myocyte stiffness differs, being higher in cells from HFpEF. Borbely et al.[58] first reported higher passive stiffness in isolated HFpEF myocytes versus controls. This stiffening was normalized by incubation of cells with protein kinase A (PKA), a change also more prominent in myocytes from HFpEF than HFrEF hearts.[60] Analogous studies have extended this to protein kinase G (PKG) stimulation as well.[69] The protein principally responsible for PKA and PKG responsive cellular stiffening appears to be titin, a macro-molecular spring whose elasticity varies with its isoform and post-translational modifications including phosphorylation and oxidation (reviewed in [70]). Titinis synthesized as either the more compliant (fetal) N2BA or stiffer (adult) N2B form.[71] Signaling by thyroid hormone, insulin, and Gq-protein coupled receptors to the PI3K-Akt-mTOR pathway enhance N2B expression. The N2BA:N2B ratio generally increases in human HFrEF, but changes with HFpEF remain less certain, with early data suggesting a decline[60] and subsequent work finding an increase over normal controls.[72] Titin phosphorylation targets two major regions, one in the N2B element (N2Bus) and the other in the in the PEVK (rich in proline, glutamate, valine, and lysine) region. The former is targeted by PKA, PKG, and CamKIIδ[73-75] all of which reduce passive stiffness.[58, 69, 70, 74] Titin oxidative formation of disulfide bonds in the N2B region, on the other hand, increases stiffness,[76] though opposite effects have been reported by S-glutathiolylation of the protein.[77]

The capacity of PKG to modify titin and lower stiffness has formed the basis for a number of therapeutic interventions that activate this pathway including natriuretic peptides and phosphodiesterase 5A (PDE5A) inhibitors.[78, 79] However, human HFpEF myocardial cGMP levels and associated PKG activity have been observed to be very low, far below that in HFrEF or hypertrophy due to aortic stenosis.[69] This is consistent with hypophosphorylated titin, and could play an important role in stiffer HFpEF myocytes. The mechanism for depressed PKG activity may involve reduced nitric oxide-dependent cGMP synthesis due to oxidative stress. ROS can interfere with NO-related signaling at multiple nodes, oxidation of soluble guanylate cyclase impairs its responsiveness to NO to generate cGMP,[80] NOS can become uncoupled by oxidation resulting in its synthesis of superoxide,[81] and NO-ROS interactions thwart downstream signaling. Importantly, the capacity of PDE5A inhibition to augment PKG activity depends upon cyclase generation of cGMP, so this imbalance has clinical implications for treatments.

Resting Systolic Function: Is it “Normal”?—Ejection fraction largely informs us about chamber dilation – since until end-stage HF, stroke volume, (SV, the numerator) is usually maintained while the denominator, end-diastolic volume rises. Preserved EF does not imply systole is normal, and indeed a key set of observations that favored the name change to HFpEF suggested the opposite.[19, 20, 82, 83] This has been recently observed using tissue Doppler speckle tracking; HFpEF patients had reduced longitudinal and circumferential strain compared to age- and gender-matched hypertensive patients with diastolic dysfunction but no clinical HF.[84] However, the studies employing catheterization with imaging or conductance catheter measurements to derive pressure-volume relations find resting load-independent indexes of systolic function are essentially normal in HFpEF.[16, 85] Isolated skinned myocyte data from HFpEF shows similar maximal calcium

activated force,[15, 54,58] but that is about all we know from human HFpEF tissue. Some measures of systole, such as end-systolic elastance (Ees) a measure of systolic stiffening, was higher in several HFpEF studies,[15, 57] thought this seems particularly true in urban populations with a high percent of AA. Rather than implying increased resting contractility, the higher Ees may reflect myocardial hypertrophy, fibrosis, infiltrative disease, and/or titin modifications.

Ventricular-Arterial Coupling

Systolic ejection involves the interaction of time-varying properties of the ventricular pump and the vascular impedance to which it is connected. Vascular stiffening has long been associated with aging and is exacerbated by comorbidities such as hypertension, obesity, diabetes, and chronic kidney disease. To preserve adequate coupling of the heart to arterial system, ventricular systolic stiffening also increases, and this combined ventricular-vascular (VV) stiffening is a feature of HFpEF.[15, 48, 86] This limits systolic reserve normally accompanying further rises in Ees, contributes to increased cardiac energy demands to enhance cardiac output,[15] and plays a central role in arterial pressure lability with small changes in chamber preload volume. VV coupling is often represented by the ratio of effective arterial elastance (Ea) given by the ratio of end-systolic pressure to stroke volume (Pes/SV) that lumps systemic resistance, pulsatile loading, and heart rate effects into a single “afterload” parameter. VV coupling is then indexed by Ea/Ees ratio that normally ranges 0.5-1.2 to optimize cardiac work and efficiency.[87] In HFpEF, Ea and Ees both increase, though similar increases are observed in patients without HF but with hypertension (±LVH).[15, 57] When both Ees and Ea are increased, modest changes in LV filling as altered by diuresis or sodium loading (e.g. dietary indiscretions) induce marked swings in blood pressure and thus cardiac work with little change in SV.[15]

Limitations of Cardiovascular Reserve

The vast majority of HFpEF hemodynamic and myocardial data pertain to resting conditions, but arguably, this syndrome is first and foremost one of limited reserve and exertional intolerance. Multiple mechanisms likely play a role, including depressed systolic augmentation, limited heart rate augmentation (chronotropic incompetence), diastolic filling abnormalities, and reduced peripheral vascular dilation.

Kitzman et al. reported among the first studies of exercise capacity in HFpEF patients and highlighted failure of these patients to increase end-diastolic volume and thus engage the Frank-Starling mechanism.[88] However, this study was very limited with 3 of the 7 patients having classic hypertrophic or restrictive cardiomyopathy, diseases known to impair preload reserve. Borlaug et al. studied 17 HFpEF patients versus a similar number of non-HF controls matched for comorbidities (in particular both LVH and hypertension), and also found reduced exercise capacity and peak oxygen consumption in the HFpEF group related to reduced cardiac output reserve.[89] However, rather than being from impaired diastolic filling, low CO augmentation was related to a failure to enhance heart rate and peripherally vasodilate.[89] Chronotropic incompetence has since been reported by multiple investigators[90, 91] and found in large trials.[35] This has implications for the use of beta-blockers and sinus node suppressors (I_f blockers) in the syndrome. The normally rapid heart

rate decline after cessation of exercise is delayed in HFpEF, and this behavior is thought due to autonomic dysfunction and an independent risk factor for cardiac death.[89, 91,92] Impaired peripheral vasodilation has been documented in exercised HFpEF patients using MRI.[93] Borlaug et al examined cardiac systolic reserve in exercising HFpEF subjects and found that in addition to peripheral dilation and HR limitations, contractility increases were also depressed, resulting in VV mismatching.[16].

Even if HR were to increase in HFpEF, studies find the ventricular response would likely be abnormal. The normal positive force-frequency was depressed in patients with LVH, many having presented with heart failure symptoms.[94] However, in two subsequent HFpEF studies, LV function with incremental pacing increased contractility over controls or showed no difference,[46, 95] though reserve was limited due to impaired diastolic filling. However, the normal controls in both studies surprisingly showed no decline in either end-diastolic filling or stroke volume at faster HRs as previously shown[94]. Instead, they stayed the same or even increased; thus, the HFpEF response was more consistent with normal physiology. Preload reserve limitations were not observed in several HFpEF exercise hemodynamic studies.[16, 89] Thus, whether diastolic filling is truly restricted in HFpEF during tachycardia, remains uncertain.

Myocardial Energetics and Skeletal Muscle Metabolism

Among potential mechanisms for limited cardiac systolic reserve with HFpEF are abnormalities of myocardial energetics including adenosine triphosphate (ATP) generation and shuttling between phosphocreatine (PCr) and ATP by the creatine kinase reaction. Smith et al used NMR spectroscopy to assess patients with non-HFrEF (few technically had HFpEF), and found myocardial [ATP] was not significantly reduced in LVH or in LVH+HF compared to controls.[96] However, cardiac [PCr] was 30% less in LVH with or without HF, reducing the PCr/ATP ratio in both groups. In addition, creatine kinase flux was 65% lower in LVH+HF versus controls, more than double the decline in LVH alone. Another study examining HFpEF did find a significant decline in PCr/ATP compared with controls.[97] In a recent study to evaluate whether skeletal muscle abnormalities contribute to decreased peak exercise oxygen consumption (peak VO_2) in HFpEF, Kitzman et al. performed needle biopsies of the vastus lateralis muscle and cardiopulmonary exercise testing to assess muscle fiber type distribution, capillary density, and peak VO_2.[98] HFpEF patients had reduced type-I oxidative muscle fibers, type I/II fiber ratio, and capillary to fiber ratio compared to healthy controls; the percent of type-II fibers was greater in HFpEF. The type-I fibers and capillary to fiber ratio was significantly associated with peak VO_2. Exercise intolerance may also be impaired by endothelial dysfunction and abnormal skeletal muscle metabolism, including reduced mitochondrial volume and enzymes, and muscle atrophy. While the specific defects remain to be identified in HFpEF, several studies have found limited cardiac reserve fails to explain exertional intolerance and have highlighted abnormal skeletal muscle performance as likely contributors.[99, 100]

Role of Inflammation

Results from LV endomyocardial biopsy[69] and analyses of inflammatory cell markers[62] suggest increased oxidative stress and depressed NO-signaling resulting in inflammation

play a key role in this syndrome.[65, 66] The multitude of HFpEF comorbidities maycontribute to a pro-inflammatory state;[101] circulating inflammatory cytokines such as interleukin-6, tumor necrosis factor-α, soluble ST2, and pentraxin 3 are elevated in HFpEF.[102-105] Systemic inflammation could lead to endothelial dysfunction supported by higher expression of vascular cell adhesion molecules such as VCAM-1, E-selectin, and reactive oxygen species (ROS).[62] Increased ROS lowers bioavailable NO and thus reducesc GMP/PKG activation, which can worsen myocyte stiffness as already noted, and also contribute to hypertrophic disease and fibrosis. Transforming growth factor beta signaling may also be increased in HFpEF myocardium,[62] though data remain very limited. The complex and cell-specific signaling linked to this cytokine suggests that therapeutic targeting could prove difficult.[106, 107]

Biomarkers in HFpEF - A Clue to Mechanisms?

Plasma biomarkers consisting of proteins, peptides, and microRNAs, can reflect chronic and acute changes in structure and function of the myocardium, as well has changes in volume status, loading conditions, and vascular tone. A number of these biomarkers are of interest in HFpEF, to aid in diagnosis, prognosis, and to help better understand mechanisms of disease. The natriuretic peptides are perhaps the best characterized biomarkers in HFpEF. B-type natriuretic peptide (BNP) is typically higher in HFpEF than in non-HF patients, but lower than in HFrEF.[108, 109] BNP linearly correlates with LV diastolic pressure and with LV diastolic wall stress in HFpEF; the smaller LV cavity size and thicker walls with resultant lower end diastolic wall stress may account for lower BNP levels.[110] Biomarkers of extracellular matrix turnover and fibrosis in HFpEF have recently been reviewed, including soluble-ST2, galectin-3; collagen pro-peptides(PICP, PINP, PIINP); collagen telo-peptides (CITP); matrix metalloproteinases (MMP-1,-2,-8-9); tissue inhibitor of MMPs (TIMP-1, TIMP-4); and osteopontin, all of which can be elevated.[110] Additional biomarkers including renal biomarkers (cystatin C, urinary albumin), cardiac troponins, and inflammatory markers (discussed previously) have also been noted to be elevated in HFpEF.[111] While nearly all of these biomarkers support the diagnosis of HFpEF to some extent, a smaller subset may help predict outcomes, and even fewer may be used to guide therapies (primarily the natriuretic peptides). MicroRNAs as biomarkers for outcome and treatment selection have been described in HFrEF, but to date, no results have been reported in human HFpEF.

Pulmonary Hypertension and the Right Ventricle

Pulmonary hypertension (PH) defined by a mean pulmonary artery (PA) pressure >25 mmHg is commonly associated with HFrEF and harbingers a worse outcome. Data on PH in HFpEF are more limited, but studies are reporting a fairly high prevalence that importantly predicts increased morbidity and mortality.[33, 112, 113] Pulmonary artery systolic pressure rises along with pulmonary capillary wedge pressure (PCWP) in patients with both hypertension and HFpEF; however, after adjusting for PCWP, pulmonary systolic pressure is still higher in HFpEF.[112] This indicates that PH is due to more than pulmonary venous hypertension (PVH). Distinguishing these factors can be challenging. By definition, pulmonary arterial hypertension (PAH) is differentiated from PVH as the latter has an elevated PCWP> 15 mmHg. Estimation of PCWP by non-invasive methods is not always possible, and PCWP obtained at the time of right heart catheterization is influenced by the

patient's volume status when the procedure is done. Robbins et al. performed a fluid challenge at the time of catheterization to differentiate PAH from PVH, and of 207 patients meeting criteria for PAH, 22% developed elevated PCWP after a fluid bolus and were thus reclassified as overt PVH.[114] Borlaug has demonstrated that many HFpEF patients who have normal PCWP at rest display marked increases with supine exercise associated with PAH.[8] The implications of such data are that many patients with PH may have an under-recognized component of PVH linked to left-sided HF (including HFpEF), that is more manifest under conditions of exertion or volume loading.[115]

An additional role of PCWP from LV disease to PAH was revealed by Tedford et al., who studied the inverse relation between total pulmonary vascular compliance (C_{Pa}) and resistance (R_{Pa}) in patients with varying levels of PAH and PCWP elevation.[116] The C_{Pa}-R_{Pa} relation is hyperbolic with a very tight interdependence between the two properties that is unique to the pulmonary vasculature. This results from having vascular compliance reside with the smaller peripheral vessels where resistance is also regulated; unlike the systemic arteries where the aorta provides most of the compliance but no resistance, and peripheral vessels provide the opposite. The C_{Pa}-R_{Pa} relation was remarkably invariantbut it did change with a rise in PCWP, with C_{Pa} declining at the same R_{Pa}. This indicates that PCWP impacts pulmonary arterial pulsatile load and thus RV systolic load, and likely has implications for HFpEF and PH. RV dysfunction is a well-established predictor of poor outcomes in increased mortality in HFrEF, and this may apply to HFpEF in that RV wall thickening was predictive of worse outcomes.[33]

Renal Dysfunction

Chronic kidney disease occurs in 26-53%of HFpEF and is associated with poor prognosis.[30, 117, 118] Beyond baseline impairment, worsening renal function during HFpEF hospital admission predicts higher mortality at 6-months, with a 7-year survival of only 9%.[118]Albuminuria is an established independent risk factor of mortality in the general population, reflecting glomerular injury, activation of the RAAS system, and systemic inflammation, and has been reported in a third of HFpEF patients.[119] During a 2.5 year follow up period, those with albuminuria at all strata of estimated glomerular filtration rate had higher rates of cardiovascular and non-cardiovascular death[119]. Finally, albuminuria can limit the efficacy of furosemide by binding the compound in tubular fluid, preventing its interaction with ion transporters.

In HFrEF, the mechanism of renal dysfunction is classically related to low cardiac output and decreased renal perfusion. Given that impaired volume homeostasis is a prominent presenting feature of HFpEF, it is no surprise that renal insufficiency is partly to blame, the question is how. Does intrinsic renal dysfunction (as a complication of other comorbidities) lead to myocardial inflammation, fibrosis, and resultant HFpEF? Does HFpEF cause renal dysfunction by triggering RAAS pathway activation, venous congestion,[120] and/or from side effects of HF medications? There are intriguing pathways that may link renal and cardiac disease such as transient receptor potential channel-6, a Gq-receptor and ROS activated non-selective cation channel that plays an important role in proteinuria and glomerular dysfunction[121] as well as cardiac hypertrophy[122] and fibrosis.[123] Impaired renal regulation

combined with enhanced cardiovascular sensitivity to fluid retention due to VV stiffening and diminished diuretic efficacy can co-conspire to worsen symptoms in the HFpEF patient.

Abdominal Contributions

In many HFpEF patients, fluid retention is less apparent in the periphery, but not infrequently occurs in the abdominal cavity. This may play a significant role in cardiorenal disease in HF beyond vascular congestion, as recently reviewed by Verbrugge et al.[124] While this pathophysiology is not unique to HFpEF, it does likely play a role particularly in fluid homeostasis, and is an area deserving attention. The splanchnic vasculature normally contains about 25% of total blood volume in capacitance veins. This capacitance function is impaired in HF, with increased neurohormonal activation resulting in venoconstriction in the setting of long-standing congestion. Splanchnic microcirculation and lymphatic flow are essential to preserve fluid homeostasis, and with HF, increased capillary hydrostatic pressure drives filtration of fluid through to the lymphatic system. Once lymph efflux is maximal, however, interstitial fluid with associated proteins cannot be adequately drained, leading to protein-rich edema and expansion of the interstitial space. Once the splanchnic vasculature and microcirculation can no longer cope with progressive volume overload, intra-abdominal pressure (IAP) increases. Normal IAP is 5-7 mmHg; intra-abdominal hypertension with IAP > 12 mmHg can lead to organ dysfunction. Consequences include abnormal hepatic regulation of renal function, splanchnic bed congestion which creates a false state of “hypovolemia”, and non-occlusive bowel ischemia which may eventually resultant in circulating endotoxin.

Treatment of HFpEF - A brief history of neutral trials

Targeting the RAAS and beta-adrenergic stimulation pathways has long been considered reasonable for HFpEF, the former based on its link to hypertension, fibrosis, and fluid imbalance, and the latter to improve time for diastolic filling. Yet despite their clear success in HFrEF, no clinical trial of these standard therapies has revealed similar mortality benefits, and very few show symptomatic improvement in HFpEF. The major recent neutral trials are summarized in a supplemental Table 2. These include studies of beta blockade (SENIORS[125], J-DHF[126], and ELANDD[127]), angiotensin converting enzyme-inhibitors (ACE-I;PEP-CHF[128]), angiotensin receptor blockers (ARB;I-PRESERVE[129]), aldosterone antagonists(ALDO-DHF[36] and RAAM-PEF[130], TOPCAT[34]), digoxin(DIG-PEF)[43], and sildenafil (RELAX)[35]. Despite broad acceptance of diastolic impairment as a contributor to HFpEF, very few of these studies actually report diastolic analysis or cardiac structural data, making it very difficult to assess the impact of therapy on these behaviors.

A few studies have showed positive signals for potential benefit in HFpEF. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study evaluated ACE-I in HF patients without demonstrable LV dysfunction, was under-powered for its primary composite endpoint of all-cause mortality and unplanned HF-related hospitalization, but did see some improvements in symptoms, exercise capacity, and fewer heart failure hospitalizations in the first observation year.[128] The Effects of Candesartan in Patients with Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction (CHARM-Preserved) trial demonstrated that compared to placebo, HFpEF patients who received the

ARB candesartan had fewer hospital admissions for HF, although there was no mortality benefit from the medication compared to placebo.[131] Many HFpEF patients are treated with ACE-I and/or ARB for hypertension, and our clinical outcome data reflects this background therapy.

In 2013, the Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients with Heart Failure with Preserved Ejection Fraction (ALDO-DHF)study tested the impact of an aldosterone antagonist in HFpEF with the primary endpoints being improved diastolic function and exercise capacity.[36] Some measures of diastolic function improved, though maximal exercise capacity, clinical symptoms, and quality of life were not changed. One critique of the study was that patients had early-stage HFpEF without overt signs of volume overload. The larger 2014 Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) also did not meet its primary composite endpoint (cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure).[34] There was a small, borderline significant decline in hospitalizations. Interestingly, a major interacting factor was where patients were recruited and the criteria used for their entry; Eastern European patients were entered based on HF hospitalization criteria but follow-up course in the placebo arm of this group was surprisingly benign. By contrast, patients in the United States metnatriuretic peptide level entry criteria and had a higher event rate. Spironolactone improved the latter group.

The Effect of Phosphodiesterase 5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction (RELAX) trial tested a new concept that by blocking PDE5A, cGMP/PKG signaling in HFpEF might be enhanced with associated benefits[35]. PDE5A hydrolyzes cGMP primarily generated by NO-soluble guanylatecyclase; by blocking the enzyme, drugs such as sildenafil can augment cGMP and thus PKG activity in multiple organs relevant to HF. Experimental studies in mice with pressure-overload,[132] cytotoxicity from doxorubicin,[133] and myocardial infarction,[134-136] have shown benefits from chronic PDE5A inhibition. PDE5A inhibition also enhanced NP-stimulated pulmonary vasodilation in a canine HF model.[137] Prior single-center studies had reported benefits of PDE5A inhibition in patients with HFrEF, particularly those with pulmonary hypertension, and in PH patients with preserved EF.[138-140] However, RELAX was neutral, reporting no benefit of sildenafil over placebo in the primary endpoint (change in peak oxygen consumption after 24 weeks of therapy) or in any of a myriad of secondary functional and structural endpoints including markers of clinical status. Some argued that choosing exercise capacity as the endpoint caused problems due to the high number of co-morbidities and non-cardiac factors that influence this in HFpEF.[141] In addition, the patient population may have played a major role in the neutral findings, as they had relatively mild diastolic dysfunction, the majority lacked LVH, and many had no overt PH and/or RV dysfunction, nor LVH (only 53% met criteria and median LV mass index was essentially normal), or systolic hypertension. This means there likely was little for PKG to impact in the heart as experimental studies showed sildenafil has negligible effect in mild LVH but far more efficacy if applied to severe disease, as only the latter triggers maladaptive signaling that PKG can offset.[142] As noted, HFpEF patients have very low myocardial cGMP[69], so there would be insufficient cGMP for PDE5a inhibition to modify. NP levels were mildly

increased in some patients in RELAX, and minimally elevated in many of the patients, so an alternative cGMP source was not active.

Lessons Learned from Trials to Date

There are a number of potential reasons why these established HFrEF therapies have failed to benefit in HFpEF. First, our fixation on RAAS signaling may indeed be misplaced. It seems unlikely that this neurohormonal stimulation is uninvolved in HFpEF, but it may not be as sustained with less impact gleaned by its blockade. Perhaps HFpEF is less a neurohormonal-driven disease as compared to HFrEF, but rather is an integrative physiology disorder where hemodynamics and the control of blood volume and its distribution are more important. In the case of sildenafil, the question remains whether one needs to stimulate cGMP generation first and then perhaps add in a PDE5a inhibitor. While combining nitrates and PDE5a inhibitors remain relatively counter-indicated, some very low doses of a synthesis stimulator such as a direct sGC activator or natriuretic peptides might still prove effective, particularly if then combined with a blocker of cGMP hydrolysis.

Another important contributing factor is the patient population enrolled in clinical trials. In comparing population-based cohort descriptions to patients enrolled in clinical trials of HFpEF, it appears that the adverse outcome rates in the placebo groups in trials are markedly less than what is observed at the population-study level (see Table 1 compared to Table 2). How do we explain this discrepancy? In comparing the cohorts, patients enrolled in HFpEF therapy trials (irrespective of which treatment arm) have a lower prevalence of hypertension (lower systolic blood pressure), less LVH (when reported), and somewhat less coronary artery disease. Each of these individual morbidities portends increased risk of adverse outcome; and together their lower rates reflect a healthier cohort in the trials. This may reflect the multicenter and often international recruitment in trials versus more local and homogeneous sources in population studies, as well as involvement in a trial itself versus uncontrolled longitudinal observations. It argues for improving our capture of the truly at risk HFpEF group, something we are not presenting doing. It also suggests that more intensive clinical engagement, as accompanies being a participant even in the placebo arm, is rather effective.

Finally, HFpEF is a simple enough label to apply to a patient, but the result is often profoundly heterogeneous, and differences among nations and medical practices can make it nearly impossible to create meaningful clinical trials. The different constellations of co-morbidities also raises the bar very high for a therapeutic home run, as these may play a greater role in symptoms and treatment responses than generally assumed. An approach to this was recently suggested by Sanjiv Shah, who described the concept of “matchmaking” HFpEF patients to clinical trials.[143] Subgroups involving major features such as hypertension/LVH, or PH, etc. may respond differentially to a given therapy, and better population selection for clinical trials could yield more promising results.

New Therapeutic Avenues for HFpEF

HMG-Co-A Reductase Inhibitors

The use of HMG-Co-A reductase inhibitors, or statins, has yet to be tested in a large-scale trial. Observational reports of statin therapy in HFpEF have shown mixed findings for effects on diastolic parameters, though meta-analyses of 11 studies, mostly retrospective, suggests a significant benefit on survival [98, 144, 145]. This is speculated to involve pleomorphic anti-inflammatory effects. Definitive trials have yet to be performed and may prove difficult given existing wide-spread use of statins in many HFpEF patients.

Ivabradine

The neutral results of β-blocker trials in HFpEF led investigators to pursue therapies targeting the sinus-node, including the inward "funny" (I_f) channel blocker, ivabradine which slows sinus rate but has no impact on contractility or the peripheral vasculature, unlike β-blockade.[144, 146] Experimental data in mice with obesity and diabetes[147] found reduced aortic stiffness and fibrosis and improvement in LV function from 4 weeks of ivabradine therapy.[147, 148] Kosmala et al. recently published findings from a 7-day randomized clinical trial of ivabradine versus placebo in 61 HFpEF patients.[149] Patients had improved peak oxygen consumption, exercise capacity, and decreased exercise-induced E/E' ratio (index of diastolic pressure). There were no adverse events. Using a fairly homogenous cohort of patients with early stage HFpEF may have helped this particular study.[149] However, heart rate lowering seems unlikely to benefit all HFpEF patients, particularly those with resting bradycardia and/or chronotropic incompetence, where further blunting a HR increase could worsen cardiac output reserve and thus exercise capacity. Also, patients with advanced diastolic disease with restrictive physiology are unlikely to benefit, since filling occurs early and rapidly in these patients anyway, and heart rate becomes a primary determinant of cardiac output. Larger-scale, multi-center studies will be needed to test the utility of this approach.

Neprilysin inhibitor (LCZ696)

Neprilysin is a zinc-dependent metalloprotease that degrades biologically active NPs, including ANP, BNP, and C-type NP. It does not affect the biologically inactive NT-proBNP.[143] Natriuretic peptides can promote myocardial relaxation, reduce hypertrophy, and are coupled to integral to diuresis, natriuresis, and modest vasodilation.[150] Clinical data for all of these effects are less well documented, but benefits have been observed. A recent randomized clinical trial compared LCZ696,[151] which combines a neprilysin inhibitor pro-drug AHU377 and the AT1 receptor blocker – valsartan, to valsartan alone in 266 HFpEF patients.[150] LCZ696 led to a greater decline in NT-proBNP; however, cardiac structure and function, and symptom composite metrics were similar between groups. Patients receiving LCZ696 had a greater reduction in blood pressure (~6 mmHg) by 12 weeks and fall in NT-proBNP remained significant after adjusting for this blood pressure change. Adverse effects were similar between the groups; overall, LCZ696 was well tolerated. The findings of this phase-2 study are promising and a large, multi-center study is underway comparing LCZ696 to enalapril (PARADIGM-HF).

Exercise Therapy

Exercise intolerance is a major complaint of all HF patients. It is an independent predictor of morbidity and mortality and is increasingly a leading outcome in pharmacologic trials of HFpEF. Exercise training has been used to improve outcomes in HFrEF, particularly in patients with ischemic disease, and is being viewed as a potential therapy for HFpEF.[152] Exercise training provides cardioprotection against ischemia-reperfusion injury (see excellent recent review by Powers[153]), in part by suppressing ROS-mediated cellular damage, decreasing cytosolic free calcium, and reducing inflammatory changes from leukocyte infiltrationand mitochondrial damage. Cardioprotection from exercise training is biphasic; the first phase is rapid in onset and short in duration (onset at 30 min, lasting 3 hours), and involves activation of the endogenous antioxidant enzyme superoxide dismutase in mitochondria of ventricular myocytes. The second phase is longer-lasting (9 days), with multiple proposed mechanisms of benefit, including improved coronary circulation, stimulation of cytosolic antioxidants, increased heat shock proteins, increase in sarcolemmal- and mitochondrial- ATP-sensitive K channels, increase in cycolooxygenase-2, increased NO signaling, and altered mitochondrial phenotype (increased antioxidant capacity). Many of these same mechanisms have been implicated in the development of HF, including HFpEF.

Kitzman et al. reported findings from the first randomized, controlled study of exercise training in older patients with HFpEF over a 16-week period.[154] The primary outcome of peak exercise oxygen uptake significantly improved in the exercise therapy group compared to controls. Improvements were also noted in exercise time, 6-minute walk distance, ventilatory anaerobic threshold, and peak power output, as well as the physical component of the quality of life score. Interestingly, exercise training did not appear to improve endothelial function or arterial stiffness in a study of exercise training in HFpEF evaluating flow-mediated arterial dilation and carotid artery stiffness.[155] These initial studies of exercise training in HFpEF are promising and suggest that exercise training should be considered part of the treatment algorithm, along with pharmacologic agents, for the management of HFpEF. Effective translation in a population that is notably sedentary and often morbidly obese, will undoubtedly pose challenges, however.

Targeting Neural Reflex Arcs: Renal Denervation and Nerve Stimulation

Long-standing, resistant hypertension is common in HFpEF patients and alternatives to traditional pharmacological therapy are being sought. Renal sympathetic denervation is an example, and early results in small, non-placebo controlled studies raised substantial optimism that this would be effective.[156, 157] However, the 2014 SYMPLICITY-HTN 3 Trial which studied 553 patients in a 2:1 randomization between active denervation or sham procedure, found no significant difference in the primary end-point of reduced systolic pressure at 6 months.[158] This was strikingly different from the prior SYMPLICITY HTN-2 trial found significant blood pressure decline along with reduced LV mass and improved diastolic function in the active treatment arm, but also lacked a true placebo control[159]. The reasons for the discrepancies between the trials are being debated, but certainly the unbridled enthusiasm that had first met this therapy has been tempered.

Additional strategies to modulate autonomic tone include vagal nerve stimulators[160] and carotid baroreceptor stimulators,[161] both of which are emerging as promising therapies with pleomorphic effects. Among the proposed mechanisms of vagal nerve stimulation are anti-inflammatory effects, increased NO signaling, anti-cytokine effects, improved baroreflex sensitivity and RAAS inhibition[162]. The INNOVATE-HF study will test vagal nerve stimulation (CardioFit system, BioControl, Israel) in HFrEF patients[162], but interest is already there for HFpEF as well. While still largely in experimental stages, spinal cord stimulators is another approach that has shown some utility in HF patients.[163] A HFrEF study (Defeat-HF, NCT01112579) has completed enrollment with results due in 2015. Lastly, endovascular cardiac plexus stimulation may offer an alternative way to increase contractility without increasing heart rate.[164]

Pumps, Devices, Monitors

Device therapy has made enormous inroads into HFrEF with pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy. The role of each in HFpEF is undefined; some patients with symptomatic chronotropic incompetence receive pacemakers, and those with a history of sudden death receive a defibrillator. Dyssynchrony in HFpEF can occur though it seems more rare than with HFrEF, and the efficacy of cardiac resynchronization therapy has not yet been demonstrated in HFpEF. If anything, inducing dyssynchrony on purpose by single-site ventricular pacing was found to benefit a group of HFpEF patients with severe concentric LVH and end-systolic cavity obliteration.[165, 166] The rationale was that such patients have excessive contraction and generating dyssynchrony increases end-systolic volume at rest, building back in some reserve capacity during exercise.

Another type of technology relates to monitor systems that provide physiological information[167] and these too may prove valuable for helping stabilize HFpEF patients and reduce their hospitalization rates. Some of the monitor data comes from existing therapy devices, such as CRT systems that also provide intrathoracic impedance measures via the RV lead,[168] or monitor heart rate variability, and patient activity level. These are limited to patients receiving the therapy. Alternatively, devices that purely work as monitors have been developed, and typically assess some pressure measure correlated with central vascular volume, with the goal of identifying critical fluid overload and symptoms before aggressive intervention is needed. These include right ventricular pressure monitors,[169] pulmonary artery pressure sensors (CardioMEMS Heart Sensor),[168] and left atrial pressure monitors (sensor system implanted transvenously into the atrial septum, oriented towards the left atrium).[170] Drug delivery systems such as furosemide pumps might be linked to hemodynamic sensors as an innovative way to treat HF patients “real time”, particularly targeting those patients who have a narrow range of filling pressure and fluid status tolerance - a common situation in HFpEF.

Miscellaneous Clinical Trials

Several other studies are currently underway examining the role of activation of the nitric-oxide soluble guanylatecyclase pathway. These are stimulated by appreciation for the hemodynamic sensitivity of HFpEF patients to vaso/venodilators, and their potential to

stimulate a PKG-signaling pathway which is otherwise deficient. These trials are generally small and many single center or involving small consortiums. They are examining the potential value of inorganic nitrite (NCT NCT01932606), isosorbide dinitrate combined with hydralazine (NCT01516346), an oral soluble guanylate cyclase stimulator BAY1021189 (dose-ranging study called SOCRATES PRESERVED, sponsored by Bayer, NCT01951638), and a trial of udenafil, another PDE5A inhibitor (NCT01599117). There are also several ongoing trials of renal denervation (RDT-PEF, NCT01840059, and RESPECT-HF, NCT02041130), as well as a trial of acute HF management in HFpEF, evaluating diuretic strategy with and without low-dose dopamine (ROPA-DOP, NCT01901809)

Concluding Thoughts

HFpEF remains among the more challenging clinical presentations to diagnose and manage. Lack of a clear and consistent mechanism among the many patients that fall into a HFpEF definition, variations in the co-morbidities that modify its presentation and course, and the long list of failed therapies, make it a poster child for “Unmet Medical Needs.” Addressing this need is all the more important given the devastating morbidity and mortality and stress on the global health care system that the syndrome exacts. We are making progress, but it has been extraordinarily slow, and some reassessment of our concepts and perhaps some paradigm changes are in order.

- First, we need to recognize that the “face” of HFpEF varies. There are marked differences in HFpEF among different populations around the world based on medical practices, urban versus rural living, racial sub-groups, etc. It is increasingly a disease of younger individuals affecting men and women equally. In many locations, obesity is a very common feature, and we need to understand much more how this impacts the syndrome.
- Second, we need to better sub-classify HFpEF patients. Clinical trials and our overall approach would likely be improved by identifying patients based on dominant mechanisms of disease and symptom severity; the grab-bag diagnosis of HFpEF does not tell us very much. For example, patients with substantial diastolic dysfunction with or without structural heart disease may behave differently from those with marked systolic hypertension and ventricular-vascular mis-coupling, or those with substantial inflammatory conditions, or chronotropic incompetence, etc.. Some sense of the severity of the defect would be helpful. The presence of diastolic abnormalities and HF symptoms does not mean that the former is necessarily causal.
- Third, we need more myocardial tissue. Not only biopsy pieces, but muscle that can be used to study live beating cells – so we can better identify what has happened and why? We recognize this is non-trivial, since these hearts are rarely ever replaced with a transplant - though if the heart is central enough to the disease and patients appear to be presenting at younger ages, perhaps this will change. The recent spread of integrative pathophysiology studies in humans is welcome, and more are needed.

- Fourth, we need to improve experimental models, if possible. Animal models are typically designed to be monothematic on purpose, and while useful, efforts to combine common co-morbidities such as obesity, hypertension, and diabetes or some other pro-inflammatory state, would be welcome. Appreciation that aortic banding or high fat diet fed rodents is not HFpEF despite having some diastolic dysfunction and a preserved EF is important. Still, there is great value in chopping up the puzzle, and experimental efforts are revealing novel signaling cascades and therapies worth trying even from models that capture one or two dimensions of the disease. However, caveat emptor.
- Fifth, we need to consider therapies outside of the traditional HFrEF-box. The failure of many clinical anti-RAAS trials and beta-blocker trials sends a message about what types of pathways and mechanisms are involved and we should listen to them. We have barked up this tree for a few decades; it is time to move on. HFpEF is truly a systems physiology disease, and treatments that integrate multiple targets – such as neuro-modulators or pleomorphic drugs – may prove most effective. We may soon have full feedback control systems that sense drug requirements and deliver them automatically; this could be a game changer. We call the disease HFpEF, but more and more data show skeletal muscle abnormalities are critical, and we need to start focusing on why and what this can mean for effective therapy.

The hope is that as we better focus on each of these issues, and gain new insights into how HFpEF works as a disease, we should finally be able to move it off the “un-met need” shelf where it has remained for some time, and onto one with our successful heart failure managements.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HFpEF	heart failure and preserved ejection fraction
HFrEF	heart failure and reduced ejection fraction
DHF	diastolic heart failure
HF	heart failure
LV	left ventricular
EF	ejection fraction
AA	African American
LVH	left ventricular hypertrophy
GRK2/GRK5	g-protein receptor kinase 2/5
RAAS	renin-angiotensin-aldosterone system
TTR	transthyretin
PI3K	phosphoinositol 3 kinase
mTOR	mammalian target of rapamycin
PKA	protein kinase A
PKG	protein kinase G
CamKIId	calcium-calmodulin activated kinase Iid
cGMP	cyclic guanosine monophosphate
PDE5A	phosphodiesterase type 5A
NO	nitric oxide
ROS	reactive oxygen species
Ees	end-systolicelastance
SV	stroke volume
Ea	effective arterial elastance
Pes	end-systolic pressure
VV	ventricular–vascular
CK	creatine kinase
PCR	phsophocreatine
VO2	oxygen consumption

BNP	B–type natriuretic peptide
PCWP	pulmonary capillary wedge pressure
PVH	pulmonary venous hypertension
PAH	pulmonary arterial hypertension
Cpa	pulmonary arterial compliance
Rpa	pulmonary arterial resistance
IAP	intra–abdominal pressure
ACE-I	angiotensin converting enzyme inhibitor
ARB	angiotensin receptor blocker

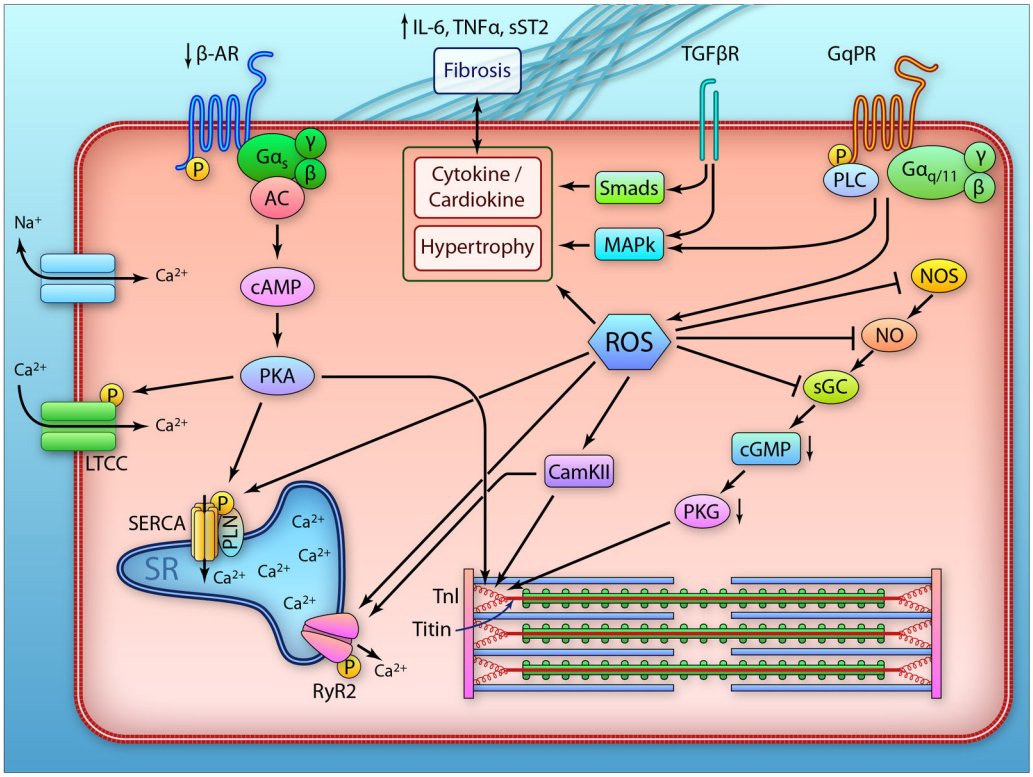

Figure 1.

Schematic of myocardial abnormalties revealed in human HFpEF. The left side shows components of the beta-adrenergic (b-AR) pathway from the receptor to adenylcyclase (AC), generation of cyclic AMP (cAMP) to activation of protein kinase A (PKA). The latter is involved with modification of L-type calcium channels, phospholamban (PLN), titin, and other regulatory thin filament proteins (e.g. troponin I, TnI) which influence myofilament stiffness and contractile activation. Evidence suggests a deficiency in this signaling pathway in HFpEF, with increased titin stiffness and depressed β-AR responsiveness. The middle section shows transforming growth factor b (TGFb) and Gq-protein coupled receptor (GqPR) signaling involving transcription factors (Smad), phospholipase C (PLC) and mitogen activated kinases (MAPk) which are involved with activation of pro-fibrotic and hypertrophic cascades. At the right is the nitric oxide synathase (NOS) pathway resulting in NO activation of soluble guanylatecyclase (sGC), generation of cyclic GMP (cGMP) and activation of protein kinase G (PKG). In the middle is reactive oxygen species (ROS) activated by TGFb, b-AR, and GqPR coupled signaling – which inhibits the NOS-cGMP generation and thereby PKG activity, stimulates CamKII which can render sarcoplasmic reticular (SR) calcium release by the ryanodine receptor (RyR2) more promiscuous. ROS and CamKII also impact titin to influence stiffening. Lastly, the upper right depicts the role of matrix modulation by cytokines/inflammation, and the by-directional interaction of these factors with the myocyte. (Illustration credit: Ben Smith)

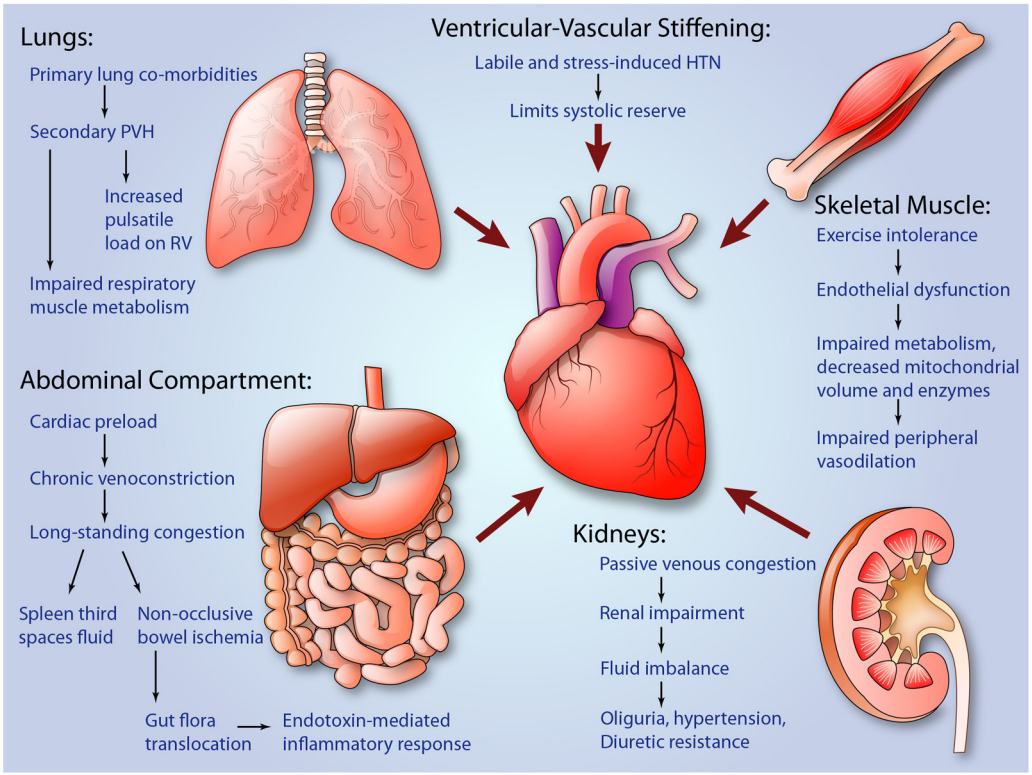

Figure 2.

Schematic of the integrative physiology of HFpEF showing various extracardiac mechanisms and how they are involved. From top left, counterclockwise: lung involvement including primary lung disease leading to PAH, secondary PVH, impaired lung muscle mechanics, and eventual increase pulsatile RV load; abdominal compartment mechanisms including splanchnic circulation (preload), bowel congestion leading to endotoxin translocation and systemic inflammation; skeletal muscle mechanisms including impaired metabolism and peripheral vasodilation; renal mechanisms including passive congestion leading to renal impairment, changes in neurohormonal axis activation, hypertension, abnormal fluid homeostasis, eventual oliguria/renal insufficiency; ventricular-vascular mechanisms including ventricular stiffening leading to systolic and diastolic impairment, diminished systolic reserve, increased cardiac energetic demands and fluid-pressure shift sensitivity. (Illustration credit: Ben Smith)

Table 1

Comparison of clinical characteristics from population-based studies of HFpEF

Characteristics	**Olmsted Co., MN[48]**	**Olmsted Co, MN (2006)[48]**	**Ontario, CA[4]**	**Framingham [171]**	**OPTIMIZE[29]**	**ADHERE[30]**	**Baltimore, MD[13]**	**NY HF Consortium[31]**	**Chicago, IL[33]**	**China[38]**
Sample size, n	244	2,167	880	220	10,072	26,322	37	619	419	132
Age, yr	76	74.4 ± 14.4	75.4 ±11.5	80	75.6 ± 13.1	73.9 ± 13.2	65 ± 10	71.7 ± 14.1	65 ± 13	72.3
Women, %	55	55.7	65.7	65	68	62	84	72.5	62	55.3
African American, %					15	17	76	30	39	
LV ejection fraction, %	62 ± 6	61 ± 7	62.4	≥ 45	61.8 ± 7.0	≥ 40	72 ± 11	60	≥ 50*	≥ 45
Outcomes										
% 1yr survival		71	78	80**	65**				86 (1.5yr)	
Comorbidities										
Hypertension, %	96	62.7	55.1		77	77	100	78.2	77	57
CAD %	53	52.9	35.5	37	32	50	42	43.1	48	39
Diabetes, %	37	33.1	31.7	22	41	45	61	45.9	33	35
Chronic kidney disease, %						26		9.5	33	9 (ESRD)
Atrial fibrillation, %		41.3	31.8	29	32	21		23.4	26	
SBP, mmHg	132 ± 23		156	145 ± 24	150 ± 33	152.5 ± 33	143 ± 25	159.7 ± 35.5	125 ± 20	
DBP, mmHg	67 ± 14			76 ± 13	75 ± 19	78.7 ± 21	69 ± 14	83.9 ± 20.4	70 ± 12	
BMI, kg/m^2	32.2 ± 20.7	29.7 ± 7.8		27 ± 5			37 ± 8	30.6 ± 8.8	32.5 ± 9.3	
Laboratory Values										
Hemoglobin (g/dl)		11.8 ± 2.1		12.4 ± 2.2				11.8 ± 2.2	11.9 ± 1.9	
Serum CR mg/dl		1.6 ± 1.1		1.5 ± 0.9	1.2	1.7 ± 1.5	1.4 ± 0.7		1.6 ± 1.5	
Medications										
Diuretic, %					57	64.8	87	63	74	
ACE-I, %					34	36.1	68	40	55 (ACE-I or ARB)	
ARB, %					14	12.7	14	10		
Beta-blocker %					50	45.5	81	35	67	
Digoxin, %					15	18.7		20		
Aldosterone antagonist, %					4	5.4	5	5		

Characteristics	Olmsted Co., MN[48]	Olmsted Co, MN (2006)[48]	Ontario, CA[4]	Framingham [171]	OPTIMIZE[29]	ADHERE[30]	Baltimore, MD[13]	NY HF Consortium[31]	Chicago, IL[33]	China[38]
Statin, %					37				23	

OPTIMIZE: Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; ADHERE: Acute Decompensated Heart Failure National Registry; LV: left ventricular; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; ACE-I: angiotensin converting enzyme-inhibitor; ARB: angiotensin receptor blocker; CR – creatinine.

*Mean/median values not given; enrollment criteria LVEF values reported.

**Estimated survival based on Kaplan-Meier curves

Table 2

Clinical characteristics of HFpEF in Negative Clinical Trials to Date

First Author/Trial	**Japanese-DHF[126]**	**ELANDD[127]**	**I-PRESERVE[129]**	**DIG-PEF[43]**	**ALDO-DHF[36]**	**RAAM-PEF[130]**	**RELAX[35]**	**TOPCAT[34, 117]**
Intervention	Carvedilol	Nebivolol	Irbesartan	Digoxin	Spironolactone	Eplerenone	Sildenafil	Spironolactone
Sample size	245	116	4128	988	422	44	216	3445
Inclusion Criteria	LVEF > 40%;	LVEF > 45%; diastolic dysfunction by Doppler echo; NYHA class II-III	LVEF > 45%; NYHA II-IV; hospitalization for HF within past 6mo	LVEF > 45%; clinical signs/sx of HF; normal sinus rhythm	LVEF > 50%; NYHA II-III, evidence of diastolic dysfunction	LVEF > 50%, NYHA II-III; elevated BNP	LVEF >50; elevated NT-pro BNP; reduced exercise capacity	LVEF > 45%; controlled HTN (SBP <140mmHg or <160mmHg if on 3+ medication; serum potassium < 5.0mmol; history of hospitalization for HF in past 12 months or elevated BNP/NT-proBNP
Primary Endpoint	Composite CV death and unplanned hospitalization for HF	Change in 6MWT	Composite CV death from any cause or hospitalization for CV cause	Combined HF hospitalization or HF mortality	Changes in diastolic function (E/e') and max exercise capacity (peak Vo2)	Change in 6MWT	Change in peak oxygen consumption	Composite of death from CV causes, aborted cardiac arrest, or hospitalization for HF
Outcome	Negative	Negative	Negative	Negative	Improved diastolic function; did not improve exercise capacity	Negative	Negative	Negative; lower hospitalization for HF in spironolactone group
One yr survival (%)	Placebo 90*; treatment 90*		Placebo, 90*; treatment 90*	Placebo 77; treatment 77	Placebo 100; treatment >99		6 month survival: Placebo, 100; treatment 97	Placebo >90; treatment >90
Patient Characteristics (means or %)								
Age, yr	73	67	72	67	67	72	68	69
Women, %	43	65	59	42	52	5	43	52
Caucasian, %			94	86			90	89
African American, %			2					

First Author/Trial	Japanese-DHF[126]	ELANDD[127]	I-PRESERVE[129]	DIG-PEF[43]	ALDO-DHF[36]	RAAM-PEF[130]	RELAX[35]	TOPCAT[34, 117]
NYHA Class, %	I (18), II (69), III (11), IV (2)	II (77), III (21)	II (21), III (77), IV (3)	I (19), II (59), III (20), IV (1)	II (85), III (15)	II (67), III (33)	II (49), III (51)	I (3), II (63), III (33), IV (0.4)
Comorbidities								
Hypertension, %	80	86	89	62	92	100	80	91
CAD, %	28	17	38	50	43	67	42	59
Diabetes, %	28	21	28	27	61	62	42	32
CKD, %			31	48			56	39
Left ventricular hypertrophy, %							48	
Vital signs								
SBP, mmHg	134	134	137		135	130	124 (median)	129
DBP, mmHg	75	81	79		79	71		76
Body mass index, kg/m^2	24	30	29.7		29	30	33 (median)	32
Admission Data								
BNP, pg/mL	219					255		234 (median)
N-terminal pro-BNP, pg/mL			360		179 (median)		757 (median)	950 (median)
Serum creatinine, mg/dl	1.0		1.0			1.6	1.3	1.1
LV mass (g), or LVMI (g/m^2)	126 g/m^2				108 g/m^2	49 g/m$^{2.7}$	77 g/m^2	
Medications								
Diuretic, %	63	49	82	82	55	95	88	82
ACE-inhibitor, %	24	75 (ACE-I or ARB)	26	86	78	95 (ACE-I or ARB)	65 (ACE-I or ARB)	65
ARB, %	51							20
Beta-blocker, %			59		69	76	77	78
Digoxin, %	19		14					
Aldosterone antagonist, %	21		15				12	
Statin, %		46	32		53		63	53

Japanese-DHF: Japanese Diastolic Heart Failure; ELANDD: Effects of Nebivolol on Clinical Symptoms, Exercise Capacity, andLeft ventricular Function in Diastolic Dysfunction; I-PRESERVE: Irbesartan in Heart Failure with Preserved Ejection Fraction; DIG-PEF: Digitalis Intervention Group-Preserved Ejection Fraction; ALDO-DHF: Effect of Spironolactone on Diastolic Function and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; RAAM-PEF: Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction; RELAX: Spironolactone for Heart Failure with Preserved Ejection Fraction; TOPCAT: Treatment of Preserved Cardiac Function with an Aldosterone Antagonist; LVEF: left ventricular ejection fraction; HF: heart failure; CV: cardiovascular; NYHA: New York Heart Association; 6MWT: six minute walk test; HTN: hypertension; SBP: systolic blood pressure: BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic

peptide; CAD: coronary artery disease; CKD: chronic kidney disease; ACE-inhibitor: angiotensin converting enzyme-inhibitor; ARB: angiotensin receptor blocker; LVMI: Left ventricular mass index (LV mass/body surface area).

* Estimated survival based on Kaplan-Meier curves