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Cellular and molecular pathobiology of heart failure with preserved ejection fraction

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Abstract

Heart failure with a preserved ejection fraction (HFpEF) affects half of all patients with HF worldwide, has an increasing prevalence, substantial morbidity and mortality, and very few treatments have proven to be effective. It arguably represents the greatest unmet medical need in cardiovascular disease and is certainly very prominent across all medicine. While initially a disorder characterized by hypertension, hypertrophy and diastolic dysfunction, the syndrome has become greatly impacted by the pandemic of obesity and diabetes and is currently recognized as a multisystem disorder involving heart, pulmonary, renal, skeletal muscle, adipose tissue, immune/inflammatory signalling and vascular systems. This has made it hard to mimic in experimental animals, as it is not simply hypertrophy and hypertension with abnormal relaxation in a mammal. However, new models involving both hemodynamic and metabolic disease, and increasing efforts to examine human pathophysiology, are revealing new signalling and potential therapeutic targets. This Review tackles the basic pathobiology of HFpEF broadly, though a major focus is on mechanisms pertinent to the heart as most of the existing research has focused on this organ. That said, there is also examination of peripheral organ systems, including skeletal muscle, lung, and kidney, as well as systemic biomarkers, and ongoing therapeutic efforts. The goal is to provide a mechanistic road-map of signalling and mechanisms that are being revealed and may finally lead to more patient-specific therapies with clinical impact.

Introduction

Heart failure with a preserved ejection fraction (HFpEF) is a leading cause of morbidity and mortality throughout the industrialized world, and its prevalence is increasing at an alarming rate. HFpEF currently represents 50% of all HF[1]. Patients with this syndrome develop classic HF symptomatology including exertional intolerance, breathlessness, extravascular

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Competing interests

The authors declare no competing interests.

fluid accumulation in the lungs, subcutaneous tissues and abdominal cavity, and intermittent cardiovascular decompensation that often leads to hospitalization for urgent diuresis. In using the term HFpEF, we are excluding diseases such as cardiac amyloidosis, genetic hypertrophic cardiomyopathy, valvular disease, and other disorders for which there is a defined etiology. HFpEF refers to the much larger population of patients for which the pathophysiology involves a multi-organ syndrome where cardiac, pulmonary, renal, skeletal, immune/inflammatory, metabolic, and other components collude to cause symptoms and outcomes. Importantly, it is a highly morbid and mortal syndrome, with recent 2-year all-cause mortality or HF hospitalization rates at 35% (compared to 43% for HF with a reduced EF; HFrEF) and a mortality of 14%[2]. There are also very few effective pharmacological or device treatments for HFpEF[1,3,4], making it a major unmet medical need.

Recognition of patients with HF symptoms but a normal-range EF began appearing in the 1970s as case reports of ischemic (but not infarcted) heart disease patients[5]. The proposed cause was a left ventricle that was stiff in diastole requiring high filling pressures, and became viewed as diastolic HF. The first prospective report of “HF with normal systolic function” appeared in 1984[6], finding nearly one-third of HF patients had this condition (mean EF of 58%). They were often hypertensive but had otherwise similar demographics, physical and radiographic findings, and measures of diastolic dysfunction as HFrEF. Even these early studies found HFpEF was heterogeneous, with many patients having normal diastolic behaviour[7]. A common presentation was an elderly woman with systolic hypertension and a small volume hypertrophied and hyperdynamic heart often obliterating the distal cavity during systole, who presented with episodic pulmonary oedema[8]. Community data confirmed HFpEF was common, finding mortality rates similar or somewhat below HFrEF[9,10], and associated with major comorbidities, including advanced age, systolic hypertension and female sex.

Based on these findings, treatments aimed to improve diastole with β-receptor and calcium-channel blockers as used for genetic hypertrophic cardiomyopathy, lower filling volumes with diuretics, and reduce blood pressure with antihypertensives — mostly angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers. While palliative, these measures did not improve overall outcome or blunt the rise in HFpEF cases, and by the early 2000s, the diastolic HF paradigm started to unravel. First off, diastolic dysfunction was common in the elderly without HF and was mild or absent in many with HFpEF[11]. Other abnormalities were revealed, including arterial stiffening and adverse ventricular–vascular interaction[12,13], chronotropic incompetence[14-16] and pulmonary hypertension with right HF[17-22], spawning the name change to HFpEF. This was a descriptive but still misleading term with respect to pathophysiology, since having a ‘preserved’ EF mostly meant the heart was not dilated, not that systolic function was necessarily normal[23-27], or the heart the principal cause of symptoms.

The most dramatic evolution in HFpEF, however, developed over the past 1–2 decades, as the syndrome became closely associated with obesity and metabolic syndrome epidemics[28-31]. In addition to diffuse hemodynamic abnormalities, HFpEF now also exhibited inflammation and circulating inflammatory biomarkers[32-35], vascular insufficiency[36-41], pulmonary and renal dysfunction, and abnormal skeletal blood flow and

metabolism[42-46]. Today, obesity and type 2 diabetes occur in most HFpEF patients, with average BMIs in the mid-30s and rising, and are major drivers of the pathophysiology. Hypertensive hypertrophic heart disease in lean patients has become rare in the USA, although it still exists notably in Asia[47], though diabetes and lower-BMI visceral adiposity are present in that population as well.

HFpEF is now widely recognized as an integrative systems disorder, with multiple organ pathologies contributing to the syndrome. While, H for *heart* remains the first letter in HFpEF, its role versus obesity, renal, pulmonary, inflammatory and skeletal muscle disease has become somewhat ambiguous. The heart within a morbidly obese patient works harder to perfuse the extra tissue and propel a higher mass (per Newton's Law). Most mechanistic understanding of human HFpEF stems from organ and systems physiology studies many described in excellent recent reviews[1,3,48-50]. Far less understood are the cellular and molecular changes characterizing the syndrome. HFpEF patients rarely receive a heart transplant, and in situ heart biopsies are performed by only a handful of centres worldwide, so tissue data, particularly from live myocytes, are extremely limited. Despite this, hypothetical schemes have been proposed highlighting roles of fibrosis, inflammation, vascular insufficiency, dysfunctional NO and cGMP signalling, abnormal metabolism and other factors[29,51].

This Review focuses on cellular and molecular mechanisms as currently understood from the available experimental and clinical data. The figures in various sections are comprehensive and include pathways reported in HFpEF models as well as those likely engaged at least in subsets of these patients. However, many are pertinent to HFrEF as well. Those that are unique to HFpEF are certainly being sought, but proof of specificity in humans remains lacking. That said, the areas discussed are all on current lists of potential therapeutic targets. We put the major focus on the heart, not because this is necessarily the root cause of HFpEF, but that most reported pertains to it. Multi-organ contributors to the syndrome are also discussed, and we conclude with a perspective of current and future therapeutic directions.

Animal models - where we've been and where we need to go

Animal models of HFpEF have largely mirrored clinical paradigms at the time they were developed, so not surprisingly, most have emphasized hypertension, left ventricular hypertrophy (LVH) and diastolic dysfunction. Pressure-load-induced LVH in the Dahl salt-sensitive rat (DSSR)[52,53] or spontaneously hypertensive rat (SHR)[54], renovascular hypertension[55], and mice with aortic-constriction or hormone-induced hypertension are prime examples. These rodent models often involve substantial systolic pressure rise, with a hyper-compensated early stage when EF is 'preserved', diastolic relaxation delayed, and compliance reduced, that is eventually followed by a dilated phase with depressed function. Recent studies have revealed metabolic abnormalities in DSSRs, such as increased glycolysis with uncoupling of glycolysis from glucose oxidation resulting in proton production[56]. During the initial months of age EF is still preserved, and calcium homeostasis and Ca^{2+} transients and myocyte shortening are normal if not increased[57]. Beyond this time, however, the LV dilates, EF declines and calcium handing looks more like HFrEF[53,58]. This

is a limitation of the model, as this transition is rare in humans[59]. Another limitation of hypertensive-hypertrophy models is their hearts are substantially benefitted by angiotensin II or other hormone blockade[60-63], which is also not true of human HFpEF. Despite the limitations, models of pressure-volume load continue to be used to test new therapies, including most recently histone deacetylase (HDAC) inhibition[64,65] and stem cells[66].

A parallel universe testing the myocardial impact of diabetes also began in the early 1980s[67]. While long associated with vascular and ischaemic heart disease, such studies revealed myocardial abnormalities as well. Flash forward 4 decades to Jia and colleagues[68], who in their recent review on diabetic cardiomyopathy, list as causative factors: mitochondrial dysfunction, oxidative stress, reduced nitric oxide bioavailability, cardiomyocyte and extracellular matrix-based stiffening, impaired cation channel homeostasis, inflammation, renin–angiotensin–aldosterone system (RAAS) activation, endoplasmic reticulum stress, microvascular dysfunction and multiple metabolic defects. Virtually the same list is found in most contemporary reviews of proposed HFpEF pathophysiology[51]. In humans, diabetes does not generally exist in a vacuum, but is often accompanied by hypertension, obesity, renal, hepatic, pulmonary and other organ diseases. HF evolving from this constellation is multifactorial. Not quite so in pure diabetic models, wherein hearts demonstrate abnormalities but less often HF. However, HFpEF is not monothematic either, and the growing role of obesity and metabolic defects in this syndrome has sparked animal models combining haemodynamic load and metabolic stress.

In 2000, Tofovic and colleagues[69] crossed the Zucker Diabetic Fatty Rat (missense mutation in leptin receptor) with an inbred SHHF rat (a cross between SHR and SHROB, the latter a SHR rat with spontaneous leptin receptor mutation) to generate the ZSF-1 rat. The ZSF-1 rat develops LVH, hypertension, diastolic dysfunction, fibrosis, obesity, hyperlipidaemia, renal dysfunction, reduced NO signalling and aortic stiffening[70]. While not developing the severe fluid dys-homeostasis found in human HFpEF, it has still become a popular model in academia and industry. It was recently used to show therapeutic benefits from novel guanylyl cyclase 1 stimulators that augment cGMP[71], nitrite to improve GLUT4 signalling via a SIRT3–AMP kinase pathway[72], and neuregulin 1 to improve diastolic distensibility by enhancing ERK1/2 activity to phosphorylate titin[73]. However, the ZSF-1 rat also benefits from ACE inhibition[74], and it does not display substantial diastolic pressure elevation or natriuretic peptide (NP) increases until old age. Also, as a genetic mix, the potency of each of its components is diluted.

Another recent model developed in C57BL/6 mice combines chronic NOS1 and NOS3 inhibition by L-NAME (*N*-nitroarginine methyl ester) with metabolic stress from a high-fat diet[75]. This rapidly gained popularity given its ease of use, short development duration, and phenotype consistency. It is also among the best-characterized models for HFpEF, including rest and exercise data, extensive histopathological, functional, and molecular assays, and does display multiple relevant features[75]. However, it also has limitations. L-NAME does not mimic the pathophysiology of hypertension, volume/salt load, and related pathophysiologies in human HFpEF, and may itself bias towards unique oxidant/nitrosative imbalances. The model is less impactful in female mice with or without their sex hormones which differs from humans where post-menopausal females comprise a majority of HFpEF patients[76].

Also, skeletal muscle changes that are prominent in human HFpEF were not observed in the model.

Lastly, in an era dominated by mouse models, it is recognized that behaviour in rodents does not guarantee translation to humans, so investigators have returned to larger mammals, including dogs, pigs and non-human primates. Studies in aged dogs subjected to peri-nephritis-induced hypertension produced hearts with characteristics and haemodynamic load responses similar to those in humans with HFpEF[12,77]. More recent pig models combine deoxycorticosterone acetate (DOCA) and salt loading to stimulate volume expansion and hypertension with a Western diet (high fat, sugar and salt) have been generated[78-80]. They develop some characteristic HFpEF cardiac morphology including left atrial dilatation with reduced systolic function, myocardial fibrosis, oxidative and nitrosative stress, and titin hypophosphorylation[78,80]. However, unlike HFpEF patients, hearts in these models have minimally elevated diastolic pressures and relaxation delay, and LV chambers are smaller, with compensatory hypertrophy[79,80]. Alas, it is proving hard to replicate the syndrome in large mammals at anywhere near the severity and associated morbidity common to humans.

Table 1 summarizes the various models discussed, highlighting what they do and do not capture with respect to HFpEF. A persistent problem with pre-clinical models of HFpEF is that while each reflect some features, none really model the human syndrome. The continued use of pure hypertension - hypertrophy models, which is no longer a common HFpEF phenotype should be discouraged. Combination models that engage multiple factors such as obesity and hemodynamic stress are better, but there also needs to be more consideration of the quantitative extent of the various components. Many HFpEF patients have Class II or higher obesity, and this is not often generated in the animal models studied. In humans, blood pressure elevation is treated and so generally below 130 mmHg systolic, so pre-clinical models with substantial untreated hypertension are less relevant. Alternatively, some studies employ very mild stressors, or induce diastolic dysfunction that while technically present is very mild and would not compromise cardiovascular function. Evidence that the model captures exertional impairment and ideally fluid retention and redistribution is also important. Another feature that maybe decisive in the human disease yet rarely appears in preclinical models is defects in skeletal muscle blood flow and metabolism. This needs more focused efforts. Therapeutic studies should ideally test several different models including perhaps one in a larger mammal, though the latter remains difficult as none have yet come close to mirroring the human syndrome. Lastly, to truly move us closer to translationally relevant models, they need to be easily implemented in multiple laboratories so that replication/validation can occur.

Cardiac molecular/cellular pathways and mechanisms

The bulk of the research into HFpEF basic mechanisms has focused on the heart, likely due to its historical dominance in the syndrome, the fact that patient symptoms are similar to those of humans in whom the heart has clearly failed, and our clinical approach. Most animal models have imposed haemodynamic and more recently combined haemodynamic and metabolic stresses, with their primary criterion being to induce diastolic dysfunction with an EF >50%. Based on these and available human data, cardiac

HFpEF mechanisms can be grouped as: cardiac hypertrophy, fibrosis, excitation–contraction coupling, sarcomere dysfunction, cGMP–PKG signalling deficiency, nitrosative–oxidative stress, microvascular insufficiency, inflammation, and mitochondrial and metabolic defects. There are undoubtedly others, but this covers the major ones.

Cardiac hypertrophy: Role of neurohormones and signaling pathway

LVH has long been considered a cardinal feature of HFpEF and major cause for diastolic dysfunction and elevated diastolic filling pressures despite a normal-range EF. That said, recent clinical trials find LVH in 30–60% of HFpEF patients[81-85] so this is certainly not a requirement for the syndrome. However, it is one of the best well studied aspects. In their excellent 2018 review of physiological and pathophysiological cardiac hypertrophy, Nakamura and Sadoshima[86] listed the components of pathological hypertrophy as: impaired calcium handling, fibrosis, oxidant stress, cell death, insufficient angiogenesis, mitochondrial dysfunction, metabolic reprogramming, cell growth and protein synthesis, and induction of fetal gene programmes. All of these are also on the hit list for HFpEF. Key molecular players in this signalling are G-protein-coupled receptors (GPCRs) and their hormone ligands (angiotensin II, endothelin 1, α-adrenergic receptors and β- adrenergic receptors); signalling kinases (p38, ERK1/2, JNK, CAMKII, PKC, PKG, PKA, mTORC1 and AMPK), epigenetic modulators (NFAT, MEF2, GATA4, class II HDACs and Hippo) and mechanosensitive plasma-membrane cation channels (TRPC and TRPV) (Figure 1). These have been well described in HFrEF, and most are also observed in models of non-dilated hypertrophy induced by pathological haemodynamic or neurohumoral stress, such as aortic banding in mice.

Activation of the RAAS is a hallmark of HFrEF and is linked to many of the above-cited defects. Genetically modified mice long ago established a critical role of $G_{\alpha q/\alpha 11}$ signalling triggered by angiotensin II and pathological cardiac hypertrophy[87-89]. There are few human data on RAAS hormone levels in ambulatory HFpEF or patients during exertion, although one study found them similarly elevated in patients with acute decompensated HFrEF or HFpEF[90]. However, the lack of benefit from multiple studies using RAAS blockade in HFpEF[50,91] makes a primary role unlikely. The exception may be aldosterone, which signals via mineralocorticoid receptors expressed in the distal convoluted tubule and cortical and medullary regions of the collecting duct in the nephron, the brain, vascular smooth muscle, cardiomyocytes, fibroblasts and inflammatory cells[92]. While classically a transcription-factor-regulating pathway, non-genomic signalling engaging MAP kinases, PKC, sSrc kinase and NADPH oxidases are reported[92]. Cardiomyocyte-targeted ablation of the mineralocorticoid receptor (MR) is protective against pressure-load stress, reduces fibrosis, and blocks the DOCA-salt induced inflammatory and fibrotic response[93,94]. Vascular MR signalling is coupled with MMP, TGFβ1, CTGF and galectin-3 expression with extracellular matrix remodelling. HFpEF patients who are obese, diabetic, have chronic kidney disease, concentric LVH and high renin levels seem particularly responsive to MR antagonism with spironolactone[95]. While the international randomized trial of spironolactone in HFpEF was neutral[96], subgroup analysis from North and South America where baseline disease was better documented and metabolite analysis supported the drug was actually taken[97], report benefits[98]. Many have focused on the drug's antifibrotic effects[99], but this role remains

unclear[100], as its capacity to reduce sodium retention to lower intravascular volume and cardiac wall stress is also likely to be important[101].

Sustained catecholamine hyperstimulation contributes to hypertrophy and myocardial dysfunction, and is a central component of HFrEF for whichh β-AR blockade is a proven therapy. No so in HFpEF. While β-AR was hypothesized to prolong diastolic filling time and lower oxygen demand, trial data is scant. The recent J-DHF trial[102] of 245 HFpEF patients treated with carvedolol is the largest, and found no overall benefit in prognosis except perhaps in patients who tolerated the highest doses but also may have been less sick. HFpEF patients also exhibit chronotropic incompetence[14,16] which limits cardiac output reserve, and this can be worsened by β-AR blockade. The funny channel blocker ivabradine slows sinus rate without negative inotropy and worsened HFpEF symptoms[103], conferring no long-term benefits[104].

Kinase and phosphatase signalling cascades in pathological hypertrophy are well recognized and reviewed elsewhere[86]. Despite their prominent roles, their relevance to human HFpEF remains unproven, though several are current therapeutic targets. Hyperactivated CAMKII contributes to the pathophysiology of atrial fibrillation[105], hypertrophy[106], mitochondrial energetics[107], inflammation[108,109], and diabetes[110], so some role in HFpEF seems likely. Pro-fibrotic signalling coupled to non-voltage gated cation channels such as transient receptor potential canonical channel type 6 (TRPC6) which are activated by CAMKII[111] are another potential contributor. The channels are normally expressed at low levels in multiple tissues, but are upregulated in a feed-forward manner coupled to stimulation of calcineurin–NFAT activation that reduces TRPC6 phosphorylation, increasing its Ca^{2+}/Na^{+} conductance, and raises expression of TRPC6[112]. While first revealed as a mechanism of pathological hypertrophy[112], TRPC6 now appears to play a prominent role in pathological fibrosis[113] via both NFAT and SRF–p38 signalling pathways[114]. Another recent discovery is role of HDACs that remove *N*-acetyl lysine from histone or non-histone proteins. Early studies focused on hypertrophic and fibrotic influences and role in redox modulation of both, and HDAC inhibitors have been shown to suppress both in experimental pressure-overload and neurohumoral activation models[115-117]. Results with HDAC inhibitors have varied. In one report, ITF-2357 improved diastolic dysfunction but without reducing hypertrophy or fibrosis in both DSSR and aged mouse models[64]. However, another study using a cat pressure-overload model found suberoylanilide hydroxamic acid, a pan-HDAC inhibitor approved for treatment of cutaneous T-cell lymphoma, reduced LVH, improving diastolic function[65]. Both studies showed enhanced myofilament relaxation rates, and the cat model revealed improved mitochondrial function associated with differential acetylation of components of the electron transport chain and metabolic pathways. These and other pathways are actively being explored (Figure 1).

Myocardial fibrosis

Hypertension and LVH stimulate interstitial fibrosis which has long been viewed as a cause for passive muscle stiffening and reduced chamber compliance in HFpEF[118,119]. Fibrosis also results from diabetic heart disease via multiple signalling cascades and alterations in the matrix proteins themselves, such as insoluble advanced glycation end-products[29,68,120-122].

Obesity is similarly linked to increased myocardial[123,124] and hepatic fibrosis[95,125], and combined haemodynamic and metabolic stress can synergize to stimulate fibrosis[75]. Pro-inflammatory and oxidant stress conditions also stimulate fibrosis. Thus, many HFpEF co-morbidities can be coupled to a profibrotic process. The still somewhat existential question is when is it pathophysiologically important? Despite a lot of research and interest, we still do not know. The presence of connective tissue per se is only a part of the story, as fibroblasts are active participants in myocyte and vascular cell crosstalk, and their molecular phenotypes and secreted signals are likely as if not more important than the collagen that is synthesized. The distribution and cross-linking of matrix proteins also potently impacts their mechanical properties so it is not simply a matter of how much fibrosis but what type and where it is. The presence of a primarily fibrotic HFpEF phenotype seems fairly rare given the mild-moderate levels observed in most patients[126].

With these caveats, it remains useful to examine recent advances in understanding the fibrotic process and potential therapeutic interventions (Figure 2). Among its signalling mechanisms are RAAS activation, insulin resistance, oxidative stress, advanced glycation end-product signalling, TGFβ, endothelin 1, Rho-kinase and leptin-mediated signalling, and upregulation of matricellular proteins (such as thrombospondin 1)[123]. Fibroblast cell types are complex and multiple, with different cell lineages differentially transforming into synthetic versus stable scar-structure-related subtypes after injury[127]. Fibroblast activation and transition to myofibroblasts has been linked to a Yap-induced Hippo suppression, transcriptionally regulating ER stress and unfolded protein responses to enhance collagen synthesis[128]. Matrix is composed of fibrillar collagen, glycoproteins (e.g. thrombospondins and tenascins), proteoglycans (e.g. versican and syndecans) and glycosaminoglycans (e.g. hyaluronan and heparan sulfate). Collagen content reflects a balance between synthesis, post-synthetic processing, post-translational modification, and degradation. Synthesis involves secretion of procollagen into the interstitium where it undergoes end-terminal cleavage by procollagen *N*-proteinase and *C*-proteinase to form mature collagen. Zinc-dependent matrix metalloproteinases (MMPs) degrade ECM to remodel the matrix (see review[129]).

Direct support for myocardial fibrosis in human HFpEF comes mostly from studies of hypertensive–hypertrophic heart disease patients showing correlates with diastolic dysfunction[130-132], from autopsy studies[37], image-based analysis of myocardial extracellular volume and correlation to diastolic dysfunction[133], epicardial biopsy analysis in hypertensive patients presenting for coronary artery bypass graft surgery[134]. In 2020, Hahn and colleagues[126] reported results from >100 endocardial biopsies from well-phenotyped HFpEF patients[126]. The population was obese (median BMI of 37.6 kg/m^2) with nearly 60% having T2DM; most also hypertensive (median systolic blood pressure: 141 mmHg), with a median sex-adjusted LV mass index of 105 mg/m^2 (90% in normal population). Interstitial fibrosis was found in most all the biopsies, but it was moderate or severe in only 26%.

Many fibrosis-related plasma biomarkers correlate with features of diastolic dysfunction in HFpEF patients including: syndecan 1, TIMP1 and MMP1/TIMP1 ratio[130], cardiotropin 1, carboxy-terminal propeptide of procollagen type I (CITP), amino-terminal propeptide of procollagen type III (PIIINP),[135], galectin 3[136,137], lysyl-oxidase, CITP/MMP1 ratio,

an inverse index of myocardial collagen cross-linking[99], interleukin-11 (IL-11), a key downstream effector of TGFβ in fibroblasts that induces myocardial fibrosis and contractile dysfunction[138], and sST2 (soluble ST2) a member of the IL-1 receptor family secreted by fibroblasts and cardiomyocytes in response to mechanical strain. Membrane bound ST2 normally binds to IL-33 ligand eliciting antihypertrophic and antifibrotic responses, but this is negated by sST2 acting as an IL-33 decoy. Other markers include osteopontin and FGF23. In a recent study examining nearly 50 biomarkers from patients in the TOPCAT trial, a machine-learning algorithm identified several profibrotic markers: FGF23, YKL40 (a hepatic fibrosis marker), IL-6, ST2 and MMP7, as being among the eight that best predicted prognosis[35]. Importantly, the tissue source for these biomarkers remains uncertain, given the multisystem disease in HFpEF, as renal, pulmonary, and vascular dysfunction could be as much if not more involved as the myocardium[139]. At least one study used one of the biomarkers, CITP/MMP1 ratio, to stratify patients with more or less collagen crosslinking, and found those with the lowest ratio (most crosslinking) were least responsive to aldosterone antagonism[99]. Demonstration of HFpEF therapy efficacy to diminish markers of fibrosis or, better yet, myocardial fibrosis itself in those impacted by it, remains lacking.

Excitation–contraction coupling

In HFrEF, the process linking myocyte depolarization to calcium–myofilament interaction and contraction, excitation–contraction coupling, is beset by multiple abnormalities[140]. The expression of proteins involved with calcium uptake into the sarcoplasmic reticulum — phospholamban and SERCA2a — is often reduced and/or the proteins are hypophosphorylated, depressing calcium transients and contraction while delaying relaxation. To compensate and lower diastolic Ca^{2+} despite reduced SR uptake, reverse mode Na^{+}/Ca^{2+} exchange is enhanced. The L-type Ca^{2+} channel ($Ca_v1.2$) current–voltage response is depressed, limiting inotropy and lusitropy. In addition, the Ca^{2+} concentration needed for 50% maximal myofilament force is lower, related to reduced phosphorylation of troponin I, and reduced myosin binding protein C phosphorylation causes depressed adrenergic reserve[141]. These changes have not yet been documented in HFpEF. When studied in hypertension–LVH models, and recently the ZSF-1 rat, the data usually show peak Ca^{2+} transients and SR calcium load as normal or even enhanced in the ‘preserved EF’ state, although Ca^{2+} decay transients can be prolonged[54,57,142,143]. Abnormal excitation–contraction coupling is described in diabetes models[68] and associated with pathological CAMKII signaling[110]. However, without obtaining live, intact myocytes from HFpEF patients, which only happens for HFrEF due to heart transplantation, the status of excitation–contraction coupling is likely to remain uncertain.

Cardiomyocyte sarcomere function

In contrast to live, beating myocytes or muscle, frozen tissue (even small pieces such as endocardial biopsy samples) can be used to study sarcomere function. While few in number, such studies have been performed in human HFpEF, with heart tissue obtained mostly from elderly patients with hypertension–hypertrophy with or without diabetes. The work reports passive force–length dependence to be stiffer but systolic force–Ca^{2+} essentially unchanged[120,144,145]. Stiffening was attributed to hypophosphorylation of the sarcomere protein and molecular spring titin, that was in turn linked to depressed protein kinase G

activity[146]. Stiffer titin correlated with reduced diastolic chamber compliance[134]. Both in vitro and in vivo, activating PKG or PKA reversed these changes and improved muscle and chamber compliance[134,147]. Analogous force–Ca^{2+} relation and titin hypophosphorylation findings have been reported in the ZSF-1 rat[148]. This was not documented in compensated (preserved EF) hypertension–LVH models[149], and remains to be determined in other contemporary HFpEF models. Myofilament acetylation also regulates sarcomere function in systole and diastole[150-152], and two recent studies reported HDAC inhibitors in experimental HFpEF models quickened myofilament relaxation kinetics associated with improved chamber relaxation[64,65]. The precise protein targets and mechanisms for this remain unknown.

PKG signalling

The most widely known cardiovascular roles for cGMP and its cognate kinase PKG are their regulation of vascular tone and endothelial function. PKG activates myosin light chain phosphatase to reduce MLC kinase activity and relax vascular smooth muscle. It also phosphorylates RhoA, suppressing Rho kinase and associated smooth muscle proliferation. Endothelial cells play a critical paracrine role, responding to ligands and mechanical stress to activate NO synthase, with NO diffusing to smooth muscle cells, activating sGC and generating cGMP. In skeletal muscle, endothelial NOS plays an important role in myocyte cGMP signalling as well. A similar cascade is often shown for the heart, arguing that depressed endothelial NO generation is a primary cause of reduced myocyte cGMP–PKG signalling. This paracrine scheme surprisingly still awaits definitive proof, as myocytes have the autonomous capacity to generate and stimulate cGMP–PKG. Nonetheless, stimulation of the pathway generally confers antihypertrophic, antifibrotic and proangiogenic effects in the myocardium[153-155] (Figure 3).

There are multiple mechanisms for PKG amelioration of heart disease, and this list continues to grow. One is its phosphorylation and inhibition of TRPC6 conductance to suppress calcineurin–NFAT signalling and thus prohypertrophic and fibrotic programmes[156,157]. Another is PKG activation of RGS2 and RGS4, inhibiting $G_{\alpha q}$-coupled signaling[158,159]. A particularly potent effect is from PKG activation of TSC2 to suppress hyperactivity of the mechanistic target of rapamycin complex 1[160]. In mice expressing a homozygous knock-in mutation of *Tsc2* that prevents this PKG modification (S1365A mutation), TAC-induced hypertrophy, LV dysfunction, and cardiovascular mortality is markedly increased and cannot be rescued by use of a PDE5 inhibitor to stimulate PKG. By contrast, mice with a heterozygous mutation, providing one wild-type allele for PKG phosphorylation, are rescued by the same treatment. PKG phosphorylates and enhances proteasome clearance of misfolded proteins[161] and stimulates autophagy[160], confers anti-inflammatory effects[29,162], improves mitochondrial energetics[163], can supress miRNA changes otherwise induced by pressure overload[164] and counters obesity[165,166]. Other than TSC2, the identification of specific PKG-modified protein residues underlying these important effects remains lacking. Sarcomere protein modifications in troponin I and titin are known and have are potent regulators of diastolic function[147,167].

Therapeutic stimulation of PKG involves either enhanced NO or NP-related cGMP synthesis, or blocking cGMP hydrolysis by inhibiting PDE1, PDE2, PDE5 or PDE9[168]. Of the PDEs, PDE5 and PDE9 are cGMP selective and have been most studied to date. Each tactic augments cGMP but does so in different cell types within different intracellular compartments, so they are not interchangeable. For example, while both PDE5 and PDE9 inhibition counter pressure-overload hypertrophy, fibrosis, and dysfunction, PDE5 depends on the presence of NOS signalling, whereas PDE9 regulates cGMP coupled to NP stimuli[155]. Conditions where NOS activation is compromised include the loss of oestrogen in post-menopausal women and, indeed, PDE5 inhibition is ineffective to counter pressure overload in ovariectomized female mice[169,170]. Effectiveness is restored by exogenous oestrogen replacement. This is related to non-nuclear dependent oestrogen–ERα-dependent signalling that couples via PI3K to NOS activation. Bypassing NOS to directly stimulate sGC and generate cGMP is effective even in these mice. These findings are potentially relevant to HFpEF, which involves many post-menopausal women. Another strategy to circumvent NOS-deficiency states leverages PDE9 inhibition, and work in progress is testing this. Stimulation of cGMP synthesis has been largely achieved by organic nitrates, and by inorganic nitrates and nitrites, the latter aimed at preventing tachyphylaxis. NP stimulation still requires peptide administration, although alternative NP-receptor agonists are being investigated.

Despite the exciting science suggesting utility of stimulating the cGMP/PKG system for HFpEF, clinical data to date has been disappointing. A major problem is that the impact on blood pressure from many of the strategies used limits their capacity to chronically engage signaling in other tissues (e.g. heart, lung, kidney). This is more a problem with NO-donors or surrogates or enhancers of natriuretic peptides, that potently alter vascular tone. PDE inhibitors are more cell-type specific and function in nano-domains, so their interference can augment cGMP signaling in tissue without altering blood pressure. Inhibitors of PDE9 are prime examples of this. They may also be unknown differences between human and rodent cGMP/PKG effects in tissue.

Oxidative–nitrosative stress

Oxidative stress is common to metabolic diseases such as diabetes and haemodynamic diseases such as pressure overload, and is thought to be a potent contributor to the pathophysiology. Specific sources of nitrosative–oxidative stress are NADPH oxidases NOX2 and NOX4[171], ROS from mitochondrial injury or dysfunction[172], xanthine oxidase[173], monoamine oxidase[174], inducible nitric oxide synthase (iNOS or NOS2)[75], and the uncoupling of NOS3 (or eNOS)[175] (Figure 4). The latest chapter in these studies revealed nitrosative stress is linked to iNOS *S*-nitrosylation of endonuclease inositol-requiring protein 1α (IRE1α), culminating in defective splicing and downregulation of protein expression of ER-stress protein X-box binding protein 1 (XBP1)[75]. The result is the HFpEF phenotype in an L-NAME plus high-fat diet mouse model. Blocking iNOS pharmacologically or genetically restored XBP1 expression and reversed the pathophysiology. XBP1 is also downregulated in human myocardium from HFpEF patients[75]. NOS3 uncoupling involves oxidation of the enzyme or its critical cofactor, tetrahydrobiopterin, reducing generation of NO to favour superoxide production. It occurs

in pressure-overload hypertrophy in mice, coupled to heart dysfunction and fibrosis[175], and in ZSF-1 rat and HFpEF pig models[39,80], but not yet documented in human HFpEF. Broad in vivo antioxidant or anti-nitrosative strategies have thus far been disappointing, although targeting specific sources – such as iNOS - remains conceptually attractive.

Mitochondrial and metabolic defects

Cardiac mitochondrial function and metabolism is abnormal in HFrEF and in the diabetic heart (see recent reviews[68,176,177]) and is likely to play an important role in HFpEF as well (Figure 5). Ultimately, this may reduce high-energy phosphate generation and reserve, with resting myocardial ATP 20–40% of normal[178-181] and reduced phosphocreatine (PCr) stores[182-184]. In human HFpEF, Phan and colleagues[185] found PCr/ATP ratio reduced by 27% versus controls accompanied by depressed exercise augmented cardiac output, oxygen uptake, and relaxation. PCr in skeletal muscle during exercise must be restored, and this process is delayed in HFpEF patients[185,186].

Both the HFrEF and diabetic hearts display changes mitochondrial biogenesis, with downregulation of PGC1α expression, which is considered a central factor for high-capacity mitochondrial oxidative function[187]. In addition, the critical feedback balance between redox modulation of metabolism and vice versa via NAD^+/NADH balance is disrupted[188]. Pathological hypertrophy results in a decline in NAD, perhaps related to oxidative stress and increased consumption of NAD by poly ADP ribose polymerases required for DNA repair[189]. In addition, reduced NAD synthetic pathways coupled to NAMPT may play a role. NAD^+ is required for metabolic substrate oxidation and is regenerated by the electron transport chain, and the ratio of NAD^+/NADH declines in HFrEF and the diabetic hearts[188,190-192]. This adversely impacts intermediary metabolism of glucose and fatty acids, increases acetyl-CoA levels which impacts lysine acetylation of proteins to contribute to heart dysfunction, and impacts glucose–fat oxidation balance[188]. Proper NAD^+/NADH ratio is also required for normal SIRT3 function[193], a deacetylase fuelling metabolism by activating glycolysis, fatty acid oxidation, the tricarboxylic acid cycle and electron transport chain, and depressed SIRT3 signalling has been described in these syndromes and experimental HFpEF[72].

Abnormalities of intermediary metabolism are also well documented HFrEF and are also thought to play an important role in HFpEF. By impairing fuel utilization and inducing conditions of substrate toxicity, they impede energy reserve and adaptability of the heart and skeletal muscle to stress. Reduced mitochondrial oxidative metabolism is accompanied by increased glycolysis[178,181,194,195], but this does not translate to higher glucose uptake via pyruvate dehydrogenase complex, uncoupling glycolysis from pyruvate oxidation[196]. Impaired insulin signalling inhibits glucose oxidation by a negative feedback regulation via the Randle cycle, further enhancing glycolysis[197]. These changes are observed in multiple models of obesity and diabetes. There is also compensatory anaplerosis, redirecting glycolysis products to ancillary biosynthetic pathways such as hexosamine biosynthetic and pentose pyrophosphate pathways, further diverting pyruvate towards anaerobic glycolysis[198].

In diabetes, impaired glucose oxidation is offset by increased fatty acid oxidation[178,199], whereas in HFrEF, fatty acid oxidation is also depressed[200]. Enzymes catalysing fatty acid β-oxidation are downregulated in HFrEF, associated with a downregulated gene regulatory network coordinated by PPARα and its transcriptional cofactor PGC1α. The resulting mismatch between enhanced fatty acid uptake and oxidation results in intramyocardial accumulation of diglycerides and ceramides, further increasing reactive oxygen species, ER stress, mitochondrial dysfunction and lipotoxicity. Elevated myocardial triglyceride levels are reported in human HFpEF, and the extent of myocardial steatosis is positively and independently correlated with impaired diastolic strain rate and reduced exercise capacity in patients with HFpEF[201,202]. Increased plasma fatty acid levels are associated with greater risk of HFPEF development[203]. Plasma metabolomic profiling in HFpEF has found altered β-oxidation intermediates[204-206], and these metabolic signatures may differentiate between HF types[206].

Lastly, both HFrEF and the diabetic heart exhibit an increase in the use of ketone bodies as fuel for oxidation[177,207-209]. Evidence for human HFpEF is scant, although peripheral ketone levels are reportedly increased[210]. Ketones can suppress glucose and fatty acid oxidation, yielding more ATP per molecule of oxygen invested, which makes them the energetically efficient fuel. Therefore, maintaining cardiac ketone levels is viewed as beneficial, and methods to augment this source is being tested for HFrEF conditions. β-Hydroxybutyrate, the major ketone body, also inhibits HDACs[211], and in light of recent reports on HDAC inhibitory beneficial effects on myofibril relaxation kinetics in experimental HFpEF[64,65], ketone body supplementation may provide additional benefits beyond metabolic regulation. The cardioprotective effect of empagliflozin is associated with increased plasma ketone levels[212] that may provide a mechanism for improving myocardial metabolism and heart function in HFpEF.

Plasma biomarkers and inflammation

An increasingly popular theory regarding HFpEF is that it reflects a pro-inflammatory state (see Figure 2). Westermann and colleagues[32] were the first to report on myocardial tissue and examined 20 right ventricular biopsy samples, finding increased staining for $CD3^+$, $CD11a^+$, and $CD45^+$ cells, (the last two are pan-leukocyte markers) as compared to eight controls. The only other report is from Hahn and colleagues[126], who examined >100 right ventricular HFpEF biopsy samples and found increased numbers of $CD68^+$ cells, indicating macrophages and other monocytes. Animal models, even those due purely to pressure-overload stress, also display myocardial inflammation[66,213,214]. Blocking specific cell types, such as infiltrating $CCR2^+$ monocyte-derived macrophages[215] or $CD4^+$ T cells[216], or using abatcept (a broad T-cell inhibitor)[217], improves cardiac remodelling induced by aortic banding in mice. Inflammation is well described in diabetes and obesity, so the combination of all three in HFpEF only further increases the likelihood of an importance of pro-inflammatory processes. The triggers stem from multiple cell types, as myocytes, fibroblasts and vascular cells all synthesize various cytokines, including IL-1, IL-6, IL-8, colony-stimulating factors such as G-CSF, M-CSF, and GM-CSF; and chemotactic factors like MCP, to enhance migration and extravasation of inflammatory cells into tissue.

The greatest support for inflammatory conditions in HFpEF comes from peripheral blood biomarker analyses, and the data are overwhelmingly clinical. Among the many biomarkers commonly identified are C-reactive protein, TNF and TNFR, IL-1β, ILT6, IL-6, IL-10 and MPO[35]. Although common, high-sensitivity CRP was found in the normal range in 40% of HFpEF patients in the RELAX trial[36]. Increases in circulating inflammatory biomarkers correlate with acute decompensation in HFpEF[34]. While providing an overall indication of an inflammatory state, it is hard to solve the inverse problem to interpret a panel of biomarkers to discern which organ(s) are inflamed. Therefore, their use has been primarily to segregate HFpEF patients into lower-risk versus higher-risk groups. Importantly, these same markers are commonly observed in HFrEF, and there is little evidence to date that this is a unique or pathognomonic feature of HFpEF. Table 2 lists major plasma biomarkers for inflammation, renal, fibrotic, and other pathways that have been generally confirmed in various studies as being indicative of specific HFpEF phenotypes.

Vascular disease: large and small vessels

At the systems level, older HFpEF patients generally have large-artery stiffening. This increases arterial blood pressure amplification late in systole due to early arriving wave reflections and reduced aortic compliance. The results is an increased in LV afterload imposed on the heart late in systole, stimulating myocardial remodelling such as hypertrophy, and depressing diastolic function detected as slowed early filling velocity and delaying relaxation[218]. The resulting suboptimal ventricular–arterial coupling[12,219,220] impairs systolic reserve by limiting the capacity of the heart to enhance stroke volume without incurring substantial metabolic costs[12,221]. Diabetes mellitus also results in aortic stiffening and thus increased pulsatile arterial load, coupled to ventricular hypertrophy, fibrosis and adverse ventricular–vascular coupling[222].

Microvascular disease also plays an important role in HFpEF. As this is harder to study in mice and even rats, some of the best preclinical work was performed decades ago in larger mammals. For example, LVH induced by aortic banding of dogs results in endocardial hypoperfusion during rapid pacing or exercise associated with depressed flow reserve[223,224]. The endocardium is particularly vulnerable to ischaemia, perhaps due to myocardial compression that results in microvascular retrograde flow during systole that must be refilled during diastole, while flow is primarily antegrade during systole in epicardial vessels[225]. Diffuse microvascular disease is also a common feature of diabetes[68]. Mechanisms include depressed nitric oxide signalling, oxidative stress, inflammation, impaired angiogenesis and other molecular abnormalities[41]. One factor attracting recent attention is the NAD-dependent deacetylase sirtuin 3 (SIRT3). SIRT3-deficient mice develop microvascular rarefaction, mitochondrial dysfunction and fibrosis, with depressed angiogenesis[226]. Application of hypertrophic stimuli results in markedly amplification of the maladaptive response[227]. Endothelial cell-targeted SIRT3 knock-down impairs glycolysis and angiogenesis and is coupled to diastolic dysfunction[228]. The protein has also been identified as a prime contributor to metformin–AMPK dependent improvement in a mouse model of HFpEF and pulmonary hypertension[72]. Proof of a role in human HFpEF remains lacking.

While precise mechanisms and therapeutic targets have yet to be identified, there is substantial support for microvascular defects in human HFpEF. Reactive hyperaemia after 5-min limb ischemia is depressed[229,230]. In coronary arteries, endothelium-dependent (flow response to acetylcholine) and endothelium-independent (flow response to adenosine) are often depressed. A reduced endothelial-independent response correlated with slower diastolic relaxation velocity and higher estimated diastolic pressures[231]. Depressed flow reserve also predicted worse outcome, including a fivefold increase in HFpEF hospitalizations[232]. Moreover, while HFpEF patients have greater resting cardiac external work, myocardial blood flow, and myocardial oxygen consumption compared with healthy controls, myocardial perfusion rises less and oxygen extraction more as work is increased by dobutamine β-adrenergic stimulation[233]. Microvascular disease also potently impacts skeletal muscle HFpEF, playing a prominent role to inadequate nutrient and oxygen supply and correlating with depressed exercise performance[45,234].

MicroRNA signatures

With the discovery that microRNAs are released into the blood stream and may convey information about disease processes, studies began looking at these as potential biomarkers to discriminate between forms of HF as well as provide prognostic insight within HFpEF itself[235,236]. The largest such study was reported from ~1,700 HF patients from Singapore and New Zealand, divided into model group to derive an optimized eight-element microRNA for differentiating between HF forms, and separate validation groups[237]. The authors also measured NT-proBNP, and found this provided much of the HF discrimination, with the additive impact of microRNAs being rather modest. KEGG pathways corresponding to the eight-element microRNA set were involved with mRNA and ER processing, ubiquitin proteolysis, Hippo pathway, extracellular matrix interactions and fatty acid biosynthesis. Somewhat worrisome is that among five such miRNA studies to date, there appears to be minimal concordance in the miRNAs identified[238].

Right ventricular Disease

Before abandoning the heart for extracardiac HFpEF contributors, it is important to note that though HFpEF traditionally focuses on left ventricular disease and disease models, growing evidence in humans supports a major role for right ventricular dysfunction[19,20,239-244]. RV dysfunction is a major risk factor for worse outcome in HFpEF patients[240,242]. It most often evolves in the setting of type II pulmonary hypertension, and longitudinal studies have shown its gradual evolution following LV disease that ultimately becomes a dominant limiting factor[239]. The dysfunctional RV is not hypercontractile in HFpEF, but exhibits reduced contractile and adverse systolic-vascular coupling during exercise[19]. Molecular underpinnings of RV disease associated with increased pulmonary afterload include many pathways shared by the LV that emphasize metabolic and energetic pathways[245], but this remains a work in progress as RV-specific pathobiology has long been neglected. Experimental studies are problematic here as small rodents do not develop the type of RV failure observed in larger mammals or humans. Ongoing studies obtaining RV endocardial biopsies from humans with HFpEF are now performing broad molecular analyses along with sarcomere studies with the hope of elucidating signatures unique to HFpEF that might be therapeutic targets in the future.

Extracardiac Components

Skeletal muscle perfusion and metabolism—In the early 1980s, as vasodilator therapy was first being tested as a treatment for HF, investigators found that exercise capacity was not only limited by the heart but also by insufficient skeletal muscle vasodilatation[246,247]. In a classic study, LeJemtel and colleagues[248] showed that lower-limb blood flow was the same in HF patients whether they exercised one or both legs, whereas controls had greater flow with one leg exercise. This indicated an inability of HF skeletal muscle to vasodilate appropriately to receive the cardiac output the heart could offer. Many studies followed identifying endothelium-dependent dysfunction and skeletal metabolic defects that limited its capacity to do the work required, including the work of breathing.

Fast forward several decades and much the same pathophysiology is now well recognized to play a critical role in HFpEF[249,250]. Morphologically and histologically, there are declines in lean skeletal muscle mass and accumulation of intramuscular fat[44], reduced force-generating type 1 fibres, lower capillary to fibre ratio[44], depressed high energy phosphate metabolism[251], and reduced mitochondrial content[252]. A major determinant of exercise intolerance is insufficient oxygen extraction by the muscle[45]. Furthermore, while exercise training in HFrEF results in increased cardiac output reserve as well as improvement in skeletal muscle flow and oxygen extraction, in HFpEF the heart is not altered whereas skeletal muscle oxygen extraction is improved[253]. Thus, the benefits of exercise on raising peak oxygen consumption in HFpEF is largely peripheral at the level of skeletal muscle. Obesity also plays an important role in this pathophysiology, as intramuscular fat is pro-inflammatory and adversely impacts muscle metabolism impairing glucose utilization and thus muscle performance[254]. Percent fat mass is a strong correlate of exercise capacity and arterial–venous oxygen difference in HFpEF patients[255].

In contrast to the heart, most data regarding skeletal muscle defects in HFpEF come from human studies, as animal models have not fully replicated the human pathophysiology. For example, while the ZSF-1 rat develops skeletal muscle with reduced fibre size, capillary density, and glycolytic metabolism, these are not reversed by endurance training[256]. The mouse L-NAME plus high-fat diet model also does not develop abnormal skeletal muscle perfusion or metabolism[75]. Skeletal muscle perfusion and metabolism have been little studied in hypertension–LVH models such as SSRs and DSSRs.

Pulmonary disease—Given the presence of elevated left ventricular diastolic pressures in HFpEF patients, it is not surprising that pulmonary disease including gas diffusion defects, vascular remodeling, and pulmonary hypertension (PH) are also common. Reduced alveolar-capillary membrane conductance and pulmonary capillary blood volume are associated with a 24% reduction in gas diffusion capacity at rest (versus controls), which rose to a 30% reduction with exercise contributing to exertional intolerance[257]. HFpEF patients with both PH and reduced diffusion capacity (<45% normal levels) have a markedly worse survival (36 vs 88% at 3 years)[258]. PH in HFpEF patients is primarily associated with post-capillary venous mechanisms, with only about 14% of patients present with both pre-capillary and post-capillary disease[21]. Autopsy studies report findings compatible similar to veno-occlusive disease[259]. Clinical studies have linked PH with reduced exercise capacity,

in part due to right–left heart interdependence and adverse right ventricle–pulmonary artery interaction, as well as to worse disease progression[20]. Elevated right atrial and ventricular volumes and pressures increase pericardial pressure to reduce LV transmural pressure and thus filling volumes. The result is reduced stroke volume and thus cardiac output[26]. The right ventricle in HFpEF may be particularly sensitive to developing fibrosis with increased pulmonary vascular load[244]. There is far less research to date on the lung and PH in animal HFpEF models, though some have proposed mechanisms. For example, augmentation of AMPK activity by the prostacyclin analogue treprostinil or metformin improves pulmonary hypertension as well as metabolic status in the ZSF-1 rat[260]. Another intriguing mechanism relates to the expression of the NPRC receptor that is more increased in the right ventricle than the left ventricle or lung in a mouse model of HFpEF with obesity[261]. Whether this applies to humans remains unclear.

Kidney and liver—Fluid and electrolyte dys-homeostasis is a common feature in HFpEF and renal insufficiency is thought to play a major role[262,263]. Whether this represents a *forme fruste* of cardiorenal syndrome[264] or a product of hypertension, diabetes, obesity, all common morbidities that adversely impact renal function[265], depressed renal function is an important contributor to the syndrome. Renal insufficiency is often linked to elevated central venous pressures and thus right ventricular workload, contributing to right ventricular failure, a major predictor of adverse outcome in HFpEF[243]. One potential biological link between renal disease and HFpEF is presence of a variant allele in apolipoprotein 1 (APOL1) which is associated with an increased risk of chronic kidney disease primarily linked to hypertension[266]. The allele is particularly prevalent in African American women. In a study from the Women's Health Initiative, postmenopausal women carrying the high-risk allele displayed a near 60% greater risk of hospitalization for HFpEF, though not of coronary artery disease, stroke or overall mortality[267]. With respect to therapy, there is ongoing interest in SGLT2 blockade, already shown to improve mortality in HFrEF patients by mechanisms that may involve the kidney. A trial of empagliflozin in HFpEF was recently completed, with results to be reported in the near future, although initial release from the sponsor suggests it did not achieve the primary outcome.

HFpEF therapeutics

The alarming state of affairs regarding HFpEF is that there exist so few therapies that impact its course and prognosis. Patients generally succumb to profound fluid volume overload that is difficult to ameliorate, dyspnoea, and severe exertional incapacity. Historically, treatment has focused on the heart and vessels, with neurohormonal blockade as has worked for HFrEF. However, with dozens of disappointing trials of RAAS blockers, this approach has been mostly abandoned. It remains possible that specific subgroups with constellations of clinical comorbidities likely coupled to molecular underlying mechanisms that are more responsive to these antagonists[268], as was recently suggested in a spironolactone study[95]. As already mentioned, β-AR blockade is increasingly being abandoned given lack of evidence of efficacy, and selective sinus-node funny channel blockade may worsen symptoms.

A fair amount of effort has already focused on enhancing cGMP–PKG signalling, but translation in the clinic has been largely elusive to date. The multicentre RELAX trial

of the PDE5 inhibitor sildenafil found no benefit on exercise performance (primary end point) nor any of a myriad of other parameters examined[81]. This may relate to lack of upregulation of PDE5 expression in HFpEF, and that cGMP primarily hydrolysed by PDE5 is coupled to nitric oxide stimulation[155] which may be compromised in HFpEF[29]. Other approaches stimulated cGMP synthesis using inorganic nitrite[269] or the sGC stimulator vericiguat[270] and were neutral as well. A second sGC stimulator, paraliciguat, was also tested in a multicentre, placebo-controlled, phase II trial of 196 patients with HFpEF over a 12-week period. With the primary efficacy being exercise tolerance, there was no significant improvement, and the effort abandoned. Another approach is PDE9 inhibition, and trials were recently initiated in HFrEF patients. There are potential synergies with neprilysin inhibition, the latter enhancing NP-stimulated cGMP synthesis, while PDE9 inhibition would suppress hydrolysis of the synthesized cGMP. One caveat to this approach is that HFpEF patients often display low NP levels due in part to either to a lack of myocardial synthesis[271] and/or to increased peripheral clearance by NPRC receptors in adipose tissue[272].

Other recent trials tested the combination of sacubitril and valsartan (Entresto) in nearly 5,000 patients, and reported a 13% ($P = 0.06$) reduced rate ratio for combined HF hospitalization and cardiovascular death[273]. Greater effects were observed in those with lower EF, women, and those with recent decompensation requiring hospitalization[273,274]. The concept that this treatment may be efficacious in the appropriate subgroup is being further evaluated. Dopamine was tested for its potential role in enhancing glomerular filtration to improve diuresis in HFpEF patients hospitalized with fluid overload, but there was no benefit found[275]. Other recent studies include a test of an IL-1 blocker anakinra, inhaled β_2-agonist albuterol, the mitochondrial fatty acid uptake inhibitor perhexiline, and SGLT2 inhibitor empagliflozin. Of these, only the albuterol data have reported, showing reduced pulmonary vascular resistance, increased compliance, and enhanced exercise reserve[276]. The EMPERIAL-Preserved study of empagliflozin in 315 HFpEF patients reported top-line results in late 2019, and was reportedly negative for the 6-min walking test primary end point. The larger EMPEROR-Preserved trial of nearly 6000 patients tests if this drug reduces the time to first composite endopint of cardiovascular death and/or heart failure hospitalization, and is expected to complete in late 2020. Other ongoing trials listed are testing the SGLT2 inhibitor dapagliflozin, inorganic nitrite, a monoamine oxidase inhibitor (AZD-4831), a xanthine oxidase inhibitor (allopurinol, Verinurad), and a cell-based therapy.

Studies involving inotropic modulation remain limited. One recent study tested the PDE3-inhibitor milrinone, a potent venous and arterial vasodilator that also increases heart rate and contractility. HFpEF patients receiving acute intravenous milrinone displayed lower central vascular pressures during exercise at greater cardiac output and heart rate [277]. The investigators followed up with a new long-active form of milrinone tested in 23 patients, and while quality of life questionnaire results were improved, there was no significant change in 6-minute walk or other measures of cardiac function[278]. Another small trial (n=38) examined levosimendan, a PDE3-inhibitor but also a calcium sensitizer and peripheral vasodilator. Top line data reported it also lowered left sided filling pressures. The role of peripheral vascular versus cardiac impacts in both studies is uncertain. As previously

discussed, the precise status of HFpEF contractility remains open to question, and likely varies among patient subgroups.

HFpEF device therapies are also being pursued, although few have trials completed and reported. One concept is to reduce sympathetic stimulation by either renal nerve denervation or splanchnic nerve resection, the latter potentially reducing venous return and thus central vascular congestion. Another is implantation of an interatrial shunt device that can reduce left atrial pressures at rest and during exercise by allowing blood to be transmitted to the right atrium[279,280]. This approach also improves pulmonary vascular function and RV load[281] One study of 44 patients (REDUCE-LAP HF-1) reported a small (3-4 mmHg) but significant decline in PCWP that persisted during exercise[282]. The early reported data from non-randomized trials involved less than a dozen HFpEF patients but do suggest efficacy[279]. The CORolla TAA is a metal-wire structure with multiple springs that can be inserted into the LV chamber, compressed during systole, and then provides an elastic recoil to enhance cardiac filling. The primary target is diastolic dysfunction, and while this may find use in some forms of restrictive heart disease, it is unclear how this will help the phenotype in obese/diabetic multisystem HFpEF, where diastolic dysfunction is often mild. Physiological rate-responsive atrial pacing is being tested to determine if restoring some chronotropic response during exercise can improve symptoms. The role of pericardial constraint is being tested by performing pericardiectomy in HFpEF patients, the goal being to reduce interventricular crosstalk and enhance LV filling particular in patients with higher pulmonary pressures. One risk is converting a normal-volume ventricle into a larger one — essentially HFpEF into HFrEF, but that remains to be seen.

Lastly, there are therapies that do not target the heart at all. Exercise training is one of the very few interventions that has been successful, although the impact remains limited since such training in an individual with a BMI >35 is difficult to institute. Diet-induced weight loss has been tried, but again, morbid obesity is difficult to counteract with diet. Bariatric surgery is more impactful, and several limited trials have been performed examining the potential of this approach[283,284]. Table 3 lists current therapy trials that have not yet been published, including pharmaceuticals, and devices, though not life-style trials.

Perspectives and Future Directions

The expanding presence of HFpEF throughout the world and no truly impactful therapy options has intensified the focus on this syndrome like never before. The NIH recently presented a roadmap for research studies, identifying major gaps in knowledge and areas in sore need of new insight and advances[4]. One broad theme is that this syndrome is a systemic one, and we need to greatly broaden the focus of research and models to incorporate the complex interactions between multiple organ systems. While small rodents are undeniably the premier model system for unlocking new mechanisms and targets, few effective therapies in these models have yet been successfully translated to humans. The major push to human iPS-derived organoids has been one answer but we doubt this will be useful for HFpEF given the systems biology involved with complex inter-organ crosstalk. Perhaps this argues for much greater attention on human studies themselves, and at a mechanistic level. We need better-defined biological targets, and that is unlikely to come

solely from biomarkers measured in the blood stream. This means more active pursuit of tissue procurement, as commonly done in oncology. HFpEF researchers need to consider doing the same, whether from the heart, skeletal muscle, fat, or other tissues. In the meantime, the resurgent interest in experimental models is moving in the right direction, with combination models that capture more of the multidimensionality that is HFpEF. There is much to uncover, and the need has never been more urgent.

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Key points

- While the historical focus of HFpEF pathophysiology has been on diastolic dysfunction, hypertrophy, and cardiac fibrosis, it actually engages many different components impacting systolic and diastolic heart function but also other organs and systems.
- Preclinical studies, particularly those combining obesity/metabolic defects with hemodynamic/cardiac disease as exists in the majority of HFpEF patients, are beginning to reveal novel molecular mechanisms and therapeutic targets.
- There is substantial overlap with proposed molecular/cellular abnormalities in HFpEF and that observed with diabetes and obesity, including metabolic defects in fuel utilization and efficiency, inflammatory responses, lipotoxicity, pathological growth, and loss of cytoprotection signaling.
- The heart is but one feature of HFpEF, albeit the one for which the vast majority of basic biology focuses on, but the syndrome also engages lung, kidney, vascular, adipose, skeletal muscle, and other abnormalities.
- In addition to exploring novel hemodynamic interventions with both drugs and devices, new therapies are targeting pleotropic signaling cascades to counter metabolic, inflammatory, and pathological-stress pathways.

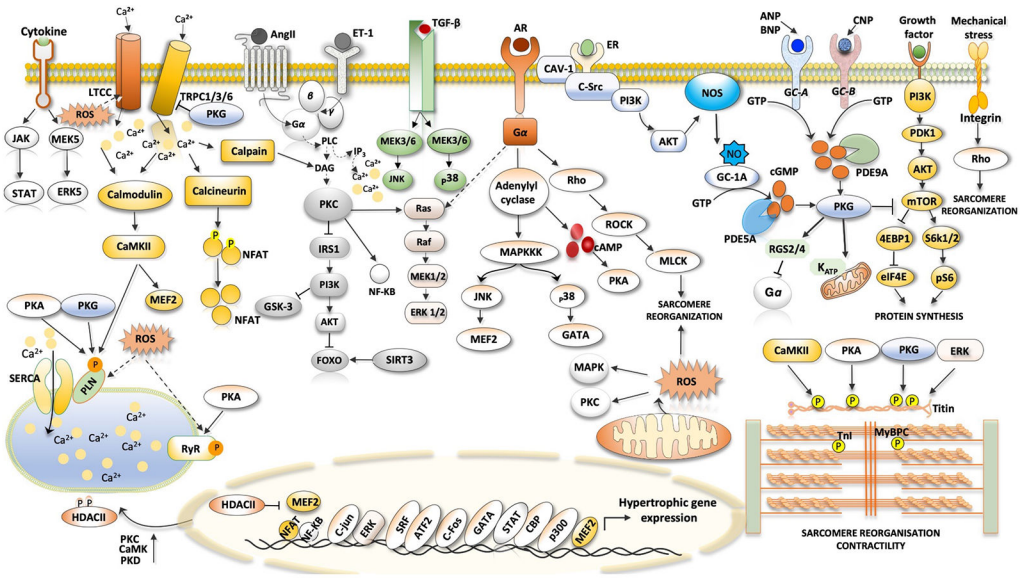

Fig. 1 |. Signalling pathways in cardiac hypertrophy.

Ventricular hypertrophy in heart failure with preserved ejection fraction, particularly in association with hypertension and neurohormonal stress, can involve many pathways identified in other hypertrophic syndromes. The figure shows the major pathways in cardiomyocytes that are thought to stimulate pathological muscle growth of the heart. The hormones angiotensin II (AngII), endothelin 1 (ET-1) and catecholamines bind to their cognate receptors, which are coupled to heterotrimeric G proteins to activate downstream signalling, such as the phospholipase C (PLC)–protein kinase C (PKC) axis. Activated PKC inhibits the insulin receptor substrate 1 (IRS1)–RACα serine/threonine-protein kinase (AKT)–forkhead box protein (FOXO) signalling pathway. β_1-Adrenergic receptor (AR) stimulated protein kinase A (PKA) raises cytosolic Ca^{2+} levels by phosphorylation of Ca^{2+}-handling proteins. Transient receptor potential channel 1 (TRPC1), TRPC3 and TRPC6 have been linked to pathological hypertrophy through elevated NFAT signalling. TRPC1 and TRPC6 are also mechanosensitive. Integrin transmembrane receptors also transduce intracellular hypertrophic signalling by activating downstream effectors such as Rho. Transforming growth factor-β (TGFβ) signalling and receptors transmitting signals through G_q-protein-coupled receptors promote activation of Rho-associated protein kinase (ROCK), extracellular-signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK), which contributes to pathological cardiac hypertrophy and fibrosis. Growth factor-mediated stimulation of mechanistic target of rapamycin (mTOR) signalling is linked to induction of protein synthesis and inhibition of autophagy. Hypertrophy is also associated with depressed cGMP–protein kinase G (PKG) signalling (both nitric oxide (NO)-mediated and natriuretic-peptide-mediated) and increased phosphodiesterase type 5A (PDE5A) and PDE9A expression. Many of these kinases can affect sarcomeric proteins, altering myofilament Ca^{2+} sensitivity and passive stiffness. Cytokines augment cardiac hypertrophy through their receptors (such as the IL-6 receptor). 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; AC, adenylyl cyclase; ANP, atrial natriuretic peptide; AT1R, angiotensin II receptor type 1; ATF2, cAMP-dependent transcription factor ATF2; BNP, B-type natriuretic peptide; CAMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CAV1,

caveolin 1; CBP, CREB-binding protein; CNP, C-type natriuretic peptide; cTnI, cardiac troponin I; DAG, diacylglycerol; eIF4E, eukaryotic translation initiation factor 4E; ER, oestrogen receptor; FOS, proto-oncogene c-Fos; GATA4, transcription factor GATA4; HDAC, histone deacetylase; IP_3, inositol trisphosphate; JAK, Janus kinase; JNK, JUN N-terminal kinase; JUN, proto-oncogene c-Jun; K_{ATP}, ATP-dependent K^+ channel; LTCC, L-type Ca^{2+} channel; MAPKKK, mitogen-activated protein kinase kinase kinase; MEF2, myocyte enhancer factor 2; MEK, MAPK/ERK kinase; MLCK, myosin light chain kinase; MYBPC, cardiac myosin-binding protein C; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; NOS3, endothelial nitric oxide synthase; NPR-A, natriuretic peptide receptor A; NPR-B, natriuretic peptide receptor B; P, phosphate; p300, histone acetyltransferase p300; PDK1, 3-phosphoinositide-dependent protein kinase 1; PI3K, phosphoinositide 3-kinase; PKD, protein kinase D; PLN, cardiac phospholamban; pS6, ribosomal protein S6 kinase; RAF, RAF proto-oncogene serine/threonine-protein kinase; RGS2, regulator of G-protein signalling 2; RGS4, regulator of G-protein signalling 4; ROS, reactive oxygen species; RYR2, ryanodine receptor 2; S6K1, ribosomal protein S6 kinase-β1; S6K2, ribosomal protein S6 kinase-β2; SERCA2A, sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase; sGC, soluble guanylyl cyclase; SIRT3, mitochondrial NAD-dependent protein deacetylase sirtuin 3; SR, sarcoplasmic reticulum; SRC, proto-oncogene tyrosine-protein kinase SRC; SRF, serum response factor; STAT, signal transducer and activator of transcription; TGFBR, transforming growth factor-β receptor.

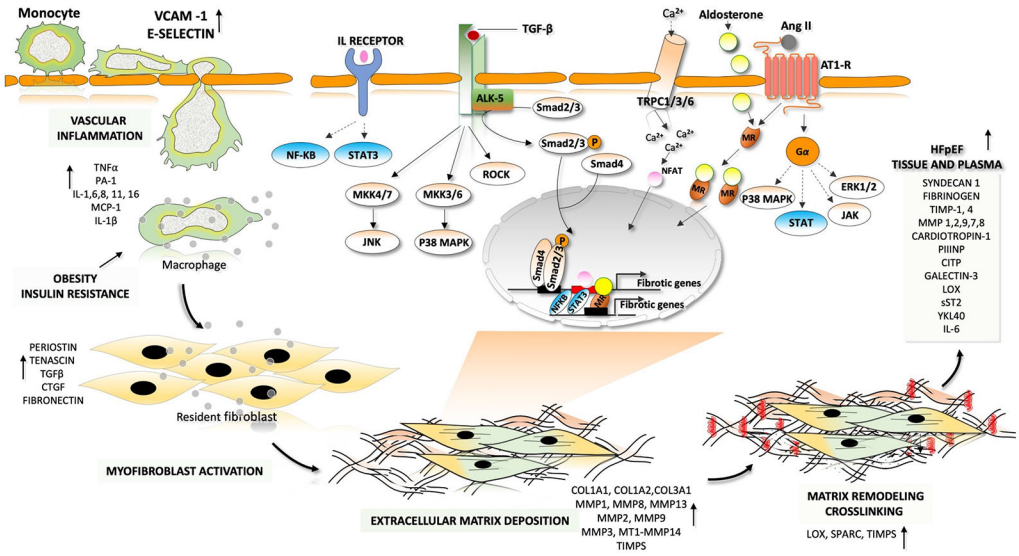

Fig. 2 |. Fibrotic–inflammatory remodelling in heart failure with preserved ejection fraction. In patients with heart failure with preserved ejection fraction, endothelial cells produce factors that induce inflammation and recruit monocytes for transendothelial migration. These factors include interleukins (IL-1, IL-6 and IL-8), colony-stimulating factors (granulocyte-colony stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) and chemotactic factors (C-C motif chemokine 2 (CCL2)). Pro-inflammatory cytokines such as tumour necrosis factor (TNF), IL-1 and IL-6 are involved in the initiation and propagation of inflammatory signals. This inflammatory signalling stimulates monocytes and endothelial cells to initiate weak interactions and the subsequent rolling of the monocytes over the endothelial cells, mediated by adhesion molecules (such as vascular cell adhesion protein 1 (VCAM1) and E-selectin). Finally, monocytes migrate through the intercellular clefts between the endothelial cells to the underlying tissue. Macrophage-derived mediators and pro-inflammatory cytokines drive the transformation of quiescent fibroblasts into proliferative and matrix-synthesizing active myofibroblasts. The communication between inflammatory cells and resident fibroblasts occurs through direct cell–cell interactions and through paracrine signalling. Sustained activation of myofibroblasts produces structural extracellular matrix (ECM) proteins and matricellular proteins. Crosslinking of collagen molecules by matrix-crosslinking enzymes, such as lysyl oxidase (LOX), prevents the enzymatic degradation of collagen, leading to an increase in collagen content and stiffness. The dynamic alterations in the composition of the ECM and the prolonged deposition of ECM modulates cardiac function. Both canonical transforming growth factor-β (TGFβ)–mothers against decapentaplegic homologue 2 (SMAD2)–SMAD3 signalling and non-canonical TGFβ signalling through Rho-associated protein kinase (ROCK), extracellular-signal-regulated kinase (ERK) and p38 contribute to the development of pathological hypertrophy and fibrosis. Phosphorylation and activation of ERK, p38, Janus kinase (JAK) and signal transducer and activator of transcription (STAT) by activation of G-protein-coupled receptors also leads to the development of fibrosis. Activation of the calcineurin–nuclear factor of activated T cells (NFAT) pathway by cardiac transient receptor potential channels (TRPCs) also has a major role in fibrotic remodelling. Mineralocorticoid receptors

(MRs) are ligand-activated transcription factors that induce transcription of profibrotic genes upon aldosterone binding. AngII, angiotensin II; AT1R, angiotensin II receptor type 1; CITP, carboxy-terminal propeptide of procollagen type I; COL, collagen; CTGF, connective tissue growth factor; JNK, JUN N-terminal kinase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MEK, MAPK/ERK kinase; NF-κB, nuclear factor-κB; P, phosphate; PIIINP, amino-terminal propeptide of procollagen type III; sST2, soluble protein ST2; TGFBR1, transforming growth factor-β receptor type 1; TIMP, metalloproteinase inhibitor; YKL40, chitinase-3-like protein 1.

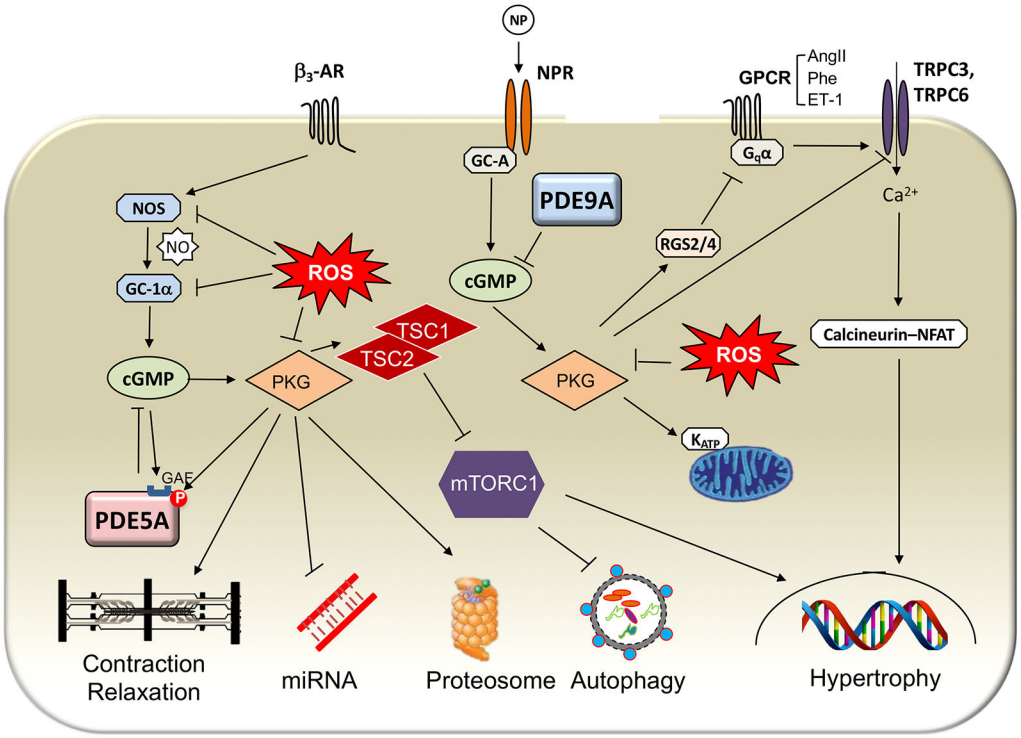

Fig. 3 |. Components of the cGMP–PKG signalling systems and their cellular effectors.

cGMP is generated by one of two different cyclases: guanylyl cyclase A (GC-A), which is coupled to the natriuretic peptide (NP) receptor (NPR), and soluble guanylyl cyclase (sGC), which is the target of nitric oxide (NO). Each relative pool of cGMP has a different primary targeting phosphodiesterase (PDE): PDE5A for GC-1α-derived cGMP and PDE9A for GC-A-derived cGMP. Increased cGMP levels in turn activate protein kinase G (PKG). PKG is the primary effector protein for many cGMP-mediated effects. Phosphorylation of sarcomeric proteins enhances relaxation and diastolic compliance and blunts β_3-adrenergic receptor (β_3-AR)-stimulated contractility. PKG stimulation, controlled by PDE5A but not PDE9A, reverses the abnormally altered expression of many microRNAs that is associated with hypertrophic remodelling induced by pressure stress. PKG activation also increases proteasome activity and stimulates autophagy, the latter coupled to the suppression of mechanistic target of rapamycin complex 1 (mTORC1) signalling. NP-stimulated PKG coupled to NPR-A (for which both atrial NP and B-type NP are ligands) has less of an effect on sarcomeres or microRNA levels, but augments autophagy. PKG stimulated by either NO or NPs activates regulator of G-protein signalling 2 (RGS2) and RGS4 to suppress G_q-coupled receptor signalling and phosphorylates transient receptor potential channel 3 (TRPC3) and TRPC6 to suppress hypertrophy and fibrosis. AngII, angiotensin II; ET-1, endothelin 1; GAF, GAF domain; GPCR, G-protein-coupled receptor; K_{ATP}, ATP-dependent K^+ channel; NFAT, nuclear factor of activated T cells; NOS, nitric oxide synthase; P, phosphate; Phe, phenylephrine; ROS, reactive oxygen species; TSC1, hamartin; TSC2, tuberin.

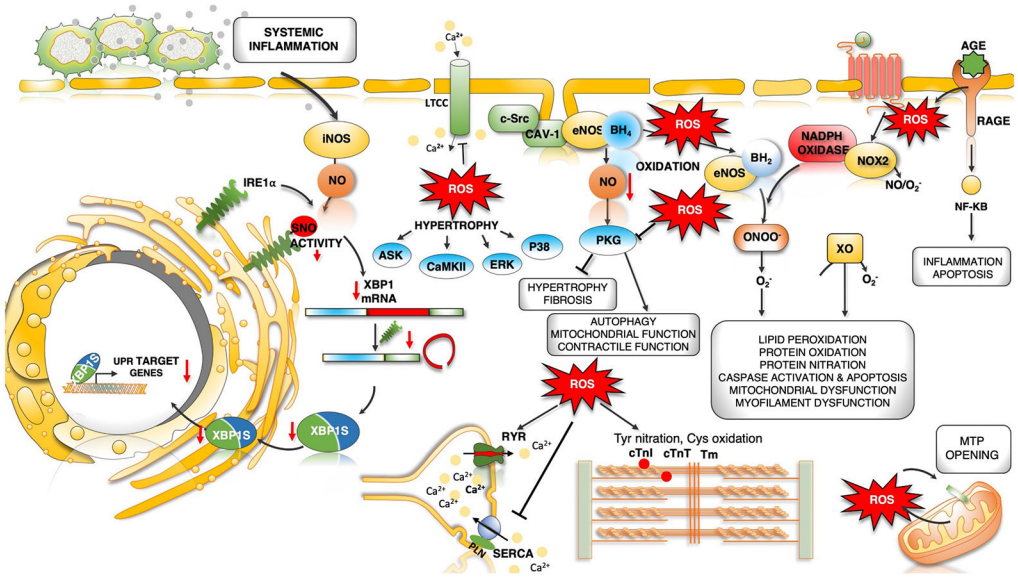

Fig. 4 |. Dysregulated oxidative and nitrosative stress in HFpEF pathogenesis.

Increased microvascular inflammation and pro-inflammatory cytokine levels result in increased expression of inducible nitric oxide synthase (NOS2) in cardiomyocytes. NOS2-derived nitric oxide (NO) mediates *S*-nitrosylation (SNO) of the unfolded protein response (UPR) regulator IRE1α, leading to a progressive decline in IRE1α-mediated generation of the spliced form of X-box-binding protein 1 (XBP1), known as XBP1s. Reduced XBP1s levels lead to decreased XBP1s-dependent expression of UPR target genes, compromised UPR and endoplasmic reticulum (ER) function, and prolonged ER stress. IRE1α activity and XBP1s levels are reduced in the hearts of patients with heart failure with preserved ejection fraction (HFpEF). Oxidative stress and increased reactive oxygen species (ROS) formation can directly modulate cardiac redox status by reacting with NO to decrease its bioavailability. Oxidative stress uncouples endothelial nitric oxide synthase (NOS3) by oxidation and depletion of its cofactor tetrahydrobiopterin (BH_4) to dihydrobiopterin (BH_2). NOS3-derived NO has antihypertrophic and antifibrotic effects primarily by activation of cGMP–protein kinase G (PKG) signalling. Uncoupled NOS3 generates oxidant species promoting protein tyrosine nitration, cysteine oxidation and lipid peroxidation, damaging proteins, lipids and DNA. Receptor-induced activation of NADPH oxidase 2 (NOX2) and mitochondrial redox mismatch are other major sources of ROS and stimulate mitochondrial transition pore (MTP) opening, Ca^{2+} overload and mitochondrial dysfunction. Advanced glycation end products (AGEs) that bind to cell surface receptors for AGEs (RAGEs) can stimulate NADPH oxidase, thereby increasing the production of ROS and aggravating inflammation by activation of the nuclear factor-κB (NF-κB) pathway. ROS can directly or indirectly activate various kinases, resulting in hypertrophy. Post-translational redox modifications of protein kinases (such as Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII), protein kinase A and PKG), sarcoplasmic reticulum (SR) proteins (ryanodine receptor 2 (RYR2) and sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2A (SERCA2A)) and myofilament proteins (cardiac troponin I (cTnI), cardiac troponin T (cTnT), tropomyosin (Tm) and cardiac myosin binding protein C can alter their activity and contribute to hypertrophy and altered excitation–contraction coupling. AngII,

angiotensin II; ASK, apoptosis signal-regulating kinase; AT1R, angiotensin II receptor type 1; CAV1, caveolin 1; ERK, extracellular-signal-regulated kinase; LTCC, L-type Ca^{2+} channel; O_2^-, superoxide anion; $ONOO^-$, peroxynitrite; PLN, cardiac phospholamban; SRC, proto-oncogene tyrosine-protein kinase SRC; XO, xanthine oxidoreductase.

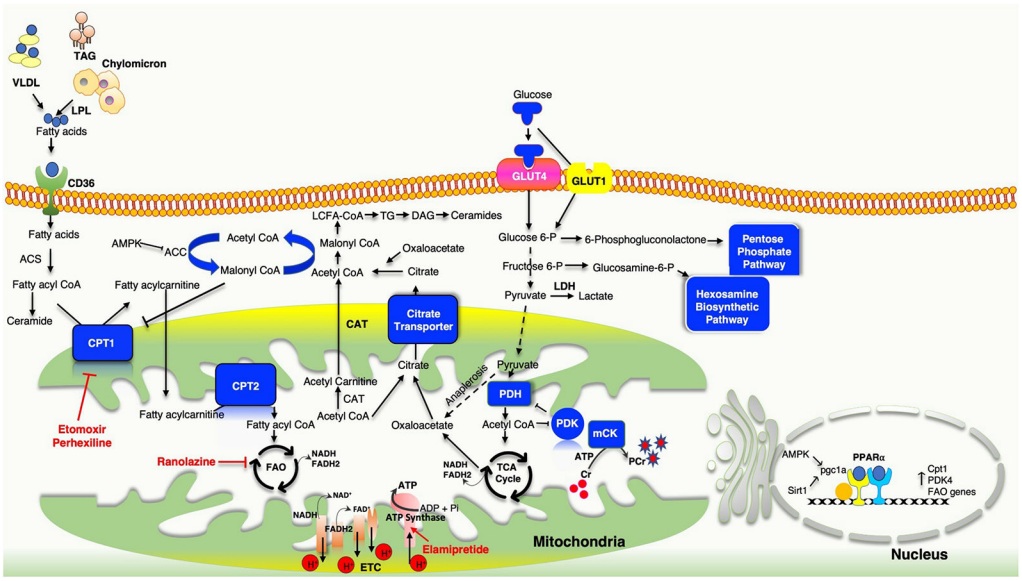

Fig. 5 |. Metabolic flexibility and HFpEF.

Heart failure involves alterations in multiple metabolic pathways that can alter mitochondrial ATP production and substrate utilization, and ultimately myocardial energy reserve and efficiency. Obesity, which is very common in patients with heart failure with preserved ejection fraction (HFpEF), induces systemic fatty acid oversupply from adipose tissue that is re-routed to peripheral organs, including the heart. Mismatch between cardiac fatty acid uptake and fatty acid β-oxidation (FAO) leads to intramyocardial accumulation of diglycerides and ceramides, uncoupling their oxidative phosphorylation. Hypoxia facilitates the metabolic shift towards glycolysis with a subsequent increase in lactate and pyruvate accumulation owing to impaired activity of pyruvate dehydrogenase (PDH). A compensatory increase in anaplerosis diverts the products of the glycolysis towards the hexosamine biosynthetic pathway and the pentose phosphate pathway. Several metabolism-modulating pharmaceuticals are being examined in HFpEF, as in other forms of heart failure. Ranolazine is a partial inhibitor of FAO, which reciprocally increases glucose oxidation and PDH activity. Etomoxir inhibits carnitine palmitoyl transferase 1 (CPT1), which controls the access of long-chain fatty acids (LCFAs) to the mitochondria for FAO. Elamipretide selectively targets the electron transport chain to increase energy efficiency. ACC, acetyl-CoA carboxylase; ACS, acetyl-CoA synthetase; AMPK, AMP-activated protein kinase; CAT, carnitine acyltransferase; CD36, fatty acid translocase; Cr, creatine; DAG, diacylglycerol; GLUT, glucose transporter; LDH, lactate dehydrogenase; LPL; lipoprotein lipase, mCK, muscle creatine kinase; PCr, phosphocreatine; PDK, pyruvate dehydrogenase kinase; PGC1α, peroxisome proliferator-activated receptor-γ coactivator 1α; P_i, inorganic phosphate; PPARα, peroxisome proliferator-activated receptor-α; SIRT1, NAD-dependent protein deacetylase sirtuin 1; TAG, triacylglycerol; TCA, tricarboxylic acid; TG, triglyceride; VLDL, very low density lipoprotein.

Table 1 |

Animal models of HFpEF

Animal Model	LVH	HTN	Obesity T2DM	Diastolic Dysfunction	Skeletal Muscle Abnl and/or Exercise Intolerance	Fluid overload >Lung wt	Improved by ACE/ARB
Dahl-salt sensitive rats	++	++	−	++	+	Not pre-HF	+/+
Spontaneously hypertensive rats	++	++	−	+	+	Not pre-HF	+/+
ZSF-1 rat	+	+	+	+	+	+	
Aortic constriction (mouse, rat)	+	−	−	+/−	ND	mild	+/+
Aldosterone Infusion (mouse, rat)	+	+	−	++	ND	mild	+
Ageing models (e.g. SAM-WD) mouse	Mild	−	+/−	+	+	−	+
L-Name + HFD, mouse	+	++	+	+	+	+	Not tested
db/db or ob/ob mice	+	+	+	+	+	ND	+
Aged dogs subjected to peri-nephritis-induced hypertension	+	+	−	+	ND	−	Not tested
Aortic Banded Cat	+	++	−	++	ND	+	+
DOCA and salt loaded pigs on HFD	+	+	+	+	+	ND	Not tested

Animal models that focus solely on LV pressure/volume overload such as the Dahl-salt sensitive or spontaneously hypertensive rat, aortic banded cat, or aldosterone infusion – generate principally cardiac disease such as hypertrophy, diastolic dysfunction, and fibrosis. Pure obesity models, such as the leptin or leptin receptor deficient models (db/db or ob/ob) generate marked obseity and some cardiac disease. Other models such as L-NAME+high fat diet (HFD) in mice, or the DOCA-HFD pig model, or the senescence accelerated mouse on western diet (SAM-WD) attempt to integrate both components. The latter two do not develop significant heart failure however, reflected by less increase in diastolic pressure and fluid accumulation in the lungs.

Table 2 |

Plasma biomarkers for HFpEF

Pathway	Biomarker	References
Inflammation	PAI-1, uPAR GDF-15 Pentraxin-3 vWF IL-1, IL-6, IL-16, IL-8 Heparin-binding EGF-like growth factor Platelet Growth Factor sTNFR1, sTNFR2, TRAIL-R2, TNF-alpha MCP-1 C-reactive protein PTX-3 CCL20 AGRP	29, 35, 285, 286, 287, 288
Remodeling/Fibrosis	sST2 Galectin-3 PIIINP ICTP Fibrinogen MMP-1, MMP-2, MMP-7, MMP-8, MMP-9, TIMP-1, TIMP-4	35, 286, 289
Renal function	UACR BUN Cystatin-C	285, 290
Hypertrophy	Natriuretic peptides, BNP, NT-pro BNP Endothelin 1 High Sensitivity Troponin I, C, or T Renin, Aldosterone/angiotensin II FGF-23, FGF-21 NEMO TIE2	35, 285, 286, 291 , 292
Vascular	FABP4 YKL40 OPG MPO Fas P-Selectin Tenascin-C Endostatin	35

PAI; Plasminogen activator inhibitor-1, uPAR; urokinase-type plasminogen activator receptor, GDF-15; Growth differentiation factor-15, vWF; von Willebrand factor, IL; Interleukin, EGF; Epidermal growth factor, sTNFR; soluble tumor necrosis factor receptors, TRAIL-R2; TNF-related apoptosis-inducing ligand receptor, TNF; Tumor necrosis factor, MCP; Monocyte chemoattractant protein-1, PTX; pentraxin 3, CCL20; C–C motif chemokine 20, AGRP; Agouti-related protein, sST2; soluble suppression of tumorigenecity 2, PIIINP; procollagen type III N-terminal propeptide, ICTP; collagen type I carboxy-terminal telopeptide, MMP; Matrix metalloproteinases , TIMP; Tissue inhibitors of metalloproteinases, UACR; urine albumin-to- creatinine ratio, BUN; blood urea nitrogen, BNP; Brian natriuretic peptide, ET1; Endothelin1, hs-TnC; high-sensitivity cardiac troponin, FGF; Fibroblast growth factor, NF-κ-B; nuclear factor kappa-light-chain-enhancer of activated B cells, NEMO; NF-κB essential modulator, TIE2; angiopoietin receptor TEK tyrosine kinase, FABP; fatty-acid-binding protein , YKL40; Chitinase 3-like 1, OPG; Osteoprotegerin, MPO; Myeloperoxidase

Table 3 |

Ongoing clinical trials in HFpEF

Status	Study Title	Interventions	Conditions
Pharmaceutical			
Active	DETERMINE-preserved	Dapagliflozin	HFpEF
Active	Developing Oral LT3 Therapy for Heart Failure - HFpEF	liothyronine	Low Triiodothyronine Syndrome
Active	(KNO3CK OUT HFPEF)	Drug: Potassium Nitrate (KNO3), Drug: Potassium Chloride (KCl)	HFpEF
Active	(EMPEROR-Preserved)	Empagliflozin	HFpEF
Active	Oral Nitrite in Patients With Pulmonary Hypertension and Heart Failure With Preserved Ejection Fraction	Sodium Nitrite	HFpEF and secondary PH
Active	Metformin for Pulmonary Hypertension HFpEF	Metformin	HFpEF with Secondary PH
Active	AZD9977 and Spironolactone on Serum Potassium	AZD9977: Spironolactone	HFpEF
Active	Open-Label Rollover Study of Levosimendan in PH-HFpEF Patients	Levosimendan 2.5 mg/ml Injectable Solution	HFpEF with PH
Active	The Efficacy and Safety of Pirfenidone in HF and Preserved Left Ventricular Ejection Fraction	Pirfenidone	HFpEF
Recruiting	Safety and Tolerability of LCZ696 in Subjects Who Completed PARAGON-HF in Japan.	Drug: LCZ696	HFpEF
Recruiting	Effect AZD4831 in Japanese and Chinese Healthy Volunteers	Drug: AZD4831	HFpEF
Recruiting	Transthyretin Cardiac Amyloidosis in HFpEF	Drug: 99mTc-PYP	HFpEF
Recruiting	Circulating NEP and NEP Inhibition Study in Heart Failure With Preserved Ejection Fraction	Drug: Entresto™ 49Mg-51 mg tablet	HFpEF
Recruiting	Effect of IV Iron in Patients With Heart Failure With Preserved Ejection Fraction	Drug: Ferric Carboxymaltose 50Mg/Ml Inj 15Ml	Iron-deficiency, HFpEF
Recruiting	Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure.	Dapagliflozin	HFpEF
Recruiting	MPO Inhibitor A_Zeneca for HFpEF	Oral Myeloperoxidase Inhibitor	HFpEF
Recruiting	Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction	Spironolactone	HFpEF
Recruiting	LCZ696 in Advanced LV Hypertrophy and HFpEF	Drug: LCZ 696 Drug: Valsartan	HFpEF with Essential Hypertension
Recruiting	A Study of Oral Nitrate in Adults With Pulmonary Hypertension With Heart Failure and Preserved Ejection Fraction	Drug: 15N Nitrate Drug: 14N Nitrate	HFpEF, PH
Recruiting	A Trial to Study BAY1753011 in Patients With Congestive Heart Failure	Drug: BAY 1753011 Other: Placebo BAY 1753011 Drug: Furosemide Other: Placebo Furosemide	HFrEF and HFpEF
Recruiting	Regression of Fibrosis & Reversal of Diastolic Dysfunction in HFPEF Patients Treated With Allogeneic CDCs	Biological: Allogeneic Derived Cells Biological: Placebo/Control Arm	HFpEF with Diastolic Dysfunction
Recruiting	Dapagliflozin in PRESERVED Ejection Fraction Heart Failure	Drug: Dapagliflozin 10Mg Oral Tablet	HFpEF

Status	Study Title	Interventions	Conditions
Pharmaceutical			
		Drug: Dapagliflozin matching placebo	
Recruiting	β-blockers Withdrawal in Patients With HFpEF and Chronotropic Incompetence: Effect on Functional Capacity (Preserve-HR)	Drug: Controlled withdrawal of beta-blockers	HFpEF, Chronotropic Incompetence
Recruiting	Cell Therapy in HFpEF	Cell Therapy	HFpEF
Recruiting	INABLE-Training	Drug: Oral Sodium Nitrite Device: Accelerometer Other: Cardiac Exercise Training	HFpEF
Recruiting	Changes in NT-proBNP and Outcomes, Safety, and Tolerability in HFpEF Patients With Acute Decompensated Heart Failure (ADHF) Who Have Been Stabilized During Hospitalization and Initiated In-hospital or Within 30 Days Post-discharge (PARAGLIDE-HF) Link	Drug: sacubitril/valsartan Drug: valsartan	HFpEF
Not yet recruiting	Effect of Dapagliflozin Plus Low Dose Pioglitazone on Hospitalization Rate in Patients With HF and HFpEF	Pioglitazone Plus dapagliffiozin	HFpEF and HFrEF
Enrolling by invitation	A Long Term Study to Find Out if Macitentan is an Effective and Safe Treatment for Patients With Heart Failure With Preserved Ejection Fraction and Pulmonary Vascular Disease (SERENADE OL)	Drug: macitentan 10 mg	HFpEF with Pulmonary Vascular Disease
Completed	A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients	Drug: sacubitril/valsartan Drug: Enalapril Drug: Valsartan	HFpEF
Completed	The Efficacy and Safety of Pirfenidone in Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction	Drug: Pirfenidone Drug: Placebo	HFpEF
Terminated	Oral Treprostinil in Subjects With Pulmonary Hypertension Associated With Heart Failure With Preserved Ejection Fraction	Drug: Oral treprostinil Drug: Placebo	HFpEF with PH
Not yet recruiting	Carvedilol SR Study for Biomarkers From Blood and Urine and Safety of in Patients With Heart Failure With Preserved Ejection Fraction	HFpEF	Carvedilol SR
Not yet recruiting	Study of Verinurad in Heart Failure With Preserved Ejection Fraction	HFpEF	Drug: Verinurad Drug: Allopurinol Drug: Placebo for verinurad Drug: Placebo for allopurinol
Devices			
Recruiting	CORolla® TAA for Heart Failure With Preserved Ejection Fraction (HFpEF) and Diastolic Dysfunction (DD)	Diastolic Heart Failure, Diastolic Dysfunction	Device: CORolla™ TAA device
Recruiting	Endovascular GSN Ablation in Subjects With HFpEF	HFpEF	Device: Ablation
Recruiting	CCM in Heart Failure with Preserved Ejection Fraction	Heart Failure, Diastolic	Device: Optimizer SMART
Recruiting	Efficacy Study of Pacemakers to Treat Slow Heart Rate in Patients With Heart Failure	Heart Failure, Diastolic, Chronotropic Incompetence	Device: Rate adaptive atrial pacing using a dual-chamber pacemaker Device: Pacemaker system will be implanted but set to Pacing Off.
Active Not Recruiting	REDUCE LAP-HF RANDOMIZED TRIAL I	Device: Inter-Atrial Shunt Device Other: Intracardiac Echo	Heart Failure

Status	Study Title	Interventions	Conditions
Pharmaceutical			
Not yet recruiting	3-Month Home-based Training With Whole Body Vibration (WBV) Device in Patients With Heart Failure and Preserved Ejection Fraction (GALILEO-HFpEF-HOME) (GALILEOHOME)	HFpEF	Device: Group 1 GALILEO WBV Other: Group 2 Control
Recruiting	REDUCE LAP-HF TRIAL II	Device: VitalPatch Biosensor Device: DynaPort Move Monitor	Heart Failure
Recruiting	Reducing Lung CongestIon Symptoms in Advanced Heart Failure	Device: V-Wave Interatrial Shunt Other: Control	Heart Failure
Recruiting	Hemodynamic-GUIDEd Management of Heart Failure	Device: CardioMEMS™ HF System	Heart Failure Heart Failure, Systolic Heart Failure, Diastolic