Impact of Comorbidities on Myocardial Remodeling and Dysfunction In Heart Failure with Preserved Ejection Fraction

L. van Heerebeek^{1,2*} and Walter J. Paulus²

¹Institute for Cardiovascular Research VU (ICaR-VU), The Netherlands

²VU University Medical Center Amsterdam, Amsterdam, The Netherlands

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***Corresponding author:** Loek van Heerebeek, Department of Physiology, Institute for Cardiovascular Research VU (ICaR-VU), VU University Medical Center Amsterdam, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands, Tel: 31-20-4448110; Fax: 31-20-4448255; E-mail: l.vanheerebeek@vumc.nl

Abstract

Heart failure (HF) with preserved ejection (HFpEF) is widely prevalent and associated with poor outcome and incompletely understood pathophysiology. In contrast to HF with reduced EF (HFrEF), modern HF pharmacotherapy did not improve outcome in HFpEF, which emphasizes the urgent need to elucidate responsible pathogenetic mechanisms in HFpEF. Over the last decennium, myocardial structure, cardiomyocyte function and intramyocardial signaling were shown to be specifically altered in HFpEF. Myocardial remodelling and dysfunction in HFpEF comprises myocardial hypertrophy and fibrosis and increased cardiomyocyte stiffness. Increased cardiomyocyte stiffness in HFpEF importantly contributes to high left ventricular (LV) diastolic stiffness and results from specific changes in transcriptional and posttranslational modifications of the giant elastic sarcomeric protein, titin. Increased systemic vascular inflammation, endothelial dysfunction and oxidative stress resulting in reduced nitric oxide (NO) bioavailability appear importantly involved in increased diastolic LV stiffness and adverse remodelling in HFpEF. Recently, a new paradigm for HFpEF was proposed, which suggests that prevalent comorbidities, such as overweight/obesity, diabetes, hypertension, chronic pulmonary obstructive disease, anemia and chronic kidney dysfunction drive myocardial dysfunction and remodelling through coronary microvascular endothelial inflammation. Additional demographic characteristics in HFpEF are older age and female predominance, which could contribute to maladaptive cardiovascular structural and functional changes in a synergistic manner with the prevalent comorbidities. Although HFpEF is associated with more impaired cardiovascular abnormalities and worse outcome beyond the level explainable by comorbidities alone, the rationale for an important involvement of noncardiac comorbidities in myocardial dysfunction and remodeling in HFpEF seems plausible. In the following review, this rationale of an important involvement of comorbidities in HFpEF pathophysiology is further addressed in light of the proposed new HFpEF paradigm.

Keywords: Heart failure; Endothelial dysfunction; Comorbidities; Nitric oxide; Oxidative stress

Introduction

Heart failure with preserved ejection fraction (HFpEF) currently accounts for 50 % of all HF patients, and its prevalence relative to HF with reduced EF (HFrEF) is rising at a rate of approximately 1 % per year [1,2]. Patients with HFpEF have a poor prognosis, with only slight lower mortality rates than patients with HFrEF [1,3]. According to current criteria, HFpEF is diagnosed in the presence of signs and/or symptoms of HF, preserved systolic left ventricular (LV) function, with a LV ejection fraction (LVEF) > 50% and LV end-diastolic volume index (LVEDVI) < 97 ml/m² and evidence of diastolic LV dysfunction [4]. Conversely, HFrEF is diagnosed in the presence of HF signs and/or symptoms and reduced LVEF [4]. In contrast to HFrEF, modern HF pharmacotherapy did not improve outcome in HFpEF, which is attributed to the incomplete understanding of HFpEF pathophysiology [5,6]. Furthermore, diastolic LV dysfunction is not the sole abnormality in HFpEF and other mechanisms were also found to contribute, such as systolic LV dysfunction [7-9], ventricular-vascular stiffening [10-13], impaired systemic vasodilatory reserve [13-15], chronotropic incompetence [12-14], and pulmonary hypertension [16,17]. HFpEF patients are generally older, more often female and have high prevalence of noncardiac comorbidities, such as overweight/obesity, hypertension, diabetes (DM), chronic obstructive pulmonary disease (COPD), anemia and chronic kidney disease [18-21]. Systemic inflammation and endothelial dysfunction are important hallmarks of these comorbidities. Recently, a new paradigm of HFpEF was suggested, which proposes that comorbidities drive myocardial dysfunction and remodelling in HFpEF through coronary microvascular endothelial inflammation [22]. This review will discuss the relevance of comorbidities for HFpEF in light of this new paradigm.

Myocardial Remodeling and Dysfunction in HFpEF

Diastolic dysfunction in HFpEF represents the dominant

abnormality and is evident from slow LV relaxation and elevated diastolic LV stiffness, which increase diastolic filling pressures and limit cardiac performance at rest, during atrial pacing and exercise [15,23,24]. Baseline characteristics of HFpEF patients in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) [25] and Irbesartan in Heart Failure with Preserved Ejection Fraction (I-preserve) [26] trials demonstrate structural cardiac remodeling in many HFpEF patients including concentric LV remodeling and hypertrophy (59-77%) and left atrial (LA) dilatation (59-66%). At the microscopic level, HFpEF patients had increased cardiomyocyte diameter and extracellular matrix (ECM) changes [27]. In HFpEF, both qualitative and quantitative ECM changes contribute to increased myocardial diastolic stiffness, such as increased deposition of interstitial collagen, higher expression of collagen type 1 and collagen crosslinking [28-30]. In addition to myocardial fibrosis, increased cardiomyocyte stiffness also importantly contributes to high diastolic LV stiffness in HFpEF [27,31,32]. Cardiomyocyte stiffness is mainly determined by the elastic sarcomeric protein titin, which functions as a bidirectional spring, responsible for early diastolic recoil and late diastolic distensibility [32]. Titin-based cardiomyocyte stiffness results from dynamic changes in expression of stiff (N2B) and compliant (N2BA) isoforms and from isoform phosphorylation status [32]. Phosphorylation of titin by protein kinase A (PKA) [33] and PKG [34] increase its compliance (Figure 1), in contrast to PKC [35], which makes it less compliant. Various studies, which procured endomyocardial tissue from HFpEF, HFrEF and aortic stenosis (AS) patients demonstrated significantly stiffer cardiomyocytes in HFpEF than in HFrEF and AS patients [36,37]. This increased cardiomyocyte stiffness was related to increased expression of the stiff titin N2B isoform relative to HFrEF, and to reduced phosphorylation of titin. Hypophosphorylation of titin resulted from lower myocardial PKG activity and reduced myocardial cyclic guanosine monophosphate (cGMP) concentration in HFpEF compared to HFrEF and AS [37] (Figure 2A). Myocardial PKG plays a pivotal role in normal cardiovascular physiology and PKG phosphorylates a vast number of target proteins, exerting a wide range of downstream effects, such as inhibition of the L-type calcium channel, enhancement of intracellular diastolic calcium reuptake through phosphorylation of phospholamban (PLB), suppression of hypertrophic signaling through inhibition of G-protein coupled receptors and the transient receptor potential canonical channel, inhibition of ischemia-reperfusion injury through phosphorylation of the ATP-sensitive potassium channel and stimulation of LV relaxation and distensibility by phosphorylation of troponin I (TnI) and titin (Figure 1) [38]. Myocardial cGMP-PKG signaling is coupled upstream to stimulation by two distinct pathways including the natriuretic peptide (NP)-particulate guanylate cyclase (pGC) pathway and the nitric oxide (NO)-soluble GC (sGC) pathway [38] (Figure 1). Although myocardial brain-type natriuretic peptide (BNP) expression is lower in HFpEF than in HFrEF, the significantly reduced myocardial cGMP-PKG activity in HFpEF, compared to HFrEF and AS could not be explained by lower myocardial BNP expression alone [37]. Because myocardial nitrotyrosine expression, which is an indirect marker of nitrosative/oxidative

stress, was 4 times higher in HFpEF than in HFrEF and AS, reduced myocardial NO bioavailability was suggested to underlie the downregulation of myocardial cGMP-PKG signaling in HFpEF [37] (Figure 2B). Increased nitrosative/oxidative stress in HFpEF was inferred from the higher prevalence in HFpEF of comorbidities as hypertension, obesity and DM, which are known to elicit inflammatory responses. Recent findings indeed demonstrate an important role for endothelial dysfunction [13,14,39] and inflammation [40] in HFpEF pathophysiology.

Endothelial Dysfunction

The vascular endothelium produces and secretes numerous compounds that regulate a variety of physiological functions, including vasomotor tone, coagulation, inflammation, permeability and cell adhesion [41]. NO is considered the key molecule in maintaining adequate vasodilatory function. Endothelial dysfunction is characterized by impaired vasomotor response, cell proliferation, platelet adhesion/aggregation, vascular permeability and leucocyte-endothelial interactions that participate in vascular inflammation [42]. Recent studies demonstrated a high prevalence of endothelial dysfunction in HFpEF patients, which was related to reduced exercise capacity [13] and worse outcome [39]. This prognostic implication suggests a causal involvement of endothelial dysfunction in HFpEF [43]. Endothelial dysfunction in HFpEF is also evident from reduced aortic distensibility [44], higher arterial load [45] and deficient vasodilatory reserve [13,14], which contribute to reduced exercise tolerance. Probably because of upregulation of endothelial nitric oxide synthase, this response was reversed following an exercise training programme [46], which improved both exercise capacity and diastolic LV dysfunction [47].

Inflammation

Myocardial inflammation was shown to contribute to ECM changes and diastolic dysfunction in HFpEF [40]. In an endomyocardial biopsy study, when compared with controls, HFpEF patients had increased inflammatory cell transforming growth factor ($\text{TGF-}\beta$) expression, which induces transdifferentiation of fibroblasts into myofibroblasts, with increased production of collagen and decreased expression of matrix metalloproteinase type 1 (MMP1), whereas both myocardial collagen and the amount of inflammatory cells correlated with diastolic LV dysfunction [40]. As compared with asymptomatic hypertensives, HFpEF patients had increased circulating biomarkers of inflammation (interleukin 6 (IL6), IL8, monocyte chemoattractant protein 1 (MCP1), of collagen metabolism (aminoterminal propeptide of collagen III, carboxy-terminal telopeptide of collagen I), and of ECM turnover (MMP2 and MMP9) [48]. In addition, MMP9, tissue inhibitor of matrix metalloproteinases type 1 (TIMP1), and the ratio of MMP9/TIMP1 correctly identified patients with a high left atrial volume index, which reflects chronic diastolic LV dysfunction [48]. Moreover, the Health ABC study reported inflammatory biomarkers such as IL6 and tumor necrosis factor α (TNF- α) to be strongly associated with incident HFpEF, but not incident HFrEF in elderly patients [49]. Serum IL16 levels were specifically elevated in HFpEF

patients compared to HFrEF and controls and associated with diastolic LV dysfunction [50]. Enhanced cardiac expression of IL16 in transgenic mice induced cardiac fibrosis and LV myocardial stiffening accompanied by increased macrophage infiltration [50]. Recently, galectin-3, a β -galactoside-binding member of the lectin family, was found to reflect inflammatory and fibrotic processes and predicted all-cause mortality and HF hospitalizations [51] especially in HFpEF patients [52].

New Paradigm of HFpEF

In the new paradigm of HFpEF, comorbidities were

proposed to contribute to high diastolic LV stiffness through induction of systemic inflammation and oxidative stress, which elicits coronary microvascular endothelial dysfunction and downregulation of myocardial NO-cGMP-PKG signaling (Figure 3). This chain of events results in increased cardiomyocyte stiffness through hypophosphorylation of titin, cardiomyocyte hypertrophy and enhanced myocardial interstitial fibrosis [22]. Prevalent noncardiac comorbidities in HFpEF share systemic inflammation and oxidative stress as a common feature and could therefore be implicated in myocardial dysfunction and remodeling in HFpEF. Therefore, an indepth overview of clinical and pathological

Figure 2: Myocardial PKG activity, cGMP concentration and nitrotyrosine expression.

A: Lower myocardial PKG activity in HFpEF (DHF) than in HFrEF (SHF) and aortic stenosis (AS) patients. B: Higher myocardial nitrotyrosine levels, indicative of nitrosative/oxidative stress in HFpEF (DHF) than in HFrEF (SHF) or AS. Reproduced with permission from van Heerebeek L et al. *Circulation* 2012; 126:830-839.

characteristics of noncardiac comorbidities relevant for HFpEF pathophysiology will be provided in the next paragraphs.

Comorbidities in HFpEF

Noncardiac comorbidities are highly prevalent in HFpEF [21], which increase hospitalization risk, with more non-HF admissions compared with HFrEF [21]. The most important are overweight/obesity, hypertension, DM, COPD, anemia and chronic kidney disease. However, HFpEF does not simply represent a collection of comorbidities as HFpEF patients exhibit a worse outcome compared with patients with various comorbidities [53]. Mortality rates were much higher in HFpEF patients (53 to 76 per 1,000 patient-years) than in non-HFpEF patients with similar age, sex and comorbidity distribution (11 to 47 per 1,000 patient-years) [53]. A comparative analysis of HFpEF patients, age- and sex-matched health controls and hypertensive controls demonstrated more cardiovascular abnormalities in HFpEF patients than in the other groups, even after accounting for age, sex, body size and comorbidities [54]. These findings support additional deterioration in HFpEF by HF-related mechanisms such as neuroendocrine activation [55] and lack of high energy phosphates [12]. Nevertheless, noncardiac comorbidities can adversely affect myocardial function and remodeling and likely play a role in HFpEF pathophysiology.

Increased age

Half of all HF diagnoses and 90% of all HF deaths occur in

patients aged above 70 years while HF incidence doubles with each decade of life [56]. Ageing is associated with various abnormalities in cardiovascular structure and function [57]. The prevalence of LV hypertrophy and HF increases dramatically with age [58]. Increased LV wall thickness has been attributed to increased myocardial collagen deposition and cardiomyocyte size [59]. At the subcellular level, ageing is accompanied by disturbed diastolic calcium handling, β -adrenergic signaling and mitochondrial dysfunction, which impair diastolic function causing progressive slowing of early LV diastolic filling rate, whereas LVEF is preserved [60]. Despite LVEDVI being unchanged or even greater at exercise, there is an age-associated deficit in the ability to reduce LV end-systolic volume index, which compromises LV stroke volume reserve with exercise [57]. Maximum cardiac output reserve also decreases with ageing due to chronotropic incompetence with a reduction in peak heart rate of 30% between 20 and 85 years of age [61]. The inability to enhance contractility and heart rate response with exercise have been allocated to disturbed autonomic control and diminished efficiency of post-synaptic β -adrenergic signaling [62]. Furthermore, ageing is associated with arterial stiffening, widening of pulse pressure and endothelial dysfunction, which are risk factors for future cardiovascular events [60]. Increased arterial stiffness is governed by structural changes in the vascular wall, such as calcification, increased collagen content and reduced elastin and by endothelial regulation of vascular

Figure 3: Comorbidities drive myocardial dysfunction and remodeling in HFpEF.

Comorbidities induce a systemic proinflammatory state with elevated plasma levels of in IL-6, TNF- α , sST2 and pentraxin 3. Coronary microvascular endothelial cells reactively produce ROS, VCAM and E-selectin. Production of ROS leads to formation of peroxynitrite (ONOO⁻) and reduced NO bioavailability, both of which lower sGC activity in adjacent cardiomyocytes. Lower sGC activity decreases cGMP concentration and PKG activity. Low PKG activity raises resting tension (F_{passive}) of cardiomyocytes because of hypophosphorylation of titin and removes the brake on prohypertrophic stimuli inducing cardiomyocyte hypertrophy. VCAM and E-selectin expression in endothelial cells favours migration into the subendothelium of monocytes. These monocytes release TGF- β . The latter stimulates conversion of fibroblasts to myofibroblasts, which deposit collagen in the interstitial space. Modified with permission from Paulus WJ et al. J Am Coll Cardiol 2013;62:263-271.

smooth muscle tone [63]. Arterial stiffness also explains isolated systolic hypertension and widening of pulse pressure, which are frequently encountered in the elderly, being associated with increased risk of cardiovascular events [64]. Combined ventricular-vascular stiffening causes labile blood pressure swings with relatively minor changes in pre- and afterload [11]. Endothelial dysfunction importantly contributes to vascular stiffening and age-associated enhanced endothelial expression of adhesion molecules and inflammatory mediators impair NO-bioavailability [57]. Increased oxidative stress and activation of the renin-angiotensin-aldosterone system (RAAS) play an important role in age-related arterial stiffening and endothelial dysfunction [57]. Conversely, physical exercise, which improves endothelial dysfunction, was found to preserve LV compliance in elderly athletes compared to sedentary seniors [65]. As a result of coronary microvascular endothelial inflammation, the vasodilator response of the coronary microvascular bed to acetylcholine was reduced in HFpEF, which correlated with

diastolic LV dysfunction [66]. Similar paracrine endocardial-myocardial interactions have previously already been reported [67].

Female gender

HFpEF patients are more likely to be female [1,2,18-20], whereas female HFpEF patients tend to have a better outcome than male HFpEF patients [68]. In the I-PRESERVE trial, women with HFpEF were older and had higher prevalence of obesity, hypertension and chronic kidney disease and lower prevalence of ischemic heart disease compared to men [68]. Obesity and DM carry a greater risk in women and inhibit or impair myocardial metabolism more severely than in men [69,70]. Gender differences also exist for cardiovascular structural and functional remodeling as women more frequently have concentric remodeling, smaller LV diastolic chamber volumes, higher EF and increased systolic and diastolic LV stiffness [71]. Furthermore, women have higher pulsatile arterial loading and increased age-dependent vascular

Figure 4: Therapeutic strategies to upregulate myocardial cGMP-PKG signaling.

NO, nitric oxide; sGC, soluble guanylate cyclase; NEP, neutral endopeptidase; pGC, particulate guanylate cyclase; PKG, protein kinase G; PDE5, phosphodiesterase-5; cGMP, cyclic guanylate monophosphate.

stiffening compared to men [71]. The impact of ageing and of gender difference was nicely demonstrated in a longitudinal community based study, which compared systolic and diastolic ventricular stiffness and arterial stiffness at baseline and after 4 years follow up. Despite effective treatment of hypertension, regression of LV mass and reduction in arterial load, LV systolic and diastolic stiffness increased over 4 years in patients with and without cardiovascular disease, which were most pronounced in women [72]. Estrogens exert several cardiovascular protective effects, including inhibition of RAAS activation and myocardial fibrosis, stimulation of NO bioavailability and mitochondrial biogenesis and regulation of cardiomyocyte calcium handling [73]. The underlying mechanisms for maladaptive cardiovascular structural and functional remodeling in elderly women are incompletely understood, but declining estrogen levels or reduced sensitivity of estrogen-based signaling could be involved.

COPD, Anemia and Renal failure

Reduced forced expiratory volume in one second in COPD independently predicts incident HF, which was attributed to the low grade systemic inflammation present in COPD [74]. COPD is both a premorbid identifier of HFpEF [75] and a contributor to HFpEF mortality [21]. In a population-based study, greater severity of COPD was linearly related to impaired LV filling, reduced stroke volume and lower cardiac output without changes in EF [76]. Anemia is more prevalent in HFpEF than in HFReEF patients [77] and associated with increased risk of HF hospitalization [78] and overall mortality [79]. Inflammation importantly contributes to anemia in HF [80], through impaired production of

erythropoietin and causing bone marrow dysfunction [81]. The presence of anemia is frequently accompanied by iron deficiency [82]. In HF with or without anemia, iron deficiency contributes to immune responses and oxidative stress [83]. Chronic kidney disease is present in approximately 30-40% of HF patients and is an important predictor of mortality [84]. HF and chronic renal failure frequently co-exist, which can be related to common risk factors, such as hypertension, diabetes and atherosclerosis, but also to common pathogenic mechanisms such as neurohumoral activation, inflammation and oxidative stress [85].

Hypertension

The prevalence of arterial hypertension in HFpEF patients amounts approximately 60-88% [1,86-89]. The risk of developing HF after adjusting for age and other risk factors is approximately 2-fold higher in hypertensive men and 3-fold higher in hypertensive women than in normotensive persons [90]. In a population-based European sample (n=1274), arterial hypertension was shown to be an independent predictor of diastolic abnormalities [91]. Adverse cardiovascular effects of hypertension include LV hypertrophy, myocardial fibrosis and elevated arterial stiffness. Elevated arterial stiffness increases myocardial afterload, which results in impaired LV relaxation and increased LV filling pressures and oxygen consumption [92]. In hypertensive patients, markers of fibrosis related to asymptomatic diastolic dysfunction [93] and myocardial collagen turnover was greater in patients with more severe diastolic dysfunction [28]. Angiotensin II (AngII) has been shown to induce MCP1 expression in macrophages and upregulate TGF- β in cardiomyocytes and fi-

broblasts in animal models of pressure overload, suggesting that activation of the RAAS could precede the onset of inflammation and fibrosis in hypertensive HF [94]. Although arterial hypertension is usually perceived to induce HFpEF through myocardial afterload excess and LV hypertrophy [95], this paradigm was recently questioned [22]. In the Valsartan in Diastolic Dysfunction (VALIDD) trial only 3% of hypertensives had significant LV hypertrophy despite all having diastolic LV dysfunction [96]. In all HFpEF registries and large outcome trials [2,18,89], arterial hypertension in HFpEF consists of elevated systolic pressure (± 148 mmHg) but normal diastolic pressure (± 83 mmHg). In HFpEF, LV cavity dimensions are small and especially in the presence of LV hypertrophy, the LV operates at a favorable Laplace relationship. LV systolic wall stress therefore remains low, despite elevated LV systolic pressure [97]. Conversely, inflammation, oxidative stress and endothelial dysfunction are importantly involved in hypertension [98,99]. Endothelial dysfunction in hypertensive patients was associated with increased plasma levels of TNF- α , IL6, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, C-reactive protein (CRP) and the von Willebrand factor, which is a marker of endothelial activation [99]. Markers of inflammation (urinary albumin, CRP, TNF- α , and TGF- β) were independently associated with asymptomatic diastolic dysfunction [100]. High circulating IL6, TNF- α , IL8 and MCP1 were detected in a cross-sectional study of 275 stable hypertensive patients with or without HFpEF [48]. In salt sensitive hypertension, high salt intake leads to systemic oxidative stress [101] possibly because of renal production of proinflammatory cytokines [102]. The RAAS is a major activator of NADPH oxidase and reactive oxygen species (ROS) production and increasing evidence reveals that the RAAS is importantly involved in linking obesity, metabolic syndrome, insulin resistance (IR), chronic kidney disease and hypertension [103]. Elevations in AngII and aldosterone have been shown to impair systemic insulin metabolic signaling that leads to endothelial dysfunction and myocardial functional abnormalities [103,104]. Some population studies and outcome trials observed a larger contribution to HFpEF development of metabolic comorbidities than of arterial hypertension. Hypertensive patients exhibit more frequent impairments of insulin metabolic signaling, dyslipidemia, microalbuminuria and obesity [105]. In the MONICA registry, LA enlargement was strongly related to obesity, mildly related to age and unrelated to arterial hypertension [106].

Metabolic risk factors

HFpEF patients demonstrate a high prevalence of obesity and DM type II (DMII) [18-21,89]. Obesity and DMII are strongly related to IR and the metabolic syndrome (a constellation of cardiovascular risk factors, including obesity, hypertension, IR, hyperglycemia, dyslipidemia, microalbuminuria and hypercoagulability) [107,108]. The prevalence of obesity, IR, DMII and metabolic syndrome increases rapidly and is expected to reach pandemic proportions in the next few decades [107], while these metabolic risk factors have all been prospectively identified as precursors of incident HF [69,109-111] and are independently associated with early development of diastolic LV dysfunction [112-115]. The frequent clustering of these

metabolic risk factors causes synergistic adverse effects on myocardial structure and function [107,108]. Furthermore, obesity, DMII and IR can have direct adverse effects on myocardial structure and function independently of common confounders as hypertension or coronary artery disease, which has been referred to as "obesity" [116], "diabetic" [117] or "insulin-resistant" [118] cardiomyopathy. Adverse myocardial structural and functional changes induced by obesity, DMII and IR include myocardial hypertrophy and fibrosis [119-121], reduced myocardial energetic reserve [122-124], impaired myocardial relaxation [115,125] and increased diastolic LV [72] and cardiomyocyte stiffness [126]. Metabolic risk factors are strongly associated with myocardial and systemic inflammation, oxidative stress and endothelial dysfunction [116-118], which importantly contribute to myocardial dysfunction and remodeling and result in downregulation of NO-cGMP-PKG signaling [127,128].

Overweight/Obesity

Obesity is becoming a global epidemic and currently 70% of US adults are overweight or obese [129]. Obesity, defined as a body mass index (BMI) ≥ 30 kg/m² and overweight (BMI: 25.0-29.9 kg/m²) are independent risk factors for cardiovascular morbidity and mortality [130] and obesity doubles the risk of HF [69,131] and DMII [132]. For each one unit increment in BMI, the risk of HF is increased by 7% in women and 5% in men [69]. In HFpEF, obesity also contributes to mortality as evident from the U-shaped relation between BMI and mortality [133]. Obesity induces maladaptive cardiac structural and functional changes. In a large population-based study, cardiac magnetic resonance imaging demonstrated that obesity was associated with concentric LV remodeling, increased LV mass/volume ratio, preserved LVEF [121,134] and LA dilatation [106]. Overweight and obesity are also associated with diastolic LV dysfunction independent of LV mass and associated risk factors [115]. Impaired myocardial relaxation results from obesity-induced myocardial mitochondrial dysfunction, lipotoxicity, uncoupled oxidative phosphorylation and disturbed cardiomyocyte calcium handling [135]. Compared to normal weight subjects, obese individuals had impaired myocardial energetics (phosphocreatine/ATP ratio) and diastolic filling rate at rest, which further deteriorated after inotropic stress [123]. Myocardial blood flow, as measured by PET, was significantly reduced in obese postmenopausal women, which was negatively correlated with waist/hip ratio [136]. Furthermore, in a comparative study including lean, overweight and obese subjects, although similar at rest, myocardial blood flow was significantly reduced in obese patients after cold pressor test - or dipyridamole-induced vasodilation [137]. Endothelial dysfunction in obesity is prevalent and caused by activation of pro-inflammatory cytokines and increased oxidative stress [137-139]. In a rodent experimental model of obesity and IR, NO bioavailability was reduced resulting in a downregulation of cGMP-PKG signaling in vascular smooth muscle cells [140]. Increased lipid deposition in adipocytes leads to the production of proinflammatory cytokines and adipokines including TNF- α , IL6, leptin and resistin, ultimately resulting in recruitment of monocytes and stimulation of monocyte differentiation into macrophages [138,141]. Adiponectin is the most abundant adipokine secreted by adipo-

cytes and couples the regulation of insulin sensitivity with energy metabolism [142]. Decreased plasma adiponectin levels are observed in patients with obesity, DMII, hypertension and metabolic syndrome and are significantly associated with low-level chronic inflammatory conditions [143]. Adiponectin also stimulates endothelial NO production [144] and has anti-inflammatory properties [145]. Approximately 30% of obese individuals are free from IR and do not manifest the panoply of cardiovascular diseases usually observed in the obese [146]. The distribution pattern of fat deposition seems crucial in this regard with visceral fat being more pathogenic than subcutaneous fat. Abdominal rather than subcutaneous, fat releases pro-inflammatory cytokines and adipokines, causing low-grade systemic inflammation, increased circulating endothelial adhesion molecules and endothelial dysfunction [147]. In subjects with normal BMI, abdominal fat distribution was associated with impaired systolic and diastolic function, increased myocardial fibrosis markers, impaired insulin sensitivity and proinflammatory activation [148]. Excess visceral fat and IR, but not general adiposity, were independently associated with incident prediabetes and DMII in obese adults [108,148]. Moreover, in mesenteric arteries of morbidly obese individuals, endothelial dysfunction was only observed in the presence of IR, which related to augmented mitochondrial superoxide production and increased systemic inflammation mediated by TNF- α [149]. In addition to its association with systemic vascular inflammation and endothelial dysfunction, IR results in compensatory hyperinsulinemia, which induces LV hypertrophy through activation of the insulin-like growth factor 1 receptors [118]. Furthermore, increased insulin levels in the setting of IR could also be important for titin-based cardiomyocyte stiffness as insulin stimulates a shift towards increased expression of the stiff titin N2B isoform [32].

Diabetes mellitus

The prevalence of DM, especially DMII, is steadily increasing and is expected to reach pandemic proportions in the next few decades [150]. DM is an important risk factor for HF and each 1% increase in hemoglobin A1c level was associated with an 8% increase in HF prevalence [118]. Diastolic LV diastolic dysfunction represents the first manifestation of myocardial involvement in DM [112,151]. HFpEF patients demonstrate a high prevalence of DMII ranging from 26-45% [1,2,18-21,86]. About 75% of normotensive, well controlled DMII patients without coronary artery disease show evidence of LV diastolic dysfunction with echocardiographic tissue Doppler imaging [112]. In a LV endomyocardial biopsy study, compared to non-diabetics, HFpEF patients with DM had higher diastolic LV stiffness and more severely hypertrophied and stiffer cardiomyocytes [126]. DM induces diastolic LV dysfunction through multiple mechanisms. DM changes the myocardial ECM as evident from enhanced interstitial and perivascular fibrosis, increased expression of collagen type I, and downregulation of collagen-degrading matrix metalloproteinases [119]. These pathologic mechanisms are mediated by hyperglycemia, oxidative stress and elevated aldosterone and AngII levels [119]. In addition to fibrosis, increased myocardial deposition of advanced glycation end-products (AGEs) also elevates diastolic LV stiffness in DM [120].

AGEs are modifications of proteins or lipids that become non-enzymatically glycosylated and oxidized after contact with aldose sugars with creation of nearly irreversible cross-links. Formation and accumulation of AGEs is enhanced by hyperglycemia, oxidative stress, aging and hypertension and represent an independent predictor of cardiac death and hospitalization [120]. Increased myocardial AGEs deposition was recently also shown in the myocardial microvasculature of diabetic HFpEF patients [126]. Myocardial AGE deposition augments diastolic LV stiffness by direct and indirect mechanisms, including formation of collagen cross-links, stimulation of collagen production and activation of AGE receptors. In addition, AGEs increase oxidative stress and proinflammatory cytokine release resulting in endothelial dysfunction and reduced NO bioavailability [120].

DM impairs myocardial bioenergetics through a shift from glucose utilization to increased fatty acid oxidation, which leads to myocardial lipotoxicity, uncoupling of mitochondrial oxidative phosphorylation and disturbed contraction/relaxation coupling [117,125]. Reduced high-energy phosphate metabolism was shown to parallel LV diastolic dysfunction in well-controlled, normotensive DMII patients without coronary artery disease [122]. Apart from disturbed myocardial energetics, DM also impairs myocardial relaxation through abnormalities in diastolic cardiomyocyte calcium handling [125]. DM induces endothelial dysfunction, reduced NO bioavailability and impaired vasodilator responses through increased systemic inflammation and oxidative stress [117,125]. Hyperglycemia induces oxidative stress via several mechanisms, which include glucose auto-oxidation, formation of AGEs, activation of the polyol pathway and increased levels of free fatty acids and leptin [152]. Previously, hyperglycemia was shown to attenuate PKC expression and activity through PKC dependent activation of NADPH oxidase-mediated oxidative stress [127].

Impact of Noncardiac Comorbidities on Myocardial Dysfunction and Remodeling in HFpEF

Although HFpEF is associated with more cardiovascular abnormalities and worse outcome beyond the level explainable by comorbidities alone, the rationale for an important involvement of noncardiac comorbidities in myocardial dysfunction and remodeling in HFpEF seems evident. Currently, there is no pharmacological therapy that improves mortality in HFpEF. Lifestyle modifications, such as exercise and weight loss have shown favourable results in high risk patients and could also be of benefit in HFpEF, perhaps in conjunction with existing or novel pharmacological strategies.

Treatment of HFpEF

Lifestyle interventions

Exercise training: Exercise training improved exercise capacity and reduced morbidity in HFrEF [153]. A modest outcome benefit with exercise training in HFrEF was also demonstrated in a large meta-analysis and the HF-ACTION trial [154,155]. Furthermore, exercise training improves endothelial

dysfunction, systemic inflammation and metabolic syndrome [156-158]. Limited data suggest that exercise training attenuates the age-dependent decline in diastolic function [65]. Conversely, exercise training did not favorably reverse cardiac stiffening in sedentary seniors without HF, but it favorably affected LV remodeling, arterial function and aerobic exercise capacity [159]. In two small studies of exercise training in HFpEF patients, 16 weeks of exercise training improved exercise tolerance without altering endothelial function, arterial stiffness or systolic [160] and diastolic function [161]. Enhanced skeletal muscle perfusion and/or oxygen utilization was suggested as a possible mechanism for exercise-mediated improvements in peak oxygen consumption [160]. In the randomized Ex-DHF trial, HFpEF patients randomized to endurance/resistance training demonstrated improved exercise capacity and quality of life [47].

Weight loss: Intentional weight loss in obese patients can improve or prevent many of the obesity-related risk factors for cardiovascular disease [162]. Weight loss ameliorates obesity related cardiac hypertrophy and diastolic dysfunction [163-165], while it improves excessive myocardial free fatty acid uptake, oxygen consumption and lowers LV filling pressures through reduction in central blood volume [166,167]. Reducing weight in obesity lowers inflammatory biomarkers and improves endothelial function and insulin sensitivity [168,169]. In normal weight adults, an average weight gain of 4.1 kg impaired flow-mediated dilation, which was restored to baseline when subjects lost this excess weight [170]. In morbidly obese subjects (BMI > 40 kg/m²), weight reduction after bariatric surgery normalized aortic function, reduced LV hypertrophy and improved LV diastolic function [134,171,172], whereas surgical-induced weight loss also improved LV relaxation, myocardial energetics and oxygen consumption [163].

Significant increases in adiponectin levels and reduction in IR were observed in diabetic and nondiabetic patients after 2 months of diet-induced weight loss [173]. A Mediterranean-style diet was shown to have beneficial effects on endothelial function in patients with the metabolic syndrome leading to an improvement of vascular inflammatory markers and IR [174]. Weight loss, a Mediterranean-style diet and exercise reduce serum concentrations of IL6, IL7 and IL18 in obese subjects [175]. The benefit of lifestyle modification on metabolic and inflammatory parameters was also recorded in postmenopausal women who after a 2-week high-fibre and low-fat diet together with aerobic exercise, had reduced serum glucose concentrations, improved insulin sensitivity and lowered hsCRP and ICAM-1 levels [176].

Modulation of Renin-Angiotensin-Aldosterone System and beta-Adrenergic Signaling

Neurohumoral and RAAS activation are centrally involved in the pathogenesis of HF [177,178]. These systems are initially able to compensate for the depressed myocardial function and preserve cardiovascular homeostasis. However, their long-term activation has deleterious effects on cardiac structure and performance, leading to cardiac decompensation and HF progression [177,178]. Modulation of the RAAS and β -adrenergic

signaling has significantly improved clinical outcome in HFrEF. Despite the rationale for also potential efficacy in HFpEF, modulation of RAAS and beta-adrenergic signaling yielded neutral results in HFpEF populations.

Modulation of renin-angiotensin-aldosterone system (RAAS)

The RAAS plays a key role in the pathophysiology of HF by controlling cardiovascular, renal and adrenal function by regulating body fluids, electrolyte balance and arterial pressure [179]. Renin, released in the kidney converts angiotensinogen into angiotensin I (AngI), which is then converted to AngII by angiotensin-converting enzyme (ACE) [180]. In addition to converting AngI to AngII, ACE metabolizes bradykinin, an active vasodilator, to an inactive metabolite. AngII is the main effector peptide of the RAAS causing an increase in blood pressure via vasoconstriction and sodium and water retention. It also mediates aldosterone and vasopressin secretion and sympathetic activation [179,180]. In addition, AngII induces inflammatory responses, oxidative stress and collagen synthesis, which are importantly involved in maladaptive cardiac remodeling and dysfunction in HFpEF. AngII exerts most of its actions by binding to the AngII type 1 (AT1) and AngII type 2 (AT2) receptors, which elicit distinct responses [179,180]. AT1 receptor activation leads to vasoconstriction, sodium reabsorption, aldosterone secretion, sympathetic activation, inflammatory responses and oxidative stress, whereas AT2 receptor stimulation mediates opposite effects, including vasodilation, NO and bradykinin production and antiproliferative effects [181]. Angiotensin II receptor blockers (ARBs) act by selectively blocking the AT1 receptor, thereby directly blocking the vasoconstrictor and growth effects of AngII [180]. Selective blockade of the AT1 receptor has additional cardiovascular benefits as AngII that is unable to bind to the AT1 receptor stimulates the unaffected AT2 receptor, resulting in vasodilation, growth inhibition and NO and bradykinin production [181]. ACE inhibitors decrease levels of circulating AngII by inhibiting ACE and reducing the conversion of AngI to AngII [181]. However, ACE inhibitors do not fully prevent conversion of AngI to AngII because other enzymes (chymase and cathepsin G) are capable of synthesizing AngII [180,181]. In addition, ACE inhibitors also interfere with the breakdown of bradykinin, resulting in beneficial increases in vasodilatory bradykinin and NO. Aldosterone is a steroid hormone and downstream effector of AngII, which is mainly synthesized by the adrenal cortex, but is also present in vascular, brain, heart and adipose tissues leading to local autocrine or paracrine effects [103,182]. Aldosterone produces a number of potentially deleterious effects in HFpEF, including sodium and water reabsorption, sympathetic nervous system activation, vasoconstriction, increased oxidative stress with inflammation, remodeling, fibrosis and endothelial dysfunction [103,182]. Targeting the RAAS with ARBs, ACE inhibitors and aldosterone antagonists has long been considered reasonable for HFpEF based on its link to hypertension, fibrosis and fluid imbalance, but despite their clear success in HFrEF, clinical trials with RAAS inhibitors in HFpEF produced neutral outcome results [25,26,87,88,183].

Modulation of beta-adrenergic signaling

Sympathetic activation of cardiac beta-adrenergic signaling pathways modulates inotropic, chronotropic and lusitropic responses, providing pivotal control over cardiac reserve responses. These effects are mediated through the 7-transmembrane spanning, G-protein coupled receptors, beta1 (β_1)-, beta2 (β_2)- and beta3 (β_3)-adrenoceptors (β ARs), which are all present in the human heart [177,178]. The β_1 AR is the predominant receptor subtype expressed in the heart and 1AR expression is downregulated in both HFpEF and HFrEF [184]. Stimulation of β_1 - and β_2 ARs increases cardiac contractility (positive inotropic effect), frequency (positive chronotropic effect) and rate of relaxation (positive lusitropic effect), as well as impulse conduction through the atrioventricular node (positive dromotropic effect) through stimulation of Gs-adenylyl cyclase(AC)-cyclic adenosine monophosphate (cAMP)-PKA signaling [177,178]. Unlike β_1 AR, which couples only to Gs, β_2 AR also couples to Gi proteins, which has negative effects on AC activity, cAMP synthesis, PKA activation and the inotropic response mediated by Gs. Persistent stimulation of 1AR and 2AR exhibits distinct outcomes in HF, with chronic stimulation of β_1 AR triggering cardiomyocyte apoptosis [185], whereas persistent stimulation of β_2 AR has cardioprotective effects, primarily mediated by β_2 AR-Gi coupling [186]. cAMP signaling is compartmentalized [187] and spatial control of signal propagation is paramount for specificity of signaling [188]. Thus, depending on their location, cAMP signals may have different functional effects and changes in the phosphorylation of individual PKA substrates may be either beneficial or harmful, depending on the specific target involved [189]. PKA represents the effector kinase of β_1 AR and β_2 AR signaling and PKA-mediated phosphorylation of its targets, such as phospholamban, L-type calcium channel, ryanodine receptor, troponin I and titin results in positive inotropic, chronotropic and lusitropic effects and lowering of cardiomyocyte stiffness [177,178,190] (Figure1). β_3 ARs are predominantly inactive during normal physiological conditions [191], but are upregulated in HF [192], while β_3 ARs are more resistant than β_1 - and 2ARs to homologous desensitization [193]. Stimulation of β_3 ARs exerts a negative inotropic effect opposite to that induced by β_1 - and β_2 ARs through activation of the NO synthase pathway, which results in activation of sGC-cGMP-PKG signaling [194]. PKG inhibits β -adrenergic contractility through crosstalk with cAMP-PKA signaling via modulation of phosphodiesterases (PDEs) type 2 (PDE2) and 3 (PDE3) and decreases myofilament calcium sensitivity via phosphorylation of troponin I [190,195]. PDE2 is a dual substrate esterase with catalytic activity for both cAMP and cGMP [190,195,196]. Without concomitant adrenergic stimulation, PDE2 can hydrolyze a cGMP pool coupled to NP/pGC [190,196]. However, in the presence of stimulation, cGMP activates PDE2 to reduce cAMP levels and diminish the PKA signal [190,196]. The source of cGMP can be both via NP/pGC or β_3 -AR/NO/sGC-coupled pathways. In addition, β_3 -AR/NO/sGC-induced cGMP increases the PKA signal through cGMP-mediated inhibition of PDE3-induced hydrolysis of cAMP [190,196]. Stimulation of β_3 ARs could thus represent a therapeutic strategy to increase cardiomyocyte cGMP-

PKG signaling and modulate cAMP-PKA signaling. The third generation beta-blocker, nebivolol, selectively inhibits β_1 ARs, but stimulates β_3 AR-NOS-cGMP-PKG signaling [197]. Nebivolol has negative inotropic effects and stimulates vasodilatation, reverses endothelial dysfunction, favourably modifies hemostatic and fibrinolytic status and has anti-inflammatory and anti-oxidant effects [197]. Unfortunately, compared with placebo, 6 month treatment with nebivolol did not improve exercise capacity in patients with HFpEF in the Effects of Nebivolol on Clinical Symptoms, Exercise Capacity, and Left Ventricular Function in Diastolic Dysfunction (ELANDD) trial [198].

Targeting Disturbed cGMP Signaling

According to the new HFpEF paradigm, prevalent comorbidities foster a systemic inflammatory state contributing to endothelial dysfunction, oxidative stress and impaired NO bioavailability with downregulation of myocardial NO-cGMP-PKG signaling. Subsequently this chain of events results in myocardial dysfunction and remodeling with increased cardiomyocyte stiffness, hypertrophy and interstitial fibrosis. Therefore targeting defective cGMP-PKG signaling could represent a novel inroad for HFpEF treatment [22] (Figure 4).

NO-donors

Acute administration of NO donors improves diastolic LV function with an earlier onset of LV relaxation, lower LV peak systolic, end-systolic and end-diastolic pressures, and with rightward displacement of the diastolic LV pressure-volume relation [199]. Aside from effects on inotropy and ventricular compliance, NO is a mediator of myocardial energetics through regulation of mitochondrial respiration, oxygen consumption and substrate utilization [200]. Current ESC HF guidelines accord a class IIa indication for administration of NO donors in patients admitted for acute HF with pulmonary edema without concomitant cardiogenic shock [201]. Unfortunately, long-term use of NO donors is frequently hampered by development of NO resistance [202]. NO resistance largely results from a combination of scavenging of NO by superoxide and of inactivation of sGC [203]. In addition, chronic treatment with nitrates may cause oxidative stress via increased expression of endothelin, hence potentially exacerbating endothelial dysfunction [204]. Conversely, chronic use of isosorbide dinitrate combined with the antioxidant hydralazine improved outcome in V-HeFT I and A-HeFT trials [205,206]. Hydralazine reduces superoxide generation by xanthine oxidase and NADPH oxidase [207]. The clinical characteristics of the A-HeFT HFrEF patients revealed a high prevalence of obesity and DM [208], conditions which are also highly prevalent in HFpEF. Combined use of isosorbide dinitrate and the antioxidant hydralazine could therefore be potentially favorable in HFpEF.

Phosphodiesterase type 5 inhibition (PDE5-I)

An alternative approach to stimulate cGMP-PKG signaling is to inhibit the action of PDE5, which breaks down cGMP and hence offsets cGMP-PKG signaling (Figure 1). PDE5A inhibitors attenuate adrenergic stimulation [209], reduce ventricular-vascular stiffening [209], antagonize maladaptive chamber

remodeling [210,211], improve endothelial function [212], reduce pulmonary vascular resistance [211,213,214] and lower diastolic LV stiffness in patients with HFrEF [211] and in HFpEF patients with pulmonary hypertension [212]. However, in the multicenter RELAX trial [215], the PDE5 inhibitor sildenafil did not improve exercise capacity in HFpEF patients. Because plasma cGMP levels were not elevated in the sildenafil treated group, questions have arisen as to whether inhibition of cGMP catabolism is effective in settings associated with impaired upstream cGMP generation, such as systemic inflammation, oxidative stress and endothelial dysfunction [216].

sGC activation and stimulation

Recently, two classes of drugs have been discovered, the sGC activators and sGC stimulators, which target two different redox states of sGC: the NO-sensitive reduced (ferrous) sGC and NO-insensitive oxidized (ferric) sGC respectively [217]. Oxidative stress favours heme-free sGC, which is unresponsive to NO. Hence, oxidative stress synergistically hampers NO-cGMP signaling through sGC oxidation and through ROS-mediated scavenging of NO [218,219], thereby compromising NO-sGC-cGMP mediated signaling [217,220]. The sGC stimulators have a dual mode of action; they sensitize sGC to low levels of NO and can stimulate sGC directly in the absence of endogenous NO. Conversely, sGC activators specifically activate the NO-unresponsive, heme-free form of the enzyme irrespective of NO bioavailability [217,220,221]. In a nonrandomized proof of concept study, the sGC activator cinaciguat acutely reduced pulmonary capillary and artery pressures, lowered pulmonary and systemic vascular resistance and improved cardiac output in patients admitted for acute decompensated HF [222]. Unfortunately, additional phase IIb studies in acute HF patients, demonstrated cinaciguat to be associated with an excess of non-fatal hypotensive episodes without improvements in dyspnea or cardiac index [223]. The sGC stimulator riociguat improved 6-minute walk distance, NP levels and functional class in patients with WHO Group 1 and Group 4 pulmonary hypertension [224,225]. A phase IIb study in HFrEF patients testing riociguat failed to show a benefit for the primary endpoint of pulmonary artery pressure, but did show improvements in pulmonary and systemic vascular resistance, cardiac output, stroke volume and quality of life [226]. Currently, a trial with a once-daily oral sGC stimulator in HFpEF, BAY1021189 is under way.

Stimulation of NP-cGMP signaling

BNP-pGC signaling failed to normalize cGMP content in HFpEF myocardium [37]. This failure relates to the low diastolic wall stress prevailing in a concentrically remodeled LV [227], and is consistent with the lower BNP levels frequently observed in HFpEF patients [52,228] and supports use in HFpEF of drugs that simulate BNP production or reduce BNP breakdown [229]. The synthetic NP nesiritide was shown to acutely reduce pulmonary capillary wedge pressure and systemic vascular resistance, while increasing cardiac index and stroke volume index in HFrEF patients [230]. Acute NP administration was recently reported to lower diastolic LV stiffness and to increase myocardial titin phosphorylation in an old hypertensive HFpEF dog model [231]

but failed to improve clinical endpoints in a large, randomized clinical trial of acutely decompensated HF patients with either LVEF < 40% and LVEF ≥ 40% [232].

Neprilysin enzymatically degrades BNP but not N-terminal pro-B-type NP (NT-proBNP), and compounds combining neprilysin inhibition with RAAS blockade are actively being tested in human HF. Recently, LCZ696, a first-in-class angiotensin-receptor/neprilysin inhibitor was tested in 301 patients with HFpEF. Compared with valsartan, LCZ696 resulted in greater reductions in NT-proBNP at 12 weeks, improved LA remodeling and was well tolerated [229].

Statins

The new HFPEF paradigm also supports use of statins. Statins exert rapid and direct effects on endothelial redox balance, which are independent of low-density lipoprotein lowering and consist of reduced superoxide anion production and restored NO bioavailability [233]. These effects reach adjacent cardiomyocytes and fibroblasts as evident in experimental hypertension or hypercholesterolemia from regression of LV hypertrophy, prevention of myocardial fibrosis and amelioration of diastolic LV dysfunction [234]. A retrospective analysis of a recent clinical study looking at myocardial nitrotyrosine content, PKG activity, hypertrophy and stiffness in HFpEF patients [37] revealed statin treated patients to have less nitrotyrosine, more PKG activity, less cardiomyocyte hypertrophy and lower cardiomyocyte stiffness. These findings are in line with the positive outcome of a small study that showed statin use to lower mortality of HFpEF patients [235]. A neutral outcome of statin use was however also reported in a large randomized heart failure trial in a subgroup of patients with relatively preserved LV EF (> 40%) [236].

Relaxin

Serelaxin, a recombinant form of human relaxin-2, administered to acute HF patients caused an improvement of symptoms and prevention of organ damage with a reduction in 180-day mortality compared with placebo [237,238]. The peptide hormone relaxin, which is known as a reproductive hormone also has potential beneficial actions in HF including stimulation of systemic endothelial function with increased NO bioavailability and inhibition of inflammation and fibrosis [239]. In HFpEF patients, serelaxin was well tolerated and improved dyspnoea and 180-day mortality [240]. However, the RELAX-AHF study was not primarily designed and powered to assess mortality [237] and the subgroup of HFpEF patients comprised 275 patients. Therefore, the effects of serelaxin on HFpEF patients should be confirmed by subsequent trials.

Conclusion

HFpEF is increasingly prevalent and is associated with a significant morbidity and mortality, while its pathophysiology and therapy remain uncertain. Besides diastolic LV dysfunction, numerous other mechanisms are thought to be involved in its pathophysiology, including impaired systolic rest and/or reserve function, abnormal ventricular-arterial coupling, myocardial energetic deficiency, pulmonary hypertension, chronotropic

incompetence, inflammation, oxidative stress and endothelial dysfunction. In addition, HFpEF patients often present with a multitude of comorbidities which themselves are also known to elicit detrimental responses in the cardiovascular system. The new HFpEF paradigm proposes an important contributory role of noncardiac comorbidities to myocardial dysfunction and remodeling. In HFpEF, comorbidities contribute to a systemic inflammatory state, which induces oxidative stress in the coronary microvascular endothelium. This reduces myocardial NO bioavailability and leads to reduced PKG activity in cardiomyocytes, which therefore become stiff and hypertrophied. Furthermore, increased age and postmenopausal hormonal changes could result in additive maladaptive cardiovascular structural and functional changes. Hence, as proposed by the new paradigm of HFpEF, noncardiac comorbidities could certainly represent prime suspects in eliciting coronary microvascular endothelial dysfunction and downregulation of myocardial NO-cGMP-PKG signaling [22].

Future Perspectives

HFpEF represents a complex disorder with a heterogeneous constellation of comorbidities and underlying pathogenic mechanisms and poses a formidable challenge for clinicians and translational researchers. Many issues regarding underlying pathophysiological mechanisms remain unresolved. For instance, patients with substantial diastolic dysfunction with or without structural heart disease in the setting of hypertensive heart disease may behave differently from those with chronotropic incompetence or from those with normal blood pressure but inflammatory activation in the setting of metabolic risk factors. In addition, pathogenic mechanisms may vary in the course of HFpEF disease trajectory and could therefore differentially influence structural and functional myocardial dysfunction at different time courses of the disease. Furthermore, the additive role of pre-existing or newly developing non-cardiac comorbidities on structural and functional remodeling in HFpEF is incompletely understood. Therefore, improved subclassification of HFpEF patients, increased procurement of HFpEF myocardial tissue, for instance through LV endomyocardial biopsy procurement, and improvement in experimental HFpEF models are important future goals in enhancing our understanding of HFpEF pathophysiology. Stimulation of crosstalk and formation of collaborative networks between translational researchers and clinicians is of great interest to enhance insight into structural and functional cardiovascular dysfunction in the setting of coexisting variable pathogenic mechanisms and comorbidities in HFpEF patients.

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