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STATE-OF-THE-ART PAPER AND COMMENTARY

A Novel Paradigm for Heart Failure With Preserved Ejection Fraction

Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation

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Over the past decade, myocardial structure, cardiomyocyte function, and intramyocardial signaling were shown to be specifically altered in heart failure with preserved ejection fraction (HFPEF). A new paradigm for HFPEF development is therefore proposed, which identifies a systemic proinflammatory state induced by comorbidities as the cause of myocardial structural and functional alterations. The new paradigm presumes the following sequence of events in HFPEF: 1) a high prevalence of comorbidities such as overweight/obesity, diabetes mellitus, chronic obstructive pulmonary disease, and salt-sensitive hypertension induce a systemic proinflammatory state; 2) a systemic proinflammatory state causes coronary microvascular endothelial inflammation; 3) coronary microvascular endothelial inflammation reduces nitric oxide bioavailability, cyclic guanosine monophosphate content, and protein kinase G (PKG) activity in adjacent cardiomyocytes; 4) low PKG activity favors hypertrophy development and increases resting tension because of hypophosphorylation of titin; and 5) both stiff cardiomyocytes and interstitial fibrosis contribute to high diastolic left ventricular (LV) stiffness and heart failure development. The new HFPEF paradigm shifts emphasis from LV afterload excess to coronary microvascular inflammation. This shift is supported by a favorable Laplace relationship in concentric LV hypertrophy and by all cardiac chambers showing similar remodeling and dysfunction. Myocardial remodeling in HFPEF differs from heart failure with reduced ejection fraction, in which remodeling is driven by loss of cardiomyocytes. The new HFPEF paradigm proposes comorbidities, plasma markers of inflammation, or vascular hyperemic responses to be included in diagnostic algorithms and aims at restoring myocardial PKG activity. (J Am Coll Cardiol 2013;62:263–71) © 2013 by the American College of Cardiology Foundation

Insight into myocardial structure and function in heart failure (HF) with preserved ejection fraction (HFPEF) has long been missing because of a lack of myocardial tissue obtained from HFPEF patients (1). Over the past decade, several groups of investigators were able to obtain myocardial tissue from patients with HFPEF (2–6) or left ventricular (LV) diastolic dysfunction (7,8). These studies revealed specific alterations in myocardial structure and function that were relevant to concentric LV remodeling and diastolic LV dysfunction characteristically observed in patients with HFPEF (9,10). Structural alterations consisted of cardiomyocyte hypertrophy (3) and interstitial fibrosis (2–4,6), whereas functional changes included incomplete relaxation of myocardial strips (7) and increased cardiomyocyte stiffness (2–4,8). The same studies also demonstrated abnormal intramyocardial signaling evident from endothelial cells expressing adhesion molecules (5), inflammatory cells secreting profibrotic transforming growth factor β (TGF-β) (5) and oxidative stress increasing nitrotyrosine content (4,5). This abundance of new data on myocardial structure, function, and signaling allows for a new paradigm on myocardial remodeling and dysfunction in HFPEF. This new paradigm reconciles the recently acquired knowledge on myocardial structure, function, and signaling with novel insights on the importance of comorbidities in HFPEF (11).

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A New Paradigm for HFPEF

As outlined in Figure 1, the new paradigm proposes that myocardial remodeling and dysfunction in HFPEF results from a sequence of events consisting of the following: 1) comorbidities and especially obesity induce a systemic proinflammatory state; 2) because of this proinflammatory state, coronary microvascular endothelial cells produce reactive oxygen species (ROS), which limits nitric oxide

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Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin II receptor blocker
BNP = B-type natriuretic peptide
cGMP = cyclic guanosine monophosphate
DM = diabetes mellitus
HF = heart failure
HFPEF = heart failure with preserved ejection fraction
HFREF = heart failure with reduced ejection fraction
IL = interleukin
LV = left ventricular
PDE5 = phosphodiesterase 5
PH-HFPEF = pulmonary hypertension secondary to heart failure with preserved ejection fraction
PKG = protein kinase G
ROS = reactive oxygen species
TGF = transforming growth factor
TNF = tumor necrosis factor
VCAM = vascular cell adhesion molecule

(NO) bioavailability for adjacent cardiomyocytes; 3) limited NO bioavailability decreases protein kinase G (PKG) activity in cardiomyocytes; 4) low PKG activity removes the brake on cardiomyocyte hypertrophy, thereby inducing concentric LV remodeling, and stiffens the cardiomyocyte because of hypophosphorylation of the giant cytoskeletal protein titin; and 5) both stiff cardiomyocytes and increased collagen deposition by myofibroblasts cause diastolic LV dysfunction, the major cardiac functional deficit in HFPEF.

Comorbidities in HFPEF and a systemic proinflammatory state. Noncardiac comorbidities are highly prevalent in HFPEF (11). The most important are overweight/obesity, hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease, anemia, and chronic kidney disease. All these comorbidities have the ability to induce a systemic inflammatory state. Chronic inflammation is obvious in chronic obstructive pulmonary disease, which is both a premorbid identifier of HFPEF (12) and a contributor to HFPEF mortality (11). In visceral obesity, adipose tissue is infiltrated by macrophages, which produce a systemic inflammatory state because of secretion of proinflammatory cytokines (13,14). Obesity also contributes to mortality as evident from the U-shaped relationship in HFPEF between body mass index and mortality (15). In salt-sensitive hypertension, high salt intake leads to systemic oxidative stress (16), possibly because of renal production of proinflammatory cytokines (17), and in HF with or without anemia, iron deficiency contributes to immune responses and oxidative stress (18). Comorbidities were recently shown to be accompanied by a greater deterioration of myocardial function and structure in HFPEF than in arterial hypertension (19). This finding supports additional deterioration in HFPEF by HF-related mechanisms such as neuroendocrine activation (20) and the lack of high-energy phosphates (21). Additional involvement of HF-related mechanisms also explains the poorer outcome of HFPEF than of comorbidities (22).

The systemic inflammatory state induced by these comorbidities has recently been shown to be predictive of incident HFPEF but not of incident HF with reduced ejection fraction (HFREF) (23). In this study, the systemic inflammatory state was evident from high circulating levels of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α). The same cytokines were also elevated in a cross-sectional study of HFPEF patients (24). Furthermore, similar cross-sectional studies revealed high plasma levels of other inflammatory markers such as soluble ST2 (25), or pentraxin 3 (26).

Coronary microvascular endothelial inflammation and NO bioavailability. The systemic inflammatory state induced by HFPEF comorbidities affects the coronary microvascular endothelium as evident from the recently established expression of endothelial adhesion molecules in myocardial biopsy samples of HFPEF patients. Both vascular cell adhesion molecule (VCAM) and E-selectin were shown to be abundantly expressed (5,27). Their expression leads to activation and subendothelial migration of circulating leukocytes (5). Proinflammatory cytokines are also known to elicit endothelial production of ROS through activation of nicotinamide adenine dinucleotide phosphate oxidases (28). This could explain the high nitrosative/oxidative stress, which was recently visualized in HFPEF myocardium using both nitrotyrosine and dihydroethidium staining (4,5). High nitrotyrosine expression also suggests

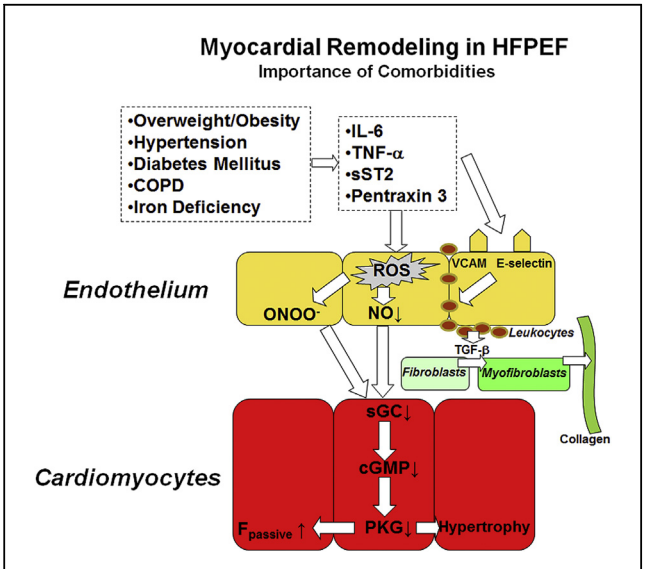

Figure 1 Comorbidities Drive Myocardial Dysfunction and Remodeling in HFPEF

Comorbidities induce a systemic proinflammatory state with elevated plasma levels of interleukin (IL)-6, tumor necrosis factor (TNF)-α, soluble ST2 (sST2), and pentraxin 3. Coronary microvascular endothelial cells reactively produce reactive oxygen species (ROS), vascular cell adhesion molecule (VCAM), and E-selectin. Production of ROS leads to formation of peroxynitrite ($ONOO^-$) and reduced nitric oxide (NO) bioavailability, both of which lower soluble guanylate cyclase (sGC) activity in adjacent cardiomyocytes. Lower sGC activity decreases cyclic guanosine monophosphate concentration and protein kinase G (PKG) activity. Low PKG activity increases 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 favors migration into the subendothelium of monocytes. These monocytes release transforming growth factor β (TGF-β). The latter stimulates conversion of fibroblasts to myofibroblasts, which deposit collagen in the interstitial space. COPD = chronic obstructive pulmonary disease; HFPEF = heart failure with preserved ejection fraction.

low NO bioavailability in HFPEF myocardium because of diversion of NO to peroxynitrite by superoxide anion.

Apart from inducing a systemic inflammatory state, certain comorbidities, such as DM, and physiological processes, such as aging, can also directly enhance endothelial ROS production. Exposure of endothelial cells to high glucose induces mitochondrial fragmentation and dysfunction, ROS production, and nitrotyrosine formation (29). Endothelial mitochondrial dysfunction has also been shown to increase with age (30).

As a result of coronary microvascular endothelial inflammation, the vasodilator response of the coronary microvascular bed to acetylcholine was reduced in HFPEF (31). The reduced vasodilator response correlated with LV diastolic dysfunction (31). Similar paracrine endocardial-myocardial interactions had previously already been reported (32). Several recent studies emphasized the importance of a deficient systemic vasodilator response for the reduced exercise tolerance of HFPEF patients (33). Probably because of upregulation of endothelial nitric oxide synthase, this response was reversed after an exercise training program (34), which improved both exercise capacity and diastolic LV dysfunction (35). Peripheral endothelial dysfunction was recently also identified as an independent predictor of outcome of HFPEF patients (36). This prognostic implication suggests a causal involvement of endothelial dysfunction in HFPEF (37).

Low NO bioavailability and PKG activity. In cardiomyocytes adjacent to dysfunctional endothelium, low NO bioavailability and high peroxynitrite level predispose to reduced cyclic guanosine monophosphate (cGMP) production by soluble guanylate cyclase (38). Both low cGMP content and low PKG activity were recently demonstrated in myocardial homogenates of HFPEF patients (4). Of interest was the inability of B-type natriuretic peptide (BNP)–particulate guanylate cyclase signaling to normalize cGMP content in HFPEF myocardium (4). This failure relates to the low diastolic wall stress prevailing in a concentrically remodeled left ventricle (39), is consistent with the lower BNP levels frequently observed in HFPEF patients (20,40), and supports use in HFPEF of neprilysin inhibition to reduce BNP breakdown (41).

Low PKG activity and cardiomyocyte hypertrophy, relaxation, and stiffness. PKG functioning as a brake on myocardial hypertrophy has been observed in a wide variety of experimental and clinical settings. In cardiomyocytes cultured from neonatal rat hearts, NO or a cGMP analogue attenuated the norepinephrine-induced hypertrophic response (42). In mice subjected to transverse aortic constriction, sildenafil, which increases myocardial PKG activity through inhibited breakdown of cGMP by phosphodiesterase 5 (PDE5), prevented or reversed cardiomyocyte hypertrophy and interstitial fibrosis by deactivating multiple prohypertrophic pathways (43). In patients with diabetic cardiomyopathy and concentric LV remodeling, sildenafil treatment reduced the LV mass/volume ratio (44). In line with these experimental and clinical findings, lower myocardial PKG activity in HFPEF than in HFREF was recently shown to correlate with a larger cardiomyocyte diameter (4). A similar relationship between myocardial PKG activity and cardiomyocyte hypertrophy was also manifest in aortic stenosis patients who had less myocardial PKG activity and more cardiomyocyte hypertrophy when DM was a comorbidity (4,45).

Deficient NO-cGMP-PKG signaling from endothelium to myocardium also affects myocardial relaxation. In isolated cardiac muscle preparations, loss of endocardial endothelium delays onset of relaxation (32). High levels of peroxynitrite increase protein phosphatase 2a activity, which lowers phospholambam phosphorylation, reduces sarcoplasmic reticular Ca^{2+} uptake, and increases diastolic cytosolic Ca^{2+} (46). Both effects could explain the development of a high resting tension at high pacing frequencies in cardiac muscle strips isolated from HFPEF patients (8).

Apart from effects on myocardial relaxation, NO-cGMP-PKG signaling from endothelium to myocardium also modulates myocardial stiffness. Coronary infusions of NO donors acutely lowered diastolic LV stiffness in human controls, in aortic stenosis, and in dilated cardiomyopathy (47). Chronic inhibition of NO synthase in rats induced leftward displacement of the diastolic LV pressure-volume relationship with shrinkage of the LV unstressed volume (48) in contrast to treatment with an endothelial NO synthase enhancer, which attenuated diastolic LV dysfunction in a rat HFPEF model (49). Oxidative stress blunting NO-mediated effects on diastolic LV stiffness was evident in a hypertensive mouse model (50). Sildenafil reduced diastolic LV stiffness in an old hypertensive dog model (51), in HFREF patients (52) and in HFPEF patients with pulmonary hypertension (53). Administration of sildenafil to old hypertensive dogs lowered diastolic LV stiffness through restored phosphorylation of the N2B segment of titin (51). The giant cytoskeletal protein titin acts as a bidirectional spring and is responsible for early diastolic recoil and late diastolic distensibility of cardiomyocytes. Its spring characteristics are modulated not only through isoform shifts but also through phosphorylation by protein kinases (54), such as protein kinase A (55), PKG (56), or protein kinase C (57). Protein kinase A or PKG makes titin more compliant in contrast to protein kinase C, which makes it less compliant. Single cardiomyocytes isolated from LV myocardium of HFPEF patients characteristically have a high resting tension (2–4,27). This high resting tension was attributed to hypophosphorylation of the N2B segment of titin (58) because of low PKG activity (4) and was corrected by in vitro administration of PKG (4).

Both stiff cardiomyocytes and fibrosis contribute to diastolic myocardial dysfunction. A recent histological study of HFPEF myocardium revealed an increased collagen volume fraction, higher expression of collagen type I, and more collagen cross-linking, which all contributed to diastolic LV dysfunction (6). The same investigators proposed myocardial collagen deposition in HFPEF to result from differentiation of fibroblasts into myofibroblasts because of TGFβ released by monocytes, which had migrated through

the inflamed microvascular endothelium (5,59,60). Microvascular inflammation also directly favors proliferation of fibroblasts and myofibroblasts because of reduced NO bioavailability (42), which leaves profibrotic action of growth-promoting hormones such as endothelin-1, angiotensin II, and aldosterone unopposed (61).

Myocardial Afterload Excess

Arterial hypertension is the most prevalent comorbidity in HFPEF (62). Although arterial hypertension has been associated with oxidative stress and vascular inflammation (63), arterial hypertension is usually perceived to induce HFPEF through myocardial afterload excess (64). The new HFPEF paradigm proposed in this review shifts emphasis to microvascular inflammation, which lowers myocardial NO bioavailability and removes the brake on prohypertrophic stimuli triggered by myocardial afterload excess. This shift of emphasis is further supported by the following arguments.

1. In all HFPEF registries and large outcome trials (62,65,66), arterial hypertension in HFPEF consists of increased systolic pressure (±148 mm Hg) but normal diastolic pressure (±83 mm Hg). In HFPEF, LV cavity dimensions are small, and, especially in the presence of LV hypertrophy, the left ventricle operates at a favorable Laplace relationship. LV systolic wall stress therefore remains low despite increased LV systolic pressure (67).
2. Some population studies and outcome trials observed a larger contribution to HFPEF development of metabolic comorbidities than of arterial hypertension. In the MONICA registry, left atrial enlargement was strongly related to obesity, mildly related to age, and unrelated to arterial hypertension (68). In ALL-HAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), which recruited 40,000 patients with arterial hypertension and 1 additional risk factor, significant baseline characteristics discriminating between in-trial HFREF or HFPEF development were, respectively, a history of coronary heart disease favoring HFREF and a high body mass index favoring HFPEF (69). In contrast, systolic or diastolic blood pressure did not discriminate between in-trial HFREF or HFPEF development.
3. Involvement in HFPEF of cardiac chambers other than the left ventricle also provides a strong argument for a microvascular inflammatory state driving myocardial remodeling. When pulmonary hypertension secondary to HFPEF (PH-HFPEF) is compared with primary pulmonary hypertension, PH-HFPEF patients had higher right atrial pressures with less right atrial dilation (70), consistent with reduced right atrial compliance in PH-HFPEF. This finding could not be attributed to pulmonary arterial load, as mean pulmonary arterial pressure was similar in both conditions but probably related to the high prevalence of obesity in PH-HFPEF

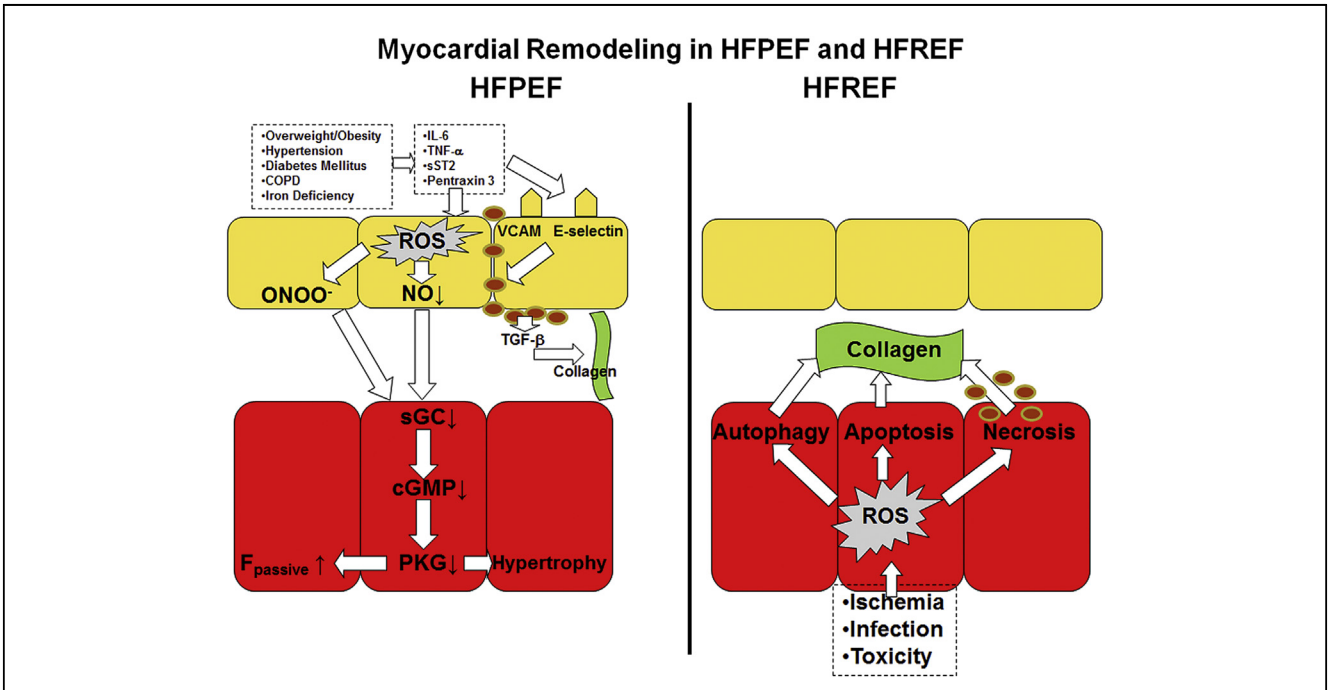

Figure 2 Myocardial Dysfunction and Remodeling in HFPEF and HFREF

In HFPEF, myocardial dysfunction and remodeling are driven by endothelial inflammation and oxidative stress. In HFREF, oxidative stress originates in the cardiomyocytes because of ischemia, infection, or toxic agents. ROS trigger cardiomyocyte autophagy, apoptosis, or necrosis. The latter attracts leukocytes. Dead cardiomyocytes are replaced by fibrous tissue. cGMP = cyclic guanosine monophosphate; HFREF = heart failure with reduced ejection fraction; other abbreviations as in Figure 1.

(46% vs. 15%). Similarly, in a study that compared HFREF with HFPEF, pulmonary capillary wedge pressure was equally increased, but left atrial volume was significantly lower in HFPEF than in HFREF (71). Finally, the same study assessed right ventricular systolic performance and found an analogy to LV systolic performance, higher right ventricular end-systolic elastance in HFPEF than in HFREF.

HFPEF Versus HFREF

The new HFPEF paradigm substantially differs from the paradigm proposed for HFREF, in which LV remodeling is driven by progressive loss of cardiomyocytes (60) (Fig. 2). This loss of cardiomyocytes results from various modalities of cell death such as exaggerated autophagy, apoptosis, or necrosis, all of which are triggered by oxidative stress present within the cardiomyocyte (72–74). The latter usually results from ischemia, infection, or toxicity. Excessive wall stress because of cardiomyocyte loss shifts the balance in the extracellular matrix between collagen deposition and degradation (75). These alterations within the extracellular matrix importantly contribute to LV dilation and eccentric LV remodeling (75). In HFREF, replacement of dead cardiomyocytes by collagen creates patchy areas of fibrosis. A comparative analysis of endomyocardial biopsy samples from HFPEF and HFREF (3,27) indeed showed the presence of replacement fibrosis in HFREF but not in HFPEF. Furthermore, electron microscopic images of LV myocardium revealed lower myofilamentary density in HFREF than in HFPEF, with some HFREF cardiomyocytes showing areas of complete myofibrillar loss (3). These biopsy findings are consistent with cell death occurring in HFREF but not in HFPEF. Potential bias of these results by the low frequency of biopsy procurement in HFPEF patients cannot, however, be excluded.

Apoptotic cardiomyocyte death also appears in late eccentric LV remodeling of transverse aortic constriction mouse models (76). Oxidative stress because of upregulated cardiac nicotinamide adenine dinucleotide phosphate oxidase activity appears to be involved. These studies support a sequence of events whereby myocardial pressure overload initially triggers concentric hypertrophy followed later by eccentric remodeling because of high oxidative stress and cell death. This evolution has also been postulated in human hypertension (77) but seriously questioned by longitudinal cohort studies with sequential cardiac imaging (78). In these studies, the evolution from concentric to eccentric remodeling appeared to be rare in the absence of interval myocardial infarction.

In advanced HFREF, systemic and coronary endothelial dysfunction is also present and attributed to increased plasma levels of TNF-α and IL-6 (79,80) (Fig. 3). However, in contrast to HFPEF, the increased plasma levels of TNF-α and IL-6 do not result from pre-existing comorbidities but are reactive to the severity of HFREF as they relate to both

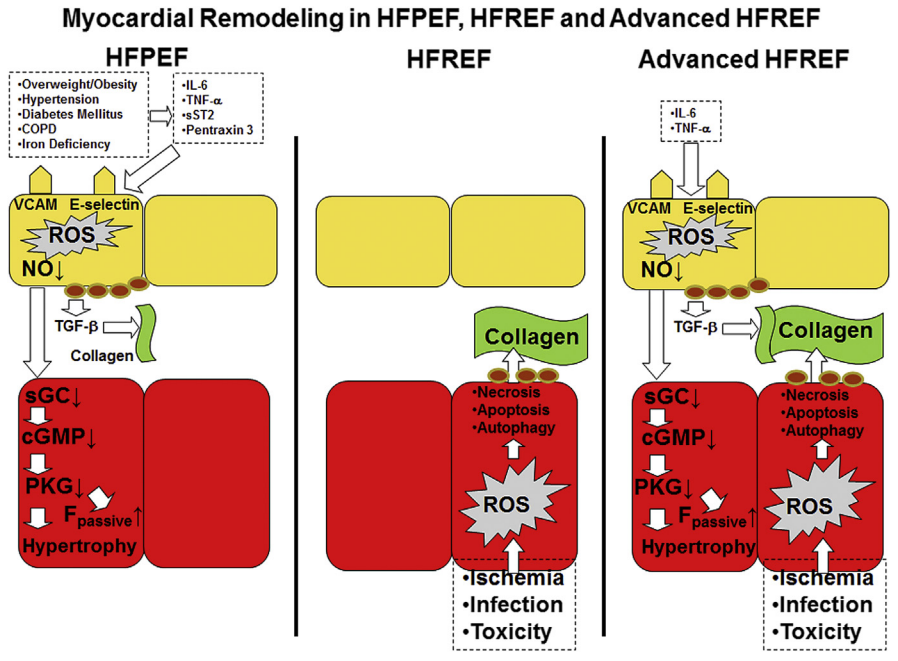

Figure 3 Myocardial Dysfunction and Remodeling in HFPEF, HFREF, and Advanced HFREF

In HFPEF, myocardial dysfunction and remodeling are driven by endothelial oxidative stress. In HFREF, oxidative stress originates in the cardiomyocytes. In advanced HFREF, both mechanisms get superimposed. Abbreviations as in Figures 1 and 2.

New York Heart Association functional class (79) and depression of LV ejection fraction (80). Similar to HFPEF, endothelial dysfunction affects diastolic LV function in advanced HFREF, as evident from the relationship between diastolic LV dysfunction and plasma levels of methylated L-arginine metabolites, which impair NO production by endothelial NO synthase (81).

Finally, although viral myocarditis usually evolves to HFREF, a recent study found parvoviral myocarditis presenting as HFPEF (31). In this study, however, the virus did not affect the cardiomyocytes but the coronary endothelium. This observation therefore fits into the proposed paradigm as HFPEF development was driven by coronary microvascular endothelial inflammation.

Diagnostic and Therapeutic Implications

The new HFPEF paradigm suggests anthropometric measures, comorbidities, vascular hyperemic responses, and plasma markers of oxidative stress or of inflammation to be useful for the diagnosis of HFPEF. No single HFPEF registry has so far reported on waist circumference, which provides an easy assessment of central obesity. The absence of HFPEF development despite the presence of central obesity probably relates to variable infiltration of visceral fat by inflammatory cells (13,82). The importance of comorbidities was recently reappraised (11,83–85), and forearm hyperemic responses were shown to be impaired in HFPEF and to provide diagnostic information (36). Finally, proinflammatory cytokines are increased in HFPEF (24) and predict future HFPEF development (23).

The new HFPEF paradigm also has important therapeutic implications as it identifies low myocardial NO bioavailability as a deficient brake on prohypertrophic stimuli in HFPEF-related LV remodeling. Future HFPEF treatment strategies should therefore aim at curing both arterial hypertension (86) and endothelial dysfunction. The latter can be achieved through correction of comorbidities and through use of NO donors, PDE-5 inhibitors, and substances with antioxidative properties such as statins and resveratrol. Long-term use of isosorbide dinitrate combined with the antioxidant hydralazine improved the outcome of HFREF patients in V-HEFT I (Vasodilator-Heart Failure Trials) and A-HEFT (African-American Heart Failure Trial) (87,88). Many A-HEFT patients were obese or had DM, and their clinical profile therefore overlaps with HFPEF. Long-term use of the PDE5 inhibitor sildenafil improved diastolic LV dysfunction in both HFREF and HFPEF, improved clinical status in HFREF, and reduced pulmonary hypertension in HFPEF (52,53). No effect of sildenafil on exercise tolerance was however observed in a large HFPEF outcome trial (RELAX study [Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure; NCT00763867]).

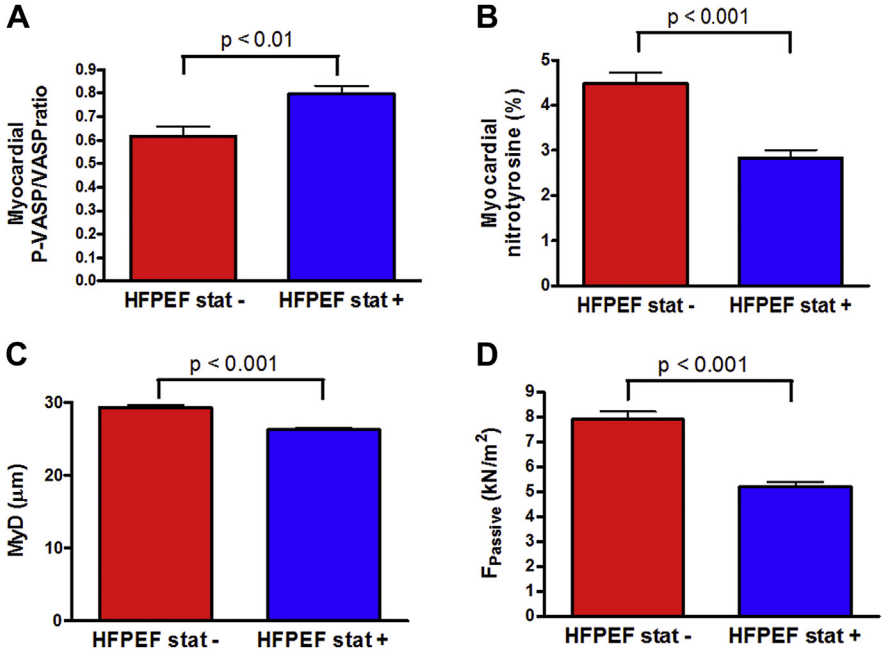

Figure 4 Effects of Statin Treatment on HFPEF Myocardium

Statin-treated HFPEF patients (HFPEF stat+) have higher myocardial PKG activity assessed by the ratio of vasodilatory-stimulated phosphoprotein (VASP) phosphorylated at serine^{239} (pVASP) to total VASP (pVASP/VASP ratio) **(A)**, lower myocardial nitrotyrosine content **(B)**, smaller cardiomyocyte diameter (MyD) **(C)**, and lower cardiomyocyte resting tension ($F_{passive}$) **(D)**. Abbreviations as in Figure 1.

The new HFPEF paradigm also supports the 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 (89). 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 (90). A retrospective analysis of a recent clinical study looking at myocardial nitrotyrosine content, PKG activity, hypertrophy, and cardiomyocyte stiffness in HFPEF patients (4) revealed statin-treated patients to have less nitrotyrosine, more PKG activity, less cardiomyocyte hypertrophy, and lower cardiomyocyte resting tension (Fig. 4). These findings are in line with the positive outcome of a small study that showed statin use to lower the mortality of HFPEF patients (91). A neutral outcome of statin use was, however, also reported in a large randomized HF trial in a subgroup of patients with relatively preserved LV ejection fraction (>40%) (92).

In HFPEF, use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) has so far been disappointing, with all large trials showing a neutral outcome (93). This neutral outcome seems to be at odds with the proposed HFPEF paradigm because ACEIs and ARBs are known to exert a vasculoprotective effect, which was evident in several large outcome trials from a reduced incidence of new atherosclerotic events (94,95). A protective effect on the macrovasculature does not, however, necessarily imply restored endothelial function. This was illustrated by PERFECT (PERindopril-Function of the Endothelium in Coronary artery disease Trial), a substudy of EUROPA (EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) (96). At 36 months follow-up, PERFECT reported no significant improvement ($p = 0.23$) in flow-mediated brachial artery dilation when taking perindopril 8 mg once daily in contrast to the significant reduction ($p = 0.001$) in myocardial infarctions observed with the same perindopril regimen in the EUROPA trial (95). A recent meta-analysis looking at the effects of ACEIs and ARBs on endothelial dysfunction emphasizes the variability of the response with the absence of a significant effect, especially in the presence of comorbidities featuring inflammation and systemic oxidative stress such as obesity, DM, and rheumatoid arthritis (97).

Conclusions

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. Myocardial remodeling in HFPEF differs from myocardial remodeling in HFREF, which is driven by cardiomyocyte death because of oxidative stress originating in the cardiomyocytes as a result of ischemia, infection, or toxicity. The new HFPEF paradigm has important diagnostic and therapeutic implications.

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