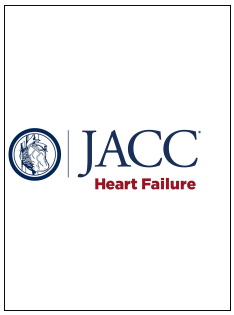

Evolutionary History of the Comorbidity-Driven Coronary Microvascular Endothelial Inflammation Hypothesis and Its Metamorphosis to the Adipokine Hypothesis of Heart Failure With a Preserved Ejection Fraction

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Abstract

For the past decade, the prevailing paradigm to explain heart failure with a preserved ejection fraction (HFpEF) has assumed that multiple comorbidities act in concert to trigger a systemic inflammatory state that causes coronary microvascular dysfunction, nitric oxide/cyclic GMP deficiency-dependent titin abnormalities, and load-dependent cellular inflammation and fibrosis of the myocardium. In contrast, the recently-proposed adipokine hypothesis elevates one comorbidity — visceral adiposity — to explain the coexistence of systemic inflammation, multiple comorbidities and HFpEF and identifies a specific proximal causal mechanism, i.e., the secretion of a proinflammatory suite of signaling molecules from dysfunctional fat. Excess visceral adiposity and adipokine imbalances have been shown not only to produce HFpEF experimentally, but also to directly cause hypertension, insulin resistance and type 2 diabetes, and chronic kidney disease. Visceral adiposity and proinflammatory adipokines can also explain features of HFpEF that are not addressed by the coronary microvascular inflammation hypothesis, e.g., atrial fibrillation, skeletal muscle and pulmonary abnormalities, and renal sodium retention and plasma volume expansion. Adipokine imbalances can also cause microvascular dysfunction, defects in cyclic GMP signaling, and in titin phosphorylation, and they can directly cause cardiac hypertrophy and fibrosis, independently of an effect on the microvasculature. The comorbidity-driven microvascular inflammation hypothesis did not identify a blood-borne molecular mediator that selectively targets the heart, and phenomapping based on the clustering of comorbidities has not yielded reproducible groupings. In contrast, selective silencing of proinflammatory adipokines only in adipose tissue causes distant effects on the heart to modulate cardiac structure and the evolution of HFpEF. Clinical trials of drugs that enhance nitric oxide/cyclic GMP signaling or have nonspecific anti-inflammatory effects have not produced favorable effects in clinical HFpEF, whereas drugs that normalize adipokine secretion (e.g., glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter 2 inhibitors) exert clinical benefits in patients with HFpEF. Finally, whereas coronary microvascular dysfunction is present in 60-70% of patients with HFpEF (with endothelium-dependent dysfunction being seen in only 30%), central obesity (assessed by an increased waist-to-height ratio) or visceral adiposity (as by mesenteric, perirenal or epicardial fat) is present in >85-95% of patients with the disorder. Therefore, when compared with the comorbidity-driven coronary microvascular endothelial inflammation hypothesis, the adipokine hypothesis provides an explanatory framework with a stronger evidentiary support and applicable to a broader range of patients with HFpEF. Further work is needed to support these observations.

The original conceptual framework for heart failure and a preserved ejection fraction (HFpEF) was based on the 1982 report by Luchi et al[1] and the 1983 report by Topol et al.,[2] which described the occurrence of heart failure without systolic dysfunction in elderly people. Topol et al suggested that these patients had a small LV chamber size and thickened LV walls, findings that were attributed to uncontrolled hypertension, even though these patients responded poorly to drugs that lowered blood pressure.[2]

Early Misconceptions About Diastolic Dysfunction in HFpEF

Based on these early reports, many physicians assumed that HFpEF was a disorder akin to genetic forms of hypertrophic cardiomyopathy. The LV end-diastolic pressure-volume relationship in hypertrophic cardiomyopathy was presumed to be shifted upwards and to the left, leading to the belief that the elevated LV filling pressures in HFpEF were related to "diastolic dysfunction."[3] Genetically-driven hypertrophic cardiomyopathy is typically seen in young to middle-aged men who are predisposed to low systolic blood pressures, because the LV is not capable of filling adequately to support stroke volume.

However, this pathophysiological characterization did not apply to elderly people with HFpEF. Elderly women with HFpEF typically have a history of hypertension (rather than hypotension). Furthermore, although they often exhibit ventricular hypertrophy, the LV cavity size is typically mildly enlarged (rather than small), and the LV end-diastolic pressure-volume relationship is not generally shifted to the left.[4,5] In fact, as the number of comorbidities of HFpEF increase, the LV end-diastolic pressure-volume relationship is progressively shifted to the right, rather than to the left.[6] — indicative of LV overfilling, rather than pointing to impaired passive ventricular compliance (Table 1).[3,4] Yet, despite the absence of a leftward and upward shift in the LV end-diastolic pressure-volume relationship, for many years, patients with HFpEF were characterized

as having “diastolic dysfunction”, and HFpEF was improperly referred to as “diastolic heart failure”.[3-5]

Development of the Comorbidity-Driven Coronary Microvascular Endothelial Inflammation Nitric Oxide-Cyclic GMP Hypothesis of HFpEF

In the 1990s and early 2000s, physicians noted two intriguing clinical features of patients with HFpEF. First, elderly women with HFpEF typically had multiple comorbidities beyond hypertension. They were usually overweight or had obesity, often had insulin resistance or diabetes, and characteristically exhibited impaired function of many noncardiac organs, particularly the liver, the kidney and the lung.[6-8] It was believed that these comorbidities might play a causal role, and thus, treatment of these comorbidities might alleviate HFpEF.[9] Second, patients with HFpEF often showed striking degrees of systemic inflammation, manifest by increases in C-reactive protein or other circulating inflammatory biomarkers.[10-12] and the inflammatory response was often manifest in the heart. Cardiac tissue from patients with HFpEF exhibited upregulation of proinflammatory pathways,[13,14] which was accompanied by variable degrees of interstitial fibrosis and coronary microvascular dysfunction and rarefaction.[14-17] Impairment of coronary microvascular function was of particularly interest, since it had emerged as a feature of hypertrophic cardiomyopathic states, including those associated with hypertension.[18,19]

Synthesizing these observations, in 2013, Paulus and Tschöpe[20] linked the coexistence of multiple comorbidities, systemic inflammation and coronary microvascular dysfunction, and proposed that the numerous comorbidities seen in elderly women with HFpEF — specifically, obesity, diabetes, chronic obstructive lung disease, hyperlipidemia and hypertension — acted together to trigger a systemic inflammatory response that was directed specifically to the endothelium of the coronary microvasculature (Figure 1). Patients with HFpEF are known to exhibit coronary microvascular

abnormalities, which are accompanied by elevated oxidative or nitrosative stress.[16,21,22] Paulus and Tschöpe proposed that coronary microvascular endothelial inflammation might reduce the production of nitric oxide and cyclic guanosine monophosphate (cGMP) and protein kinase G in neighboring cardiomyocytes,[14,20,22] leading to cardiac hypertrophic responses and reduced titin phosphorylation, causing both increased cardiomyocyte stiffness and myocardial fibrosis.[13,20] The possibility that comorbidity-driven coronary endothelial inflammation-induced nitric oxide-cyclic GMP deficiency might be the primary mechanism responsible for HFpEF became known as the Paulus-Tschöpe hypothesis. The hypothesis was the first framework to propose a shift away from hypertension and towards systemic inflammation as a causal mechanism in HFpEF.[24]

Evaluation and Clinical Testing of the Paulus-Tschöpe Hypothesis

Since the formal presentation of this synthesis, major questions have emerged with respect to the Paulus-Tschöpe hypothesis.

- First, although 60-70% of patients with HFpEF demonstrate evidence of coronary microvascular dysfunction,[16] coronary microvascular dysfunction is also characteristic of patients with HFrEF.[25,26] Therefore, this microvascular abnormality may be related to increased left ventricular filling pressures rather than to left ventricular hypertrophy or systemic inflammation.[27,28]

- Second, coronary microvascular dysfunction in HFpEF is often endothelium-independent,[29] and furthermore, there is little evidence that coronary microvascular endothelial dysfunction is related to microcirculatory endothelial inflammation in the clinical setting. Endomyocardial biopsies of patients with HFpEF have shown mild macrophage infiltration in cardiac tissue with upregulation of profibrotic pathways along with increased expression of endothelial adhesion molecules that are capable of triggering

an inflammatory response — but these changes have been observed without specific localization to the microvascular endothelium and without demonstration of endothelial inflammation.[14,15,30-32] To date, there has been no histological evidence of coronary microvascular endothelial inflammatory lesions on microscopy in cardiac tissue derived from patients with HFpEF.

- Third, as Paulus and others have recognized, coronary microvascular endothelial dysfunction does not precede — and thus, may not be well-positioned to cause — the development of cardiomyocyte abnormalities in experimental HFpEF.[33]

- Fourth, deficient protein kinase G signaling resides among the myriad of reversible abnormalities in cellular biology that have been reported in experimental and clinical HFpEF.[14,23,34,35] However, the expression of protein kinase G in healthy cardiomyocytes is typically low,[36] and defects in protein kinase G signaling are not specific to HFpEF.[23,37] Abnormalities of protein kinase G signaling have been seen in patients with HFrEF, and additionally, titin hypophosphorylation is not only seen in experimental HFpEF, but also in experimental volume overload states and in clinical HFrEF.[23,38-41] Accordingly, the clinical relevance of defective protein kinase G signaling and titin phosphorylation in HFpEF is uncertain, since these abnormalities (typically believed to be indicative of increased cardiomyocyte stiffness) are often observed in states of enhanced (not diminished) ventricular capacitance and distensibility (as seen in HFrEF).

- Fifth, the results of randomized clinical trials of therapeutic interventions has raised important questions about the relevance of derangements in nitric oxide-cGMP in HFpEF (Table 1). In the NEAT-HFpEF and INDIE-HFpEF trials,[42,43] treatment with nitric oxide donors — i.e., isosorbide mononitrate and inhaled inorganic nitrite — did not improve exercise capacity or maximal oxygen consumption, and active treatment was accompanied

by an impairment in daily activity assessed by accelerometry. In the VITALITY-HFpEF and CAPACITY-HFpEF trials,[44,45] cGMP signaling achieved by soluble guanylyl cyclase stimulation with vericiguat and praliciguat did not improve quality of life scores or lead to clinical improvement. In the RELAX trial, augmentation of cyclic GMP with the use of sildenafil, an inhibitor of phosphodiesterase 5, did not yield beneficial effects on exercise capacity and clinical status.[46] Therefore, regardless of the mechanism by which nitric oxide and cyclic GMP signaling has been pharmacologically enhanced, the results of clinical trials indicate that such augmentation does not appear to be beneficial in HFpEF, thus suggesting that that deficient nitric oxide-cyclic GMP signaling is not likely to be a driving mechanism of HFpEF in the clinical setting.

Reshaping of the Paulus-Tschöpe Hypothesis Into the Comorbidity-Driven Metabolic/Hemodynamic Inflammation/Fibrosis Hypothesis

In response to these concerns, the Paulus-Tschöpe hypothesis was reshaped to expand its original focus beyond nitric oxide-cGMP signaling and coronary microvascular inflammation. A revised framework (summarized in 2021 by Paulus and Zile[47]) proposed that the multiple comorbidities of HFpEF (e.g., obesity, diabetes, chronic kidney disease and anemia) caused a "metabolic load", which promoted systemic inflammation — which was presumed to be mediated by canonical cytokines (e.g., tumor necrosis factor-alpha, interleukin-1 and interleukin-6) and immunoglobulin cell adhesion molecules (e.g., intercellular and vascular cell adhesion molecule 1 [ICAM-1 and VCAM-1]), Figure 1.[48,49] The action of these mediators might lead to nitric oxide-cGMP depletion and oxidative stress in the coronary endothelium, and thus to abnormalities of titin phosphorylation and splicing, whereas systemic inflammation (acting directly on cardiomyocytes) was postulated to lead to the accumulation of degraded proteins in the heart. Furthermore, the framework proposed that systolic hypertension imposed an additional "hemodynamic load" that could lead to fibroblast activation and the recruitment of proinflammatory and profibrotic macrophages and T-

cells,[31,32,50-52] causing the matricellular protein-dependent accumulation of collagen in the interstitial space. The combined effects of "metabolic loading" and "hemodynamic loading" were hypothesized to cause elevated cardiomyocyte and myocardial stiffness.

However, the reshaping of the Paulus-Tschöpe Hypothesis — now described as the comorbidity-driven metabolic/hemodynamic inflammation/fibrosis hypothesis — has not been well-supported by the results of experimental studies and clinical trials (Table 1).

- First, the comorbidities grouped together under "metabolic load" (e.g., diabetes, chronic kidney disease and anemia) are physiologically diverse and have not been shown to be act as upstream etiological factors in promoting a common mechanism of systemic inflammation, and they have not been demonstrated to function through shared cellular pathways in promoting cardiomyocyte stress.

- Second, a specific mediator of HFpEF that was proposed in the reshaped framework — increased levels of growth differentiation factor-15 — suppresses endothelial inflammation and alleviates cardiac hypertrophy, myocardial fibrosis and the diastolic filling abnormalities of HFpEF.[35,53,54] These favorable effects are opposite to those that might promote the development of HFpEF.

- Third, the presence of multiple comorbidities is not a unique feature of HFpEF, and it is also common to patients with HFrEF, where they have not been proposed to exert a special pathophysiological role. Phenomapping based on the clustering of comorbidities has not yielded reproducible groupings, and instead, it reflects mathematical partitioning rather than a biological or clinical reality.[55] Advocates of comorbidity clustering have recognized the limitations of this approach.[56]

- Fourth, drugs that are directed to the treatment of the comorbidities of HFpEF — acting to lower blood glucose in patients with type 2 diabetes, to improve glomerular function or to correct anemia — do not predictably ameliorate and may exacerbate the clinical course of heart failure.[57-60] Similarly, drugs that mitigate hemodynamic load (e.g., irbesartan) do not appear to exert favorable effects on the clinical course of HFpEF, especially in the current era.[61,62]

- Fifth, anti-inflammatory treatments that target canonical cytokines or cellular inflammatory responses have not been shown to be effective in HFpEF. IL-1 antagonism with anakinra has not improved functional capacity in patients with HFpEF,[63] and the silencing of IL-6 does not prevent experimental pressure overload- or inflammation-induced cardiac remodeling.[64,65] Inhibition of IL-6 with tocilizumab has not been accompanied by favorable effects on heart failure, and IL-6 inhibition with siltuximab is accompanied by fluid retention and edema.[66,67]

- Sixth, colchicine — which acts to inhibit activation of the NLRP3 inflammasome and suppress interleukin-1b — does not produce symptomatic benefits or prevent worsening heart failure events in patients with established heart failure, even though the drug reduces systemic inflammation.[68-71] Dedicated trials of colchicine in HFpEF have been terminated without reported results.[72,73] In a post hoc analysis, selective suppression of interleukin-1b with canukinumab appeared to reduce heart failure events, but the relevance of this observation to HFpEF is not clear.[74]

- Seventh, the anti-inflammatory action of myeloperoxidase inhibition (an action that would be expected to minimize cellular inflammatory responses in the myocardium) has not yielded favorable effects in patients with HFpEF in randomized placebo-controlled trials.[75,76] The anti-inflammatory effects of uric acid reduction with verinurad in patients

with HFpEF and hyperuricemia has not produced clinical benefits.[77] Neprilysin inhibition with sacubitril/valsartan produced exceptionally modest changes in circulating biomarkers of collagen deposition (despite marked increases in cGMP), and these actions were not shown to be associated with the magnitude of the effects of the drug on heart failure outcomes.[78] The antifibrotic actions of pirfenidone produced only small decreases in extracellular volume by cardiac magnetic resonance imaging, and it did not produce favorable effects on health status or diastolic function in clinical HFpEF.[79]

Therefore, based on the totality of evidence, it is not clear that the mechanisms or therapeutic targets specifically identified in the comorbidity-driven metabolic/hemodynamic inflammation/fibrosis hypothesis provide a coherent framework for understanding the pathogenesis or guiding the treatment of clinical HFpEF.

Evolution of the Visceral Adiposity-Adipokine Imbalance Hypothesis of HFpEF

In 2017-2024, several investigators began to assemble the elements of an alternative framework to explain the association of comorbidities, systemic inflammation and HFpEF.[80-84] Increased circulating levels of leptin and suppressed circulating levels of adiponectin — hormones characteristically secreted only by adipocytes (i.e., adipokines) — were found to be consistent features of experimental and clinical HFpEF.[82,85-88] Derangements in these and other adipokines were also shown to contribute to cardiac hypertrophy and fibrosis, to abnormalities in calcium handling proteins, to coronary microvascular dysfunction, and to systemic inflammation.[35,82,89-92] Interestingly, the characteristic pattern of derangement in the expression of levels of leptin and adiponectin seen in HFpEF were also commonly observed in patients with diverse comorbidities, i.e., hypertension, insulin resistance and diabetes and chronic kidney disease,[62,93,94] suggesting that imbalances in the expression of proinflammatory and cytoprotective adipokines might provide the link between these diverse comorbidities, systemic inflammation and the cardiac structural and functional abnormalities of HFpEF.

Furthermore, several investigators noted that derangements of these adipokines and the evolution of HFpEF appeared to be related to an expansion and biological transformation of epicardial adipose tissue and other visceral fat depots.[81,95,96] The epicardial fat depot shares an unobstructed circulation with the adjoining myocardium. An increase in epicardial fat mass could therefore act as a transducer, promoting the secretion of proinflammatory adipokines and focusing their effects onto cardiomyocytes, cardiac fibroblasts and the coronary microcirculation. Epicardial adiposity was also strongly associated with the development of atrial myopathy and atrial fibrillation,[97-100] two common features of the HFpEF clinical phenotype. Therefore, it seems plausible that an expansion of visceral fat depots surrounding the heart and other organs — leading to secretion of a proinflammatory suite of adipokines — could explain the pathophysiological attributes and clinical characteristics of HFpEF.

Formulation and Testing of the Adipokine Hypothesis

A formal construct of an adipokine-driven framework (presented in 2025) noted that obesity and dietary nutrient excess are obligatory drivers of the most relevant experimental models of HFpEF[35] and that changes in visceral adiposity and circulating adipokines are observed years before and predict the diagnosis of HFpEF in the general community.[95,96,101-107] Importantly, the degree of visceral adiposity tracks with the severity of HFpEF,[35,108] and adipokine derangements occur in parallel in central obesity and HFpEF and are correlated with an adverse prognosis.[35]

According to the adipokine hypothesis, adipose tissue transmits its healthy or deranged biology to other organs by virtue of adipokine signaling molecules.[35] The 2025 framework greatly expanded the number of HFpEF-relevant adipokines to include > 100 signaling molecules — including bioactive lipids and microRNAs.[35,109,110] Experimental and clinical HFpEF was accompanied by suppression of adipokines that acted to inhibit hypertrophy, inflammation, fibrosis and microvascular dysfunction in the heart as well as renal tubular sodium reabsorption. In contrast, in experimental and clinical HFpEF, the dominant adipokines secreted from dysfunctional fat promoted hypertrophy, inflammation, fibrosis and coronary microvascular dysfunction in the heart while simultaneously causing renal sodium retention and plasma volume expansion,[35] thus explaining the LV overfilling that is characteristic of adiposity-related HFpEF.[80]

Features That Distinguish the Adipokine Hypothesis From Coronary Microvascular Inflammation Model of HFpEF

Several important features distinguish the adipokine hypothesis from the earlier comorbidity-driven coronary microvascular inflammation model of HFpEF.

- First, the adipokine hypothesis explains the coexistence of systemic inflammation, comorbidities and HFpEF by identifying a shared proximal causal mechanism for all three features. Whereas the Paulus-Tschöpe model postulates that all comorbidities contribute directly and independently to systemic inflammation, and thus, to the development of HFpEF, the adipokine hypothesis elevates one comorbidity — visceral adiposity — to a role of primacy and proposes that excess visceral adiposity and adipokine imbalances are the common upstream causal mediator of HFpEF, its comorbidities and the systemic inflammatory state. It is therefore noteworthy that the proinflammatory myocardial gene expression in patients with HFpEF — often cited to support the comorbidity-driven framework — is fully explained by increases in body mass index.[111]

- Second, excess visceral adiposity and adipokine imbalances have been shown to directly cause hypertension, insulin resistance and type 2 diabetes, chronic kidney disease and atrial fibrillation.[35,62,93,94,97,98] Interestingly,, imbalances in adipokines can also cause all the pathophysiological abnormalities identified in the Paulus-Tschöpe hypothesis. Abnormalities in adipokines has been shown to cause microvascular dysfunction, defects in cyclic GMP and protein kinase G signaling, and in titin phosphorylation.[90,112-115] In addition, adipokines can promote both cardiac hypertrophy and fibrosis, independently of any effect on the microvasculature,[35] thus explaining why coronary microvascular dysfunction is not necessary for the development of cardiac hypertrophy and fibrosis.[33] Finally, the mechanisms identified by some investigators as driving myocardial fibrosis in

in the comorbidity-driven model of HFpEF — secreted protein acidic and rich in cysteine (SPARC) and tissue inhibitor of metalloproteinases 1 (TIMP1) — are established adipokines that are secreted by dysfunctional adipose tissue.[35]

- Third, visceral adiposity can explain other common features of HFpEF, including the development of atrial myopathy and atrial fibrillation, skeletal muscle and pulmonary abnormalities as well as renal sodium retention and plasma volume expansion.[32,116-119] These additional features of HFpEF are not addressed by the comorbidity-driven coronary microvascular inflammation hypothesis.

- Fourth, the adipokine hypothesis identifies a specific array of blood-borne signaling molecules that are increased in patients with HFpEF and have been shown to cause HFpEF under experimental conditions.[35] In contrast, the Paulus-Tschöpe hypothesis did not identify specific mediators by which comorbidities (acting individually or collectively) might directly drive the development of HFpEF.

- Fifth, experimental HFpEF is characterized by the upregulation of proinflammatory adipokines selectively in adipose tissue, and selective silencing of these adipokines only in adipose tissue causes distant effects on the heart to modulate cardiac structure and the evolution of HFpEF.[35] In contrast, the Paulus-Tschöpe hypothesis did not have strong support from experimental tissue-selective knockout and overexpression models of HFpEF.

- Sixth, glucagon-like receptor 1 agonists, sodium-glucose cotransporter 2 inhibitors and mineralocorticoid receptor antagonists — drugs known to produce beneficial effects in randomized placebo-controlled trials in clinical HFpEF — are known to act directly on adipocytes in a manner that causes disproportionate decreases in visceral adiposity while acting to normalize the adipokine imbalance characteristic of patients with HFpEF.[35]

These findings contrast with the lack of support for defective nitric oxide-cGMP signaling in clinical trials of HFpEF.[42-46]

- Seventh, whereas coronary microvascular dysfunction is present in 60-70% of patients with HFpEF[16,25] (with endothelium-dependent dysfunction being seen in only 30%[29]), central obesity (assessed by an increased waist-to-height ratio) or visceral adiposity (as by mesenteric, perirenal or epicardial fat) is present in >85-95% of patients with the disorder.[119-122] The adipokine hypothesis applies not only to people with obesity, but it is particularly relevant to those with excess visceral adiposity, a nearly universal finding in HFpEF.[119] Therefore, the adipokine hypothesis may provide an explanatory framework for a broader range of patients with HFpEF than the comorbidity-driven coronary microvascular endothelial inflammation hypothesis.

Summary and Conclusions

The development of comorbidity-driven inflammation hypothesis of HFpEF marked a major step forward in identifying systemic inflammation as a critically important mechanism in driving the development of HFpEF. The original framework focused on the coronary microcirculation and deficient nitric oxide-cGMP-protein kinase G signaling, but it was subsequently reshaped to propose that multiple comorbidities act systemically to drive inflammatory and fibrotic responses throughout the myocardium, but without identification of a specific mediating mechanism. In contrast, the adipokine hypothesis identifies one specific comorbidity — visceral adiposity — as the root cause of HFpEF, and it establishes the secretion of proinflammatory, prohypertrophic and profibrotic adipokines from expanded and inflamed visceral fat depots as the molecular mediators not only of the systemic inflammatory response, but also of the development of cardiac hypertrophy, fibrosis and microcirculatory dysfunction. Visceral adiposity and the secretion of proinflammatory adipokines are also the causal mechanisms that drive the development of HFpEF-

associated comorbidities as well as atrial fibrillation, sodium retention and skeletal muscle abnormalities. When compared with the comorbidity-driven nitric oxide-cGMP deficiency hypothesis, the adipokine hypothesis has stronger support from experimental studies and randomized clinical trials. Because it is focused on excess visceral adiposity rather than coronary microvascular inflammation, the adipokine hypothesis may also apply to a broader proportion of patients with HFpEF. Importantly, the adipokine hypothesis identifies a new suite of target molecules for the development of novel interventions for HFpEF, beyond those identified by earlier conceptual frameworks that focused largely (and often futilely) on the treatment of comorbidities.

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Figure 1.
Proposed Conceptual Frameworks to Explain the Pathogenesis of Heart Failure With a Preserved Ejection Fraction
The figure illustrates the evolution of thinking with respect to conceptual frameworks of HFpEF that have focused on the importance of inflammation as a mediating event. The early models that focused on comorbidity-driven coronary microvascular inflammation and myocardial fibrosis have undergone a metamorphosis to the adipokine hypothesis, which elevates visceral adiposity and identifies the secretion of proinflammatory adipokines as a proximal causal mechanism.Abbreviations: cGMP = cyclic guanosine monophosphate; HFpEF = heart failure with a preserved ejection fraction; NO=nitric oxide

Table 1.
Defining Elements and Key Limitations of Conceptual Frameworks Used to Explain Coexistence of Systemic Inflammation and Multi-Organ Comorbidities in Heart Failure With a Preserved Ejection Fraction

	Defining Elements	Strengths and Key Limitations
Comorbidity-driven coronary microvascular dysfunction resulting in nitric oxide-cyclic GMP deficiency and titin abnormalities	Multiple coexisting comorbidities, acting in concert, were postulated to promote systemic inflammation, which led to inflammation of the coronary microvasculature and secondary changes in cardiomyocytes.	Proposed framework did not identify a molecular mediator by which multiple comorbidities, acting in concert, would cause systemic inflammation. No benefit was seen with drugs that increase nitric oxide or cyclic GMP in randomized clinical trials of patients with HFpEF.
Comorbidity-driven metabolic/ hemodynamic cardiac inflammation/ fibrosis hypothesis	Multiple coexisting comorbidities, acting in concert, caused metabolic and hemodynamic loading, leading to cardiomyocyte accumulation of degraded proteins along with cardiac immune cell and fibroblast activation and myocardial fibrosis	No mediator identified by which multiple comorbidities might induce metabolic loading. Many drugs that treat the comorbidities of HFpEF do not ameliorate and may exacerbate the clinical course of heart failure. Treatments that target canonical cytokines or cellular inflammatory responses have not been shown to be effective in patients with established HFpEF.
Visceral adiposity-adipokine imbalance hypothesis	Expansion of visceral fat mass leads to proinflammatory transformation of adipose tissue, leading to altered secretion of messenger molecules, which cause systemic inflammation; multiple comorbidities; cardiac hypertrophy, fibrosis, microvascular dysfunction; and the sodium retention of HFpEF	Experimental HFpEF leads to upregulation of proinflammatory adipokines selectively in adipose tissue, and suppression of adipokines selectively in adipose tissue ameliorates HFpEF. Established drugs for HFpEF act to normalize adiposity and adipokine balance. Selective pharmacological targeting of novel adipokines has not yet been evaluated in clinical trials of HFpEF.

Abbreviations: GMP = guanosine monophosphate; HFpEF = heart failure with a preserved ejection fraction; LV = left ventricular.