



# Heart Failure With Preserved Ejection Fraction and Adipose Tissue: A Story of Two Tales

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## OPEN ACCESS

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equally to this work

### Specialty section:

This article was submitted to  
Cardiovascular Metabolism,  
a section of the journal  
Frontiers in Cardiovascular Medicine

**Received:** 22 May 2019

**Accepted:** 22 July 2019

**Published:** 02 August 2019

### Citation:

Oh A, Okazaki R, Sam F and  
Valero-Muñoz M (2019) Heart Failure  
With Preserved Ejection Fraction and  
Adipose Tissue: A Story of Two Tales.  
*Front. Cardiovasc. Med.* 6:110.  
doi: 10.3389/fcvm.2019.00110

Heart failure with preserved ejection fraction (HFpEF) is characterized by signs and symptoms of heart failure in the presence of a normal left ventricular ejection fraction. Although it accounts for up to 50% of all clinical presentations of heart failure, there are no evidence-based therapies for HFpEF to reduce morbidity and mortality. Additionally there is a lack of mechanistic understanding about the pathogenesis of HFpEF. HFpEF is associated with many comorbidities (such as obesity, hypertension, type 2 diabetes, atrial fibrillation, etc.) and is coupled with both cardiac and extra-cardiac abnormalities. Large outcome trials and registries reveal that being obese is a major risk factor for HFpEF. There is increasing focus on investigating the link between obesity and HFpEF, and the role that the adipose tissue and the heart, and the circulating milieu play in development and pathogenesis of HFpEF. This review discusses features of the obese-HFpEF phenotype and highlights proposed mechanisms implicated in the inter-tissue communication between adipose tissue and the heart in obesity-associated HFpEF.

**Keywords:** HFpEF, adipose tissue, obesity, natriuretic peptides, cardiac remodeling

## HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF): A NEW TERM FOR AN OLD DISEASE

Heart failure (HF) is a clinical syndrome caused by structural and functional abnormalities in the heart that impair the ability of the ventricles to fill or eject blood. The cardinal manifestations of HF are breathlessness, dyspnea and fatigue, which may lead to limited effort tolerance; and fluid retention, thus resulting in pulmonary congestion and/or peripheral edema (1, 2). HF is a leading cause of morbidity and mortality both in the United States and worldwide. As of 2012, 5.8 million Americans had HF with the number of individuals with HF projected to continue to increase in the next 20 years (3–5).

Segregating patients with HF by left ventricular (LV) ejection fraction (EF) is an important phenotypic marker as it indicates unique pathophysiological mechanisms and thus subsequent responses to therapy (6–8). Patients with clinical HF and normal or preserved EF represent a phenotype that is different from those with reduced EF (HFrEF). HFpEF is due to the inability of the heart to fill with blood because it may be thick or stiff. HFpEF patients are often touted as elderly, predominantly female, obese, have long-standing hypertension, may have diabetes, and some degree of LV hypertrophy (9, 10). HFpEF was initially labeled as “diastolic HF” because impaired filling of the LV was thought to be the underlying etiology to differentiate it from “systolic HF” (HFrEF) (11). However, LV diastolic dysfunction is not unique to HFpEF and is also observed in patients with HFrEF (9, 12). Similarly, “diastolic HF” patients may have some degree of impaired

systolic function (13, 14). Thus, the term “diastolic” HF was abandoned and replaced by HFpEF. The definition of HFpEF moved away from a primary focus on echocardiographic evidence of diastolic dysfunction, and toward a definition inclusive of cardiac structural abnormalities resulting from high filling pressures, diastolic abnormalities, elevated biomarkers, and increased left heart filling pressures by invasive hemodynamic measurements in the setting of an EF  $\geq 50\%$  (15–17).

In contrast to HFrEF, there are no evidence-based therapies, to date, which have shown improved outcomes in HFpEF (2), likely because of the marked heterogeneity of the HFpEF syndrome (16, 18). It has been suggested that phenotyping patients into pathophysiologically homogeneous groups in clinical trials may result in better outcomes (19–21). Increased adiposity in obesity has been suggested to be a therapeutic target in HFpEF (22). This review, therefore, summarizes the current understanding of HFpEF in context of obesity, and how “crosstalk” exists between the heart and the adipose tissue in these two conditions.

## The Obese-HFpEF Phenotype

Obesity has reached epidemic proportions worldwide and is a major comorbidity in HFpEF patients (23–25). The prevalence of being overweight and obese is as high as 84% in clinical trials, epidemiological studies and HF registries (26–28) and presently there are >1.8 million persons in the U.S. with an overweight or obesity-associated HFpEF phenotype (22). Earlier studies suggested that symptoms in obese HFpEF patients were simply related to excess body mass and not to cardiac abnormalities (29). However, recent disease paradigms have incorporated obesity into the pathophysiology of HFpEF (24). Obesity and related cardio-metabolic traits are also more strongly associated with the risk of future HFpEF rather than HFrEF (30), suggesting that obesity-associated HFpEF represents a distinct clinical phenotype within the broad spectrum of HFpEF (24, 31). Studies from murine models have highlighted the relationship between obesity, diastolic dysfunction and HFpEF. Increased adiposity and metabolic alterations in obesity were associated with cardiac structural remodeling and diastolic dysfunction in mice and rats (32, 33), and have recently been described to induce HFpEF (34–38). These models are useful tools to investigate mechanisms linking obesity and HFpEF and to explore the use of potential therapies in this specific phenotype (39). However, there is no animal model that can completely mimic the human disease, partly because human HFpEF is heterogeneous and encompasses a broad range of signs, symptoms, and disease presentation (39). Thus, the paucity of highly characterized HFpEF animal models that reflect cardiopulmonary and metabolic changes seen in obesity associated-HFpEF in humans contributes to the lack of understanding of the mechanisms underlying HFpEF and the development of treatments.

## THE ADIPOSE TISSUE AND THE HEART CROSS-TALK IN HFPEF

There is an increasing appreciation of the complex connection between the adipose tissue and the heart, which highlights

the importance of the heart-adipose-axis in the pathogenesis of cardiovascular disease and specifically HF (40). However, the putative mechanisms that connect both tissues and link obesity and HF have not been fully elucidated (23, 41). It was long assumed that the burden of obesity in HF was a physical/mechanical one (42). Thus, hemodynamic alterations that result from excessive adipose accumulation in obese patients would have subsequent effects on cardiac morphology and ventricular function (43). Although volume overload plays a role in HF and specifically HFpEF, in recent years, the endocrine, metabolic and cellular signaling behind the obesity-related HFpEF phenotype has received much attention.

Current evidence supports the hypothesis that obesity-related HFpEF may result from adipokines imbalance, neprilysin over-activity and/or augmented mineralocorticoid signaling (44). Adipose tissue is a potent endocrine organ that synthesizes and secretes a number of adipose-specific cytokines, *aka* adipokines, such as leptin or adiponectin, which elicit a variety of local and systemic responses (45). Leptin originates mainly from subcutaneous adipose tissue (46) and circulating levels of leptin directly correlate with fat mass in both obese rodents and humans (40). Leptin plays an important role in the regulation of the sympathetic nervous system, affecting heart rate and blood pressure (47) and exert its effects by activating various mediators including the Janus kinases (JAK)/Signal Transducer and Activator of Transcription proteins (STAT), the phosphoinositide 3-kinase (PI3K)/ cGMP-dependent protein kinase B (PKB) and the p38 mitogen-activated protein kinase (p38-MAPK) pathways (48). Alterations in leptin signaling have deleterious effects in cardiac remodeling in pre-clinical models of obesity (33). Additionally, leptin is a major stimulus for the production of aldosterone in obesity (49, 50), and might be responsible for the exacerbated mineralocorticoid receptor signaling in obesity-related HF (51, 52). In addition to aldosterone-mediated changes in cardiac structure, such as exacerbated cardiac remodeling (53, 54), increased leptin results in impaired calcium handling and impaired relaxation in the heart (55, 56). However, although the contribution of leptin to the genesis and progression of the obese-HFpEF phenotype has been speculated (42), there are no mechanistic or clinical evidences to support leptin's role in the HFpEF phenotype. In contrast to leptin, adiponectin levels are highest in lean subjects but decline as body mass increases (57). Adiponectin have multiple beneficial effects in the heart and the vasculature (45) and, not surprisingly, depressed levels in obesity are associated with inflammation and greater cardiovascular risk (58–60). Experimental evidence showed that adiponectin has anti-inflammatory properties (61) and modulates oxidative stress-induced autophagy (62) and cardiac remodeling (63). These beneficial effects of adiponectin have been linked to direct effects of this adipokine on the cellular in the heart and blood vessels. It has been postulated that the ability of adiponectin to attenuate cardiac hypertrophy and fibrosis is likely due to its ability to stimulate AMP-activated protein kinase (AMPK)-dependent and extracellular-signal-regulated kinase (ERK) signaling within cardiac myocytes and endothelial cells (63–65). However, although adiponectin levels are not predictive of HF development in humans (66), human studies

indicate that elevated circulating adiponectin is associated with increased mortality in chronic HFrEF patients (67–69). These findings have been partly explained by the fact that adiponectin upregulation seems to be linked to cachexia and adiponectin raised levels may just reflect the hyper-catabolic state in severe HF (70, 71). This is consistent with the fact that overweight and obese HFrEF patients had normal levels of adiponectin (72). In contrast, circulating levels of adiponectin are markedly reduced in obese HFpEF patients, particularly in women (73), and it has been suggested that adiponectin may prevent some of the pathophysiologic mechanisms underlying the obese-HFpEF such as myocardial hypertrophy, cardiac fibrosis, oxidative stress, and inflammation (44, 60). The relationship of adiponectin to aldosterone appears to be polar opposite in HFpEF, as adiponectin deficiency in a preclinical model of hypertension-associated HFpEF where aldosterone is elevated, exacerbated cardiac remodeling, diastolic dysfunction and pulmonary congestion (74); and adiponectin overexpression protected against the progression of HFpEF by regulating oxidative stress and modulating calcium-handling proteins, specifically cAMP-dependent protein kinase (PKA) phosphorylation of phospholamban (75).

Chronic, low-grade inflammation is also a hallmark of obese adipose tissue (76) and systemic metabolic inflammation, accompanied by an increased activity of the inducible nitric oxide synthase (iNOS) and augmented nitrosative stress, may play an important role in the pathophysiology of obesity-associated HFpEF (77). This is supported by the hypothesis that imbalance in the nitrate-nitrite-nitric oxide pathway plays a role both in the peripheral abnormalities that contribute to HFpEF, such as increased arterial stiffness and abnormalities in skeletal muscle fiber type and capillary density (78). Increased oxidative stress in the coronary microvascular endothelium due to decreased nitric oxide bioavailability and reduced cGMP dependent protein kinase (PKG) activity in cardiac myocytes, results in increased cardiac stiffening and hypertrophy (5) thus contributing to the cardiac abnormalities. Additionally, the clinical relevance of proinflammatory cytokines in obesity-associated HFpEF is being actively investigated, with promising targets including inflammasome, toll-like receptors, cytokines and macrophages (79, 80). Notably, interleukin 1 (IL-1) has been strongly associated with adverse cardiac remodeling and heart failure and strategies targeting the IL-1 pathway are currently undergoing clinical evaluation (81, 82).

### Obesity and Exercise Tolerance in HFpEF

Decreased exercise tolerance is an early symptom of HFpEF and is a major determinant of prognosis and associates with a reduction in quality of life (83). Exercise capacity is defined as the rate of O<sub>2</sub> consumption (VO<sub>2</sub>) at peak exercise, and any factor that limits peak VO<sub>2</sub>, by impeding O<sub>2</sub> delivery and/or utilization, can cause exercise intolerance (84). Although exercise intolerance in HFpEF was classically attributed to changes in cardiac output, new findings suggest that peripheral, non-cardiac factors play an important role in the limitations in exercise capacity in patients with HFpEF (85). Of these, obesity has been also proposed to be a major driver of exercise intolerance, independent of the effects

of cardiac function (86). Interestingly, the pattern of regional adipose deposition, with increased intra-abdominal and inter-muscular fat appear to associate with decreased peak VO<sub>2</sub>, and may thus be related to adverse consequences in exercise tolerance in HFpEF beyond total body adiposity (87).

It has been suggested that higher levels of exercise training may attenuate the increased risk of HF associated with obesity (88). Exercise, in addition to caloric restriction-induced weight loss, are the only interventions shown to improve exercise capacity outcome in HFpEF (89–92). Furthermore, a recent study demonstrated that exercise training improved not only exercise capacity but also body composition, with a reduction in total fat mass and thigh muscle/inter-muscular fat ratio, and with reduced inflammation and LV mass (92). Similarly, preclinical studies in obese HFpEF rats showed that exercise training improved exercise capacity (36). Further studies are warranted in order to investigate specific mechanisms involved.

### The Obesity Paradox

Although obesity is linked to the development of HF (23) and associates with abnormal hemodynamics and adverse cardiac remodeling in HFpEF (93), in epidemiological studies mild to moderate overweight or obesity status (body mass index, BMI, of 30–34.9) was reported to have a protective effect in patients with HF (94, 95). This phenomenon was termed “the obesity paradox” and initially observed in small population studies (96, 97) and confirmed in large observational studies in both HFrEF and HFpEF patients (26, 98–101). However, other studies have not shown that the obesity paradox exists in HFpEF (102–104), and thus, the causal link between this scientific observation and its clinical implications are limited and remain hotly debated. Several hypotheses are proposed to explain the presence or absence of the obesity paradox (105, 106), and have been extensively reviewed (107–109).

### Cardiac Natriuretic Peptides and Obesity in HFpEF

Cardiac natriuretic peptides are mainly released from the heart in response to myocardial stress and have a key role in cardiovascular homeostasis (110). There are three types of natriuretic peptides in humans, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). ANP and BNP are released from the atria and ventricles of the heart respectively and are the most physiologically active natriuretic peptides. In contrast, CNP is thought to act locally, as a paracrine/autocrine regulator, since it is cleared rapidly from the circulation and present at very low concentrations in plasma (111) with effects primarily on bone growth (112). ANP and BNP bind to two homodimeric receptors, natriuretic peptide active and clearance receptors (NPRA and NPRC respectively), which are expressed in many tissues, including white and brown adipose tissue (113). This broad distribution is indicative of the wide biological effects of the natriuretic peptides. Although ANP and BNP were initially characterized by their actions promoting diuresis and natriuresis, contributing to maintenance of extracellular fluid volume and vascular tone (114), they mediate actions beyond simply control of blood pressure and

volume homeostasis. These include but are not limited to obesity and metabolic regulation, atherosclerotic and thrombotic control, and cardiac remodeling (115).

ANP and BNP are synthesized as precursor pro-hormones (proANP and proBNP) which are then processed to their biologically active forms ANP and BNP, and biologically inactive N-terminal proANP (NT-proANP) and NT-proBNP forms (116). Of these, BNP and NT-proBNP have demonstrated diagnostic and prognostic value in patients with HF (117). Increased BNP is independently associated with the increased risk of developing HF even within an asymptomatic general population (118) and once HF manifests, higher BNP levels are associated with increased risk of adverse events (119). Whereas, BNP and NT-ProBNP are elevated in clinical HF regardless of the LV EF, these levels are usually higher in HFrEF than in HFpEF (120, 121). Circulating BNP levels are also typically lower in patients with obesity compared to normal weight counterparts given a similar degree of clinical HF. This is evident in HFpEF, where obese patients with HFpEF usually have lower circulating BNP and NT-ProBNP levels than non-obese patients (24, 122). However, despite the reduced levels of natriuretic peptides in obese patients, they still serve as an important tool in HF both for screening and prognostic purposes, albeit at a lower threshold (93, 123, 124). Obesity in mice and rats is associated with a reduction in natriuretic peptides levels (125, 126), even in the setting of impaired cardiac function (127).

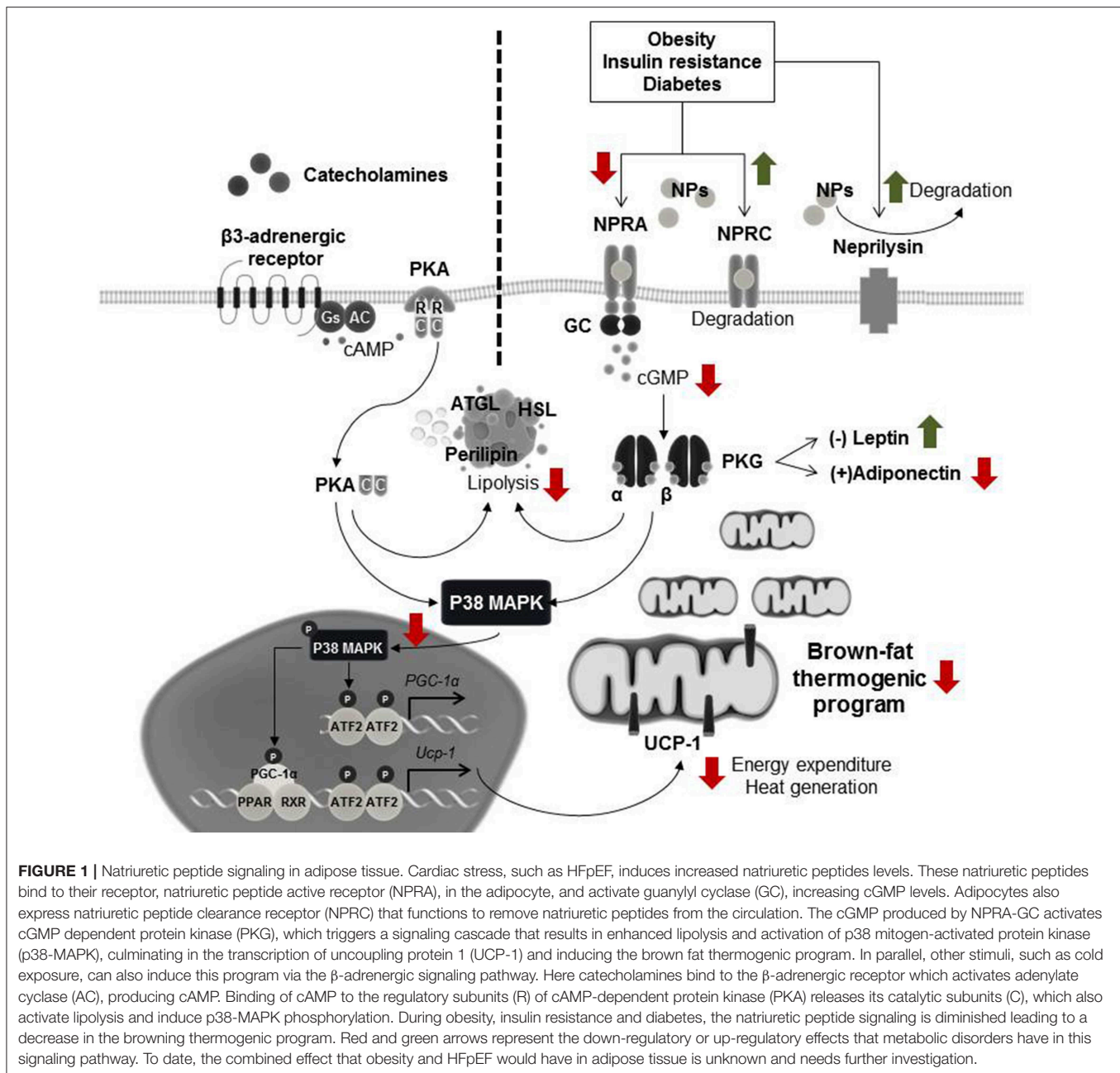
## The Natriuretic Handicap

The inverse relationship between circulating cardiac BNP and obesity (defined by BMI) is termed the “natriuretic handicap” and has been described in both healthy subjects and patients with HF (31, 128). It has been hypothesized that BNP levels are reduced in obesity due to the differential expression of their clearance receptor (NPRC) resulting in enhanced degradation in adipose tissue (129). Additionally, others showed that obese patients have decreased natriuretic peptides production (130, 131); consistent with pre-clinical studies in murine obesity models showing reduced levels of natriuretic peptides cardiac mRNA expression (126, 132). Other mechanisms linking natriuretic peptides reduction and insulin resistance have also been proposed to explain this inverse relationship (133, 134). ANP and BNP can be also degraded by extracellular proteases such as neprilysin (116, 135). Neprilysin is secreted by adipocytes and promotes adipogenesis, creating a positive feedback loop. People with obesity have increased levels of neprilysin in proportion with their body mass (136) and neprilysin levels are particularly elevated in obese patients with HFpEF (137). NT-proBNP is mainly cleared by renal excretion and is not a substrate for neprilysin degradation (138). A recent phase II clinical trial investigated the effect of an angiotensin receptor neprilysin inhibitor (LCZ696) in overweight/obese HFpEF patients for 36 weeks and found left atrial reverse remodeling and improvement in NYHA class. These results were accompanied with a reduction in NT-proBNP suggesting that LCZ696 reduced left ventricular pressures and wall stress (139), and provided the rationale for an outcomes trial in HFpEF, which is presently underway (140).

## Cardiac Natriuretic Peptides Signaling in the Adipose Tissue

White adipose tissue was previously thought to only function as an energy storage unit with limited metabolic activity, and human brown adipose tissue to be active only in infants before disappearing in childhood. It is now known that both, white and brown adipose tissues have in highly active roles in metabolic regulation (141–143). We and others recently showed that cardiac natriuretic peptide signaling causes alterations in energy expenditure and metabolism, and promotes brown adipose-like features in white adipose tissue depots (144–147) and that this is evident in HFpEF (146). Natriuretic peptide signaling is mediated predominantly through the binding of NPRA, which possesses intrinsic guanylyl cyclase activity. Conversely, NPRC serves primarily as the clearance receptor, sequestering natriuretic peptides from the circulation for internalization and subsequent degradation (112). Thus, the ratio of NPRA to NPRC is an important regulator of overall natriuretic peptide activity (148). Upon binding of natriuretic peptides to NPRA in the adipocyte, the receptor's guanylyl cyclase is activated, producing cGMP, which then activates intracellular PKG (112, 149). PKG phosphorylates several lipolytic proteins, including hormone-sensitive lipase (HSL), perilipin, and adipose triglyceride lipase (ATGL), resulting in the breakdown of stored lipids into free fatty acids. In parallel, PKG phosphorylates p38-MAPK, which modulates the brown-fat thermogenic program by increasing transcription of proteins such as uncoupling protein-1 (UCP-1) and peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC-1 $\alpha$ ) (146, 149). UCP-1 is responsible for the uncoupling of oxidative phosphorylation and PGC-1 $\alpha$  is the key regulator of oxidative metabolism (141, 150). UCP1 and PGC-1 $\alpha$  promote mitochondrial biogenesis and coupled and uncoupled respiration resulting in enhanced energy expenditure and thereby limiting adipose tissue expansion (110). Natriuretic peptide signaling in adipose tissue shares activity homology and similar potency with sympathetic activation via  $\beta$ -adrenergic receptors (145). Sympathetic stimulators, such as cold temperature, increase circulating catecholamines that bind to  $\beta$ -adrenergic receptors on adipose tissue (151–153). This increases PKA via a cAMP-dependent mechanism. PKA shares homology with PKG thus both sympathetic nervous-system and natriuretic peptide signaling increase metabolic activity in adipose tissue by activating lipolysis, and modulating the brown-fat thermogenic program through p38-MAPK (113, 147, 149) (**Figure 1**).

Metabolic disorders such as obesity and type 2 diabetes are associated with dysregulation of the natriuretic peptide system (154, 155). The natriuretic peptide receptor ratio in adipose tissue was inversely associated with obesity, glucose intolerance and insulin resistance in a cross-sectional analysis of subjects with a wide range of BMI and glucose tolerance (156). Insulin, which modulates blood glucose levels, exerts potent lipogenic effects, and is also an important regulator of natriuretic peptide activity. A low insulin fasting-state leads to an increase in NPRA mRNA and a decrease in NPRC mRNA whereas conversely, in hyperinsulinemic ob/ob



mice, levels of NPRC mRNA are increased and levels of NPRA mRNA are decreased (157, 158). Similarly NPRA mRNA levels are lower in human adipocytes obtained from individuals with pre-diabetes and type 2 diabetes. Treatment with BNP also increases glucose uptake in adipose tissue independent of insulin levels. This is mediated via PKB phosphorylation and the mechanistic target of rapamycin complex (mTORC)1/2 activation, leading to translocation of glucose transporter 4 (GLUT4) to the cell membrane (159). Thus, insulin inhibits natriuretic peptides, while natriuretic peptides increase insulin sensitivity and help to control blood glucose levels.

There is also interplay between natriuretic peptides released from the heart and adipokines released by adipose tissue. ANP decreases the secretion of leptin in cultured human subcutaneous adipose tissue (160) and isolated human adipocytes from obese individuals (161). An inverse relationship between circulating BNP and plasma levels of leptin also exists in HFpEF patients (162). Yet, adiponectin synthesis and secretion has been positively associated with natriuretic peptides. ANP acutely increased systemic levels of adiponectin in healthy subjects (163) and both, ANP and BNP, promoted the expression and secretion of adiponectin in human adipocytes in culture and in chronic HFpEF patients (164). These findings are also consistent

with observational studies showing positive associations between circulating levels of adiponectin and BNP in healthy subjects without HF (165) and HFpEF patients (67). Thus, higher adiponectin levels tend to be associated with reduced LV systolic function in humans (166).

## CONCLUDING REMARKS

HFpEF is a major public problem that is increasing in prevalence yet lacking in evidence-based therapies. A more tailored approach in HFpEF is needed to investigate the pathophysiological mechanisms that underlie this syndrome. Obesity-associated HFpEF is an important sub-phenotype of HFpEF, with evidence supporting crosstalk between the heart and the adipose tissue. Thus, the ability to modulate the signaling pathways that regulate adipose tissue and the heart in HFpEF

might have clinical implications and be translated into effective therapies for HFpEF, particularly obesity-associated HFpEF.

## AUTHOR CONTRIBUTIONS

FS and MV-M discussed and conceived the outline of the manuscript. AO, RO, and MV-M drafted the initial version of the manuscript. FS and MV-M reviewed the manuscript. All authors approved the final version of the manuscript.

## FUNDING

This work was funded in part by federal funds from the NIH (HL117153 and HL145985 to FS). MV-M was supported by a postdoctoral fellowship from the American Heart Association (17POST33660439).

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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