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STATE-OF-THE-ART REVIEW

Obesity-Related Heart Failure With a Preserved Ejection Fraction

The Mechanistic Rationale for Combining Inhibitors of Aldosterone, Neprilysin, and Sodium-Glucose Cotransporter-2

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ABSTRACT

Obesity-related heart failure with a preserved ejection fraction (HFpEF) is an important phenotype prevalent in the community, especially in people with metabolic disorders (e.g., dyslipidemia, diabetes). These individuals exhibit a marked expansion of plasma volume, but ventricular distensibility is limited, most likely as a result of cardiac microvascular rarefaction acting in concert with myocardial and pericardial fibrosis. Consequently, the increase in plasma volume causes a disproportionate increase in cardiac filling pressures, leading to heart failure, even though systolic ejection is not impaired. The features of this syndrome appear to be related (in part) to the overproduction of adipocyte-derived cell-signaling molecules, including aldosterone and neprilysin. The resulting sodium retention and plasma volume expansion is exacerbated by their mutual actions to promote cardiac and systemic inflammation and fibrosis. Inhibitors of aldosterone, neprilysin, and the sodium-glucose transporter-2 (SGLT2) can ameliorate the plasma volume expansion and pro-inflammatory and profibrotic pathways, potentially opposing the action of diverse adipocytokines. All 3 classes of drugs can reduce the quantity of visceral adipose tissue and ameliorate its abnormal biological properties. This mechanistic framework is supported by the results of large-scale randomized trials with mineralocorticoid receptor antagonists and SGLT2 inhibitors and is being further tested in an ongoing large-scale trial of neprilysin inhibition. The promise of using mineralocorticoid receptor antagonists, neprilysin inhibitors, and SGLT2 inhibitors (alone or in combination) in the management of obesity-related HFpEF suggests that physicians might finally have a phenotype of HFpEF that they can understand and treat.
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The most common phenotype of heart failure in the community is heart failure with a preserved ejection fraction (HFpEF), and the vast majority of afflicted individuals are overweight or obese (1–4). Although obesity increases the risk of myocardial infarction, which may impair systolic function, obese people are at markedly increased risk of heart failure independent of the occurrence of ischemic cardiac injury (5,6). Similarly, although type 2 diabetes is accompanied by a heightened risk of coronary arterial occlusive events and segmental loss of myocardial tissue, the disorder is particularly likely to lead to HFpEF, particularly the phenotype that is associated with obesity (7).

Two central pathophysiological abnormalities contribute to obesity-related HFpEF: sodium retention and systemic inflammation. Obese people exhibit heightened renal tubular sodium reabsorption and plasma volume expansion that is directly related to their body mass index (2,8,9); this sodium retention

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ABBREVIATIONS AND ACRONYMS

HFpEF = heart failure with a preserved ejection fraction

SGLT2 = sodium-glucose transporter-2

underlies the hypertension that is common in obesity-related HFpEF (1). At the same time, when people become obese, their adipose tissue undergoes a biological transformation to an inflammatory state, which can adversely influence the structure and function of the vasculature and most visceral organs (10). Vascular inflammation likely contributes to stiffness of large arteries and great vessels, to endothelial dysfunction in arterioles, and to a marked reduction in capillary density (i.e., microcirculatory rarefaction) (11–16). Inflammation may also cause microvascular abnormalities and fibrosis in the heart, lungs, and kidneys, leading to the comorbidities that are characteristic of HFpEF (1,15–18).

Normally, the heart would be expected to respond to the obesity-related expansion of plasma volume by meaningful ventricular dilatation; however, if inflammation of epicardial adipose tissue leads (by a paracrine effect) (19) to dysfunction and fibrosis of the underlying myocardium, ventricular distensibility becomes limited (2,20). As a result, cardiac volumes are increased but only modestly; they are not normal or small as is the case in hypertrophic cardiomyopathy, yet they are insufficient to accommodate the marked increase in plasma volume in these patients (2,21). Consequently, cardiac filling pressures rise remarkably and disproportionately, leading to the signs and symptoms of heart failure (particularly congestion), even though systolic ejection is not substantially impaired. In addition, the systemic inflammation in obesity-related HFpEF can cause changes in mitochondrial function and in the mass and composition of skeletal muscle (22–26). These abnormalities, acting in concert with the vascular derangements that accompany inflammation (12–14), can contribute to the exercise intolerance of patients with this disorder.

CLINICAL AND PHYSIOLOGICAL CHARACTERISTICS OF OBESITY-RELATED HFpEF

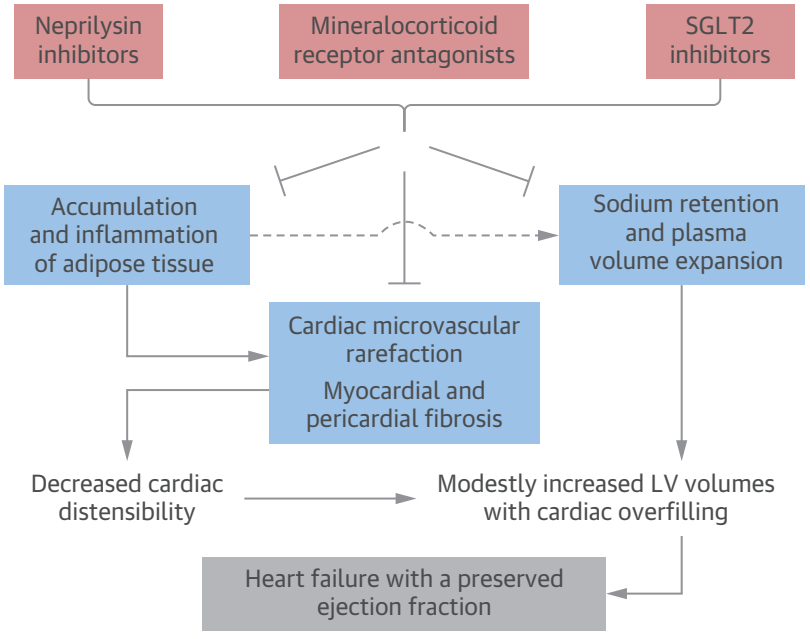
How does a physician make the diagnosis of obesity-related HFpEF? It is tempting to think that a practitioner can simply measure body weight or body mass index, but such an approach has 2 important limitations. First, the pattern of distribution and biological activity of excess adipose tissue is more important than the total fat mass. Specifically, inflammation of perivisceral fat (especially that surrounding the heart) is likely to be more significant than the accumulation of quiescent fat in subcutaneous tissues (19). Second, obese people are predisposed to another form of heart failure (i.e., high-output heart failure) (27), which also is accompanied by measured ejection fractions that are in the normal range. In contrast to their counterparts with a high-output state, patients with obesity-related HFpEF have a distinct biomarker signature (i.e., circulating natriuretic peptides are significantly lower than expected from their heightened level of cardiac filling pressures) (2). In fact, patients with HFpEF have substantially lower levels of natriuretic peptides than those with a reduced ejection fraction, although the latter have much larger left ventricular volumes (28). The lower-than-expected level of natriuretic peptides may be related to a muting of cardiac wall stress if cardiac or pericardial fibrosis or microcirculatory rarefaction were to limit the capacity of the left ventricle to enlarge in response to plasma volume expansion (2,29–31). In addition, metabolic disorders (such as obesity and diabetes) are accompanied by increased activity of neprilysin (thus accelerating natriuretic peptide degradation) as well as enhanced expression of clearance receptors in adipocytes (32,33). Levels of natriuretic peptide levels are so depressed by adiposity and so limited by the muted cardiac wall stress that levels of natriuretic peptides in obese people with HFpEF are often below traditional diagnostic cutpoints, even when these patients are hospitalized with unequivocal decompensation (34,35). Accordingly, the combination of signs and symptoms of heart failure, a preserved ejection fraction, plasma volume expansion, and cardiac overfilling, together with disproportionately low levels of natriuretic peptides and only modestly increased ventricular volumes, characterizes the phenotype of obesity-related HFpEF (2–4).

How can obesity-related HFpEF be treated? Weight loss (by caloric restriction or bariatric surgery) leads to dissipation of the systemic inflammatory response, prevents the development of heart failure, and improves the clinical status of patients with an established diagnosis of HFpEF (35–38), but long-term maintenance of weight reduction by dietary measures is difficult, and bariatric surgery cannot readily be applied to millions of affected people. Therefore, it would be desirable to interrupt the pathogenetic mechanisms of the disorder pharmacologically.

MINERALOCORTICOID RECEPTOR ANTAGONISTS IN OBESITY-RELATED HFpEF

Because sodium retention is a central feature of obesity-related HFpEF, diuretics emerge as a logical therapeutic option. Patients with obesity are particularly responsive to diuretics, but they are also likely

CENTRAL ILLUSTRATION **Potential Therapeutic Approaches to Inhibiting the Pathophysiological Mechanisms That Contribute to Obesity-Related Heart Failure With a Preserved Ejection Fraction**



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Three classes of drugs—mineralocorticoid receptor antagonists, neprilysin inhibitors, and SGLT2 inhibitors—can antagonize sodium retention and plasma volume expansion as well as inhibit the accumulation and inflammation of perivisceral fat and its potential to cause cardiac microvascular rarefaction and myocardial and pericardial fibrosis, which (acting in concert) can impair cardiac distensibility. The syndrome of obesity-related heart failure with a preserved ejection fraction is the result of the interaction of sodium retention and the decreased capacity of the left ventricle to dilate to accommodate the increase in plasma volume. LV = left ventricular; SGLT2 = sodium-glucose transporter-2.

to experience worsening renal function following natriuresis (39); therefore, the sodium retention in these patients might best be addressed by antagonizing a causal mechanism: aldosterone. Obesity is strongly associated with the overproduction of aldosterone (40). The renin-angiotensin system is activated by obesity (41), and the adipokine leptin can directly enhance aldosterone secretion from the adrenal (42). Moreover, adipocytes synthesize aldosterone directly (43), and the increased neprilysin activity in obesity minimizes the influence of natriuretic peptides that can inhibit aldosterone secretion (44). Hyperaldosteronism not only causes sodium retention, but also promotes the accumulation and inflammation of epicardial adipose tissue and the development of microvascular rarefaction and fibrosis in the underlying cardiac muscle (45-50). The transformation of perivisceral fat to a maladaptive proinflammatory phenotype may depend on mineralocorticoid receptor signaling (46-48).

Mechanistic studies and clinical trials support a role for mineralocorticoid receptor antagonists in obesity-related HFpEF (**Central Illustration**). Experimentally, blockade of the mineralocorticoid receptor decreases oxidative stress, reduces cardiac inflammation and fibrosis, and ameliorates heightened cardiac diastolic filling pressures (51-54). In clinical trials, spironolactone has improved echocardiographic measures of left ventricular filling pressures and, occasionally, enhanced exercise capacity (55-57). Mineralocorticoid receptor antagonism may attenuate biomarkers of fibrosis and normalize estimated elevated cardiac filling pressures in obese people who do not yet have a diagnosis of heart failure (58).

Two large-scale clinical trials suggest that inhibition of the production or action of aldosterone may reduce the risk of major adverse cardiovascular outcomes in obese patients with HFpEF. In the I-PRESERVE (Irbesartan in Patients With Heart Failure and Preserved Ejection Fraction) trial, where

mineralocorticoid receptor antagonists were infrequently prescribed, patients were more likely to exhibit a benefit of treatment with the angiotensin receptor blocker irbesartan if they had lower baseline levels of natriuretic peptides (and higher values for body mass index), suggesting that responders had the features of obesity-related HFpEF (59). In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, although regional heterogeneity confounded the interpretation of the results, patients with a higher body mass index also appeared more likely to respond to mineralocorticoid antagonism (60). An augmented effect of spironolactone in obesity-related HFpEF might have been even more readily distinguished if visceral adiposity had been assessed directly rather than being estimated using body mass index. Intriguingly, when the analyses of the trial were restricted to the regions where patients were confirmed to have taken their study medications, patients were more likely to have benefitted from spironolactone if they had circulating natriuretic peptides that were lower than the median value (61), a pattern that was strikingly similar to that reported in the earlier I-PRESERVE trial (59). These findings, taken together, suggest that the benefits of drugs that interfere with the renin-angiotensin-aldosterone system may be most readily discerned in patients who have the pathophysiological and clinical features of obesity-related HFpEF.

INHIBITION OF NEPRILYSIN AND SODIUM-GLUCOSE TRANSPORTER-2 IN OBESITY-RELATED HFpEF

Might pharmacological interventions other than mineralocorticoid receptor antagonists be useful in treating obesity-related HFpEF? Maturing adipocytes express increased levels of neprilysin on their cell surfaces, and soluble levels of neprilysin are increased in states of adiposity (32,62). The increased activity of the renal sympathetic nerves characteristic of obesity can also lead to an increase in the expression of neprilysin in the kidney (63,64). Neprilysin inhibitors not only augment the actions of endogenous peptides that have direct natriuretic effects, but also act to lower circulating levels of aldosterone because the potentiated natriuretic peptides suppress the secretion and antagonize the actions of aldosterone (44,65). Enhancement of the effects of natriuretic peptides has also been shown to exert important lipolytic and anti-inflammatory effects, inhibit cardiac fibrosis, and promote capillary vasculogenesis (66–69). Interestingly, although the antiadipogenic effects of endogenous natriuretic peptides may be attenuated by obesity, they are preserved in heart failure (67). As a result, neprilysin inhibition may help to address both plasma volume expansion as well as cardiac fibrosis and microcirculatory rarefaction (and thus, the resulting decreased ventricular distensibility) seen in obesity-related HFpEF (**Central Illustration**).

Finally, sodium-glucose transporter-2 (SGLT2) inhibitors may also alleviate many of the pathophysiological derangements in obesity-related HFpEF. These drugs block sodium-retentive mechanisms in the renal tubules that are activated in obesity (70); as a result, they cause a marked reduction in plasma volume and hemoconcentration (71,72). Furthermore, experimentally, SGLT2 inhibitors reduce the accumulation and dysfunction of epicardial fat and inhibit proinflammatory and profibrotic processes in the myocardium, thus ameliorating the development of the HFpEF phenotype (73–76). As a result of these actions, SGLT2 inhibitors are poised to antagonize the deleterious biological effects of many adipocytokines (e.g., leptin) that can contribute to sodium retention and systemic inflammation (77). Incretin-based drugs may also diminish the accumulation of epicardial fat, but may promote inflammation in adipose tissue and can aggravate cardiac fibrosis (78,79). By contrast, SGLT2 inhibitors not only exert lipolytic effects, but may also ameliorate the effects of systemic inflammation on the vasculature and visceral organs (73–76,80,81). These favorable effects may explain why, in 2 large-scale trials in type 2 diabetes, the use of empagliflozin and canagliflozin decreased the risk of new-onset heart failure (71,81,82). In contrast, incretin-based drugs have not reduced (and may increase) the risk of serious heart failure events in patients with type 2 diabetes or left ventricular dysfunction who are prone to HFpEF (83–85). The possibility that SGLT2 inhibitors and mineralocorticoid receptor antagonists may be working through overlapping mechanisms (i.e., interference with sodium retention and cardiac inflammation, microvascular rarefaction, and fibrosis) is reinforced by the finding that concurrent use of spironolactone and eplerenone appeared to attenuate the benefits of empagliflozin in a large-scale trial (86).

The totality of evidence is consistent with the hypothesis that obesity-related HFpEF is a distinct phenotype that may result from augmented mineralocorticoid signaling and overactivity of neprilysin, together with increased effects of other adipocytokines (e.g., leptin) (71). If this hypothesis is supported by future research, then strategies that counter these mechanisms (e.g., the combined use

of mineralocorticoid receptor antagonists, neprilysin inhibitors, and SGLT2 inhibitors) might be an effective approach to the treatment of obesity-related HFpEF.

IMPLICATIONS FOR CLINICAL TRIALS AND CLINICAL PRACTICE

Ongoing trials with sacubitril/valsartan and empagliflozin in patients with HFpEF are well-positioned to test the hypothesis that antagonizing the mechanisms that lead to obesity-related HFpEF may be effective in the management of this disorder (87,88); however, examination of the eligibility criteria for these trials reveals an intriguing paradox. The entry criteria for both trials excludes the participation of patients who have only modest elevations of natriuretic peptides as well as those who have marked increases in body mass index (i.e., >35 to 40 kg/m^2). These criteria were imposed with the intent of ensuring that patients had dyspnea related to heart failure and with the goal of increasing the event rate in the placebo group, thereby enhancing the efficiency of the trials. Yet, the exclusion of patients with the most marked phenotypic expression of obesity-related HFpEF would seem inconsistent with the primary objective of these studies (i.e., to evaluate the effects of inhibitors of neprilysin and SGLT2 in patients with HFpEF most likely to respond favorably to treatment); furthermore, these exclusions can further constrain enrollment rates. Nevertheless, most of the participants in these trials will likely have obesity-related HFpEF, and the trials should be able to determine if measures of adiposity and inflammation influence the magnitude of any observed treatment effect. Future studies should seek to include the participation of morbidly obese patients with HFpEF, even though they are not likely to fulfill many of the conventional natriuretic peptide criteria for enrollment in heart failure trials.

The potential implications for clinical practice are real. For decades, physicians have focused on the role of large-vessel coronary artery disease and hypertension in the pathogenesis of left ventricular dysfunction, only to ignore the major role that obesity plays in the development of chronic heart failure in the modern era. Recognition of the contribution of adipocytes to the systemic and cardiovascular derangements of heart failure, especially in obesity-related HFpEF, represents an important conceptual breakthrough. Reports of the benefits of bariatric surgery and caloric restriction provide strong proof-of-concept, which is supported by the findings in large-scale clinical trials and may be additionally strengthened by the results of ongoing studies. After being long mystified by the extraordinary diversity of physiological derangements that are commonly grouped together under the syndrome of HFpEF, physicians might finally have a distinct phenotype that they can understand and treat.

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