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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. (J Am Coll Cardiol HF 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

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