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EDITORIAL COMMENT

The HFpEF Obesity Phenotype

The Elephant in the Room*

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In this issue of the *Journal*, Dalos et al. (1) report the results of an important study that focused on New York Heart Association (NYHA) functional class and its determinants in patients with heart failure with preserved ejection fraction (HFpEF). The investigators recruited a large number of patients and performed extensive phenotyping, including invasive hemodynamic assessment, and then followed the patients for an average of 22 months.

SEE PAGE 189

NYHA functional class is an appropriate focus because it is a universally known, quick, and easy estimate of exercise intolerance, which is the primary symptom in heart failure (HF) and a major determinant of these patients' severely reduced quality of life. In patients with HF with reduced ejection fraction, NYHA class and its determinants have been extensively studied, and it is a potent predictor of clinical endpoints, including survival. However, far less is known regarding NYHA class, its determinants, and its prognostic ability in patients with HFpEF.

Dalos et al. (1) found that during <2 years of follow-up, one-third of patients reached the combined endpoint of HF hospitalization or cardiac death, confirming the adverse prognosis of HFpEF. NYHA class III or IV was a strong (hazard ratio: 2.13) independent predictor of outcome, along with N-terminal pro-brain natriuretic peptide (BNP) and right ventricular function. Correlates of worse NYHA class included age, BNP, Doppler diastolic filling, and diastolic pulmonary artery pressure. However, the most novel finding was that increased body mass index (BMI) was strongly associated with worse NYHA class ($p = 0.004$); the investigators conclude that increased BMI is a key contributor to symptoms of breathlessness in patients with HFpEF. This finding is credible and has important implications.

There are multiple mechanisms whereby increased adiposity worsens symptoms of exercise intolerance in patients with HFpEF (**Figure 1**). Increased adiposity promotes inflammation, hypertension, insulin resistance, and dyslipidemia and also impairs diastolic, systolic, arterial, skeletal muscle, and physical function (2–5), all of which are abnormal in patients with HFpEF and contribute to its pathophysiology (2,6,7). Obesity underlies the Paulus hypothesis of HFpEF pathogenesis that implicates the inflammation-induced dysregulation of the nitric oxide–cyclic guanosine monophosphate–protein kinase G signaling cascade (6). Adiposity-induced inflammation has wide-ranging adverse effects, including endothelial dysfunction, capillary rarefaction, and mitochondrial dysfunction in both the cardiac and systemic beds (6). Thus, the contribution of obesity to HFpEF extends far beyond that of merely increased mechanical load.

In addition to its strong promotion of inflammation with associated adverse effects, several additional

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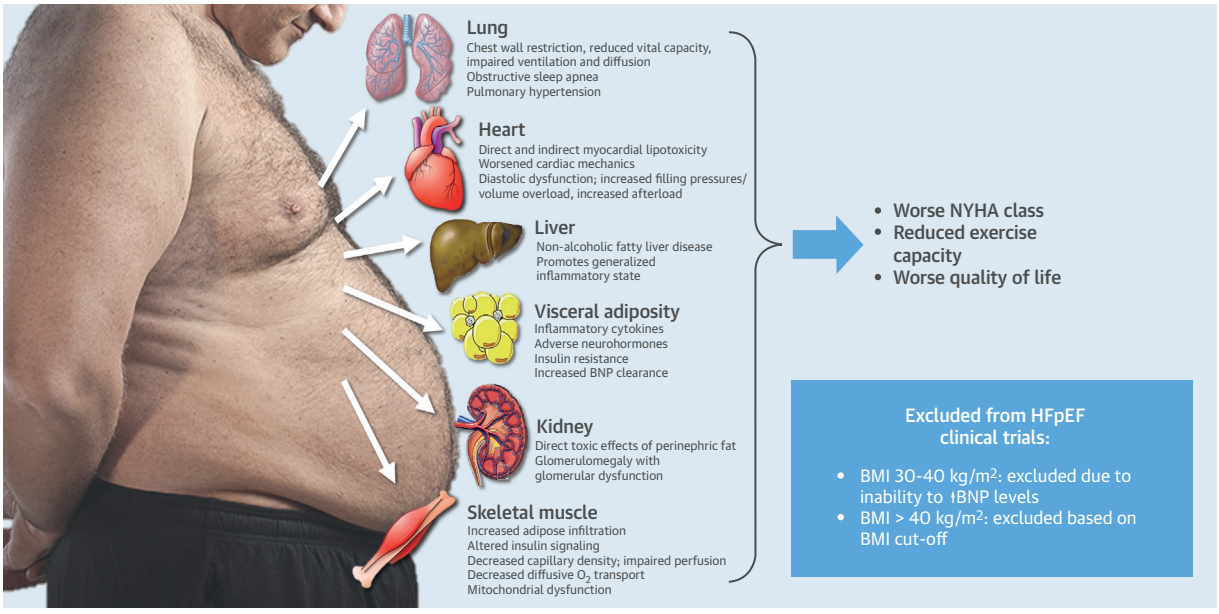
FIGURE 1 Model of the Mechanisms of the Impact of Regional Adipose Depots on Exercise Intolerance in Patients With Heart Failure With Preserved Ejection Fraction and the Ways Obese Patients With Heart Failure With Preserved Ejection Fraction Are Excluded From Clinical Trials



BMI = body mass index; BNP = brain natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; NYHA = New York Heart Association.

lines of evidence support that obesity is not merely an epiphenomenon or a prominent comorbidity for HFpEF but is intimately involved in its pathogenesis. Adipose tissue is metabolically active and, in addition to inflammatory cytokines, elaborates a range of other cardiovascular active substances, including angiotensin-II and aldosterone. Evolving data indicate that the location of increased adipose tissue may be more important than the overall quantity. Increased paracardiac fat is associated with increased cardiac events and adverse changes in myocardial function (8). Fatty liver infiltration is also associated with cardiac dysfunction (9), and increased perinephric fat is associated with renal dysfunction. In both HFpEF and HF with reduced ejection fraction, there is a large increase in adipose tissue within the skeletal muscle, even in nonobese patients, and this is a significant independent contributor to exercise intolerance specifically in HFpEF (2,10). Increased adipose in skeletal muscle can impair perfusion, reduce capillary density, and impair mitochondrial function (2,10).

Increased BMI is tied with hypertension as the third strongest independent risk factor (age and sex are the first two) for the development of HFpEF (11,12). In Western countries, >80% of older patients with HFpEF (more than twice the general population) are overweight or obese, with a median BMI of about 33 kg/m^2 (13–16). Thus, obesity is a common, modifiable risk factor for HFpEF, more than twice as common as other risk factors often cited, such as diabetes and atrial fibrillation.

Given these data, it is remarkable that there has been so little attention to increased adiposity in HFpEF and no multicenter trial that has addressed it. This is in stark contrast to hypertension and its effects, which have been the focus of most trials to date, with little pay-off. In the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial, systolic blood pressure decreased by a level that would usually translate into significant improvement in clinical outcomes in a range of populations (17). Yet in I-PRESERVE (and in 4 other HFpEF trials in which blood pressure was lowered with medications in patients with HFpEF), there was no improvement in the primary outcome. This suggests the need for new paradigms and therapeutic targets.

Unfortunately, obesity has not only been overlooked as a potentially pivotal factor in HFpEF pathophysiology and treatment, it has been actively avoided. Some multicenter trials, including the ongoing PARAGON (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved