COMMENTARY

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Do Most Obese People with Exercise Intolerance and a Normal Ejection Fraction Have Treatable Heart Failure?

Heart failure is a syndrome of exercise intolerance that results from an abnormal elevation in left ventricular filling pressure.[1] However, the diagnosis can be difficult to make in clinical practice, particularly in obesity. Despite reduced exercise capacity, obese people may not report exertional dyspnea to their physicians,[2] possibly because they have a preconception that their body mass should limit effort tolerance or because they elect to restrict their activities to minimize the possibility of experiencing unpleasant symptoms.

Therefore, unless a motivated practitioner asks about and confirms the presence of exercise impairment, such individuals may not undergo an echocardiographic evaluation. If performed, in many obese people this test would demonstrate an abnormality in early diastolic mitral annular velocity, which is indicative of increased left ventricular filling pressures, and often, the additional finding of mild left atrial enlargement.[3,4] However, if the left ventricular ejection fraction is normal, these abnormalities are likely to be ignored or regarded as evidence of "diastolic dysfunction" that is attributed to associated hypertension.[5] Moreover, many physicians find it difficult to examine a morbidly obese patient for the presence of distended jugular venous pressures or fluid retention. Given the pandemic of obesity in the United States, it is appropriate to ask: Are physicians systematically ignoring the diagnosis of heart failure in obese people? Can the limitations imposed by this disorder be effectively treated?

The combination of exercise intolerance and increased left ventricular filling pressure or increased left atrial chamber size on echocardiography is supportive of the diagnosis of heart failure. Yet physicians may be reluctant to assign such a serious diagnosis unless it can be confirmed, typically by ordering a blood test to measure natriuretic peptides. However, the results of this test will be difficult to interpret. Patients with obesity predictably have levels of natriuretic peptides that are disproportionately lower than might be predicted from the elevation of left ventricular filling pressures.[5,6] A modest rise in natriuretic peptides in an obese individual suggests a very meaningful increase in left ventricular filling pressures.[6] The only examination that can confirm the abnormality in cardiac filling pressures is right heart catheterization, which cannot be performed routinely in obese people with exercise intolerance.

What mechanisms are in play in obese people with exercise intolerance and increased cardiac filling pressures on echocardiography? Obesity is characteristically accompanied by increased levels of aldosterone.[7] Adipocytes can synthesize aldosterone directly or by secreting leptin, which stimulates the production of aldosterone by the adrenal gland.[8,9] Furthermore, maturing adipocytes shed neprilysin from their surfaces, which contributes to the depression of circulating levels of natriuretic peptides, and in turn, to further increases in aldosterone secretion.[10-12] Hyperaldosteronism leads to a major expansion of plasma volume, which—when ejected by a normally functioning heart—results in an increased cardiac output and blood pressure, but at the cost of an increase in cardiac filling pressures.[13] Consequently, many (perhaps most) obese people with exercise intolerance, mild-to-moderate increases in blood pressure, and "diastolic dysfunction" on echocardiography may have a form of volume-overload (high-output) heart failure.[13]

Two studies have characterized the clinical features of heart failure in obese people with a left ventricular ejection fraction in the normal range. Younger individuals with few comorbidities and normal renal function commonly exhibit a state of high-output heart failure,[13] whereas older people (especially women) with multiple comorbidities and mild-to-moderate renal insufficiency typically manifest the syndrome of heart failure with a preserved ejection fraction.[6] Regardless of the phenotype, obese patients with heart failure can

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be treated. In 3 clinical trials, patients with heart failure and features of obesity (identified either by abdominal girth or by disproportionately low levels of natriuretic peptides) were particularly likely to respond favorably to drugs that inhibit the synthesis or action of aldosterone (eg, angiotensin receptor blockers or mineralocorticoid receptor antagonists).[14-16] By reducing hyperaldosteronism or its effects, these drugs ameliorate the plasma volume expansion that underlies the increased cardiac filling pressures and exercise intolerance of obese people.

How common might this syndrome be in clinical practice? Amazingly, there is a direct relationship between body mass and increased cardiac filling pressures in the general population.[17,18] Therefore, many obese individuals would exhibit evidence of increased left ventricular filling pressures if they were assessed by echocardiography, especially if the test were performed during exercise.[19] Because the elevation in cardiac filling pressures is due to hyperaldosteronism, it is not surprising that, in randomized controlled trials of obese patients with heart failure and a preserved ejection fraction, mineralocorticoid receptor antagonism with spironolactone ameliorated echocardiographic measures of left ventricular filling pressures, often with benefits on exercise capacity.[20,21] Importantly, spironolactone improves echocardiographic estimates of cardiac filling pressures in obese people who do not have a clinical diagnosis of heart failure.[22]

These observations suggest that the exercise intolerance in many obese individuals represents a form of heart failure rather than a response to an increased mechanical demand or physical deconditioning. Given the enormous prevalence of and disability caused by this condition, it is time that the effects of mineralocorticoid receptor antagonism on exercise tolerance in obese people with a normal ejection fraction and without overt fluid retention be evaluated in a formal large-scale clinical trial carried out in the general population.

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