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EDITORIAL COMMENT

The Obesity Paradox in Heart Failure

Is it All About Fitness, Fat, or Sex?*

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Substantial evidence points out that obesity impacts most of the cardiovascular (CV) disease (CVD) risk factors, including adversely effecting lipids, increasing arterial pressure, elevating glucose, and increasing the risk of metabolic syndrome and diabetes mellitus, and increasing systemic inflammation (1). Obesity also has many deleterious effects on CV structure and function and hemodynamics (**Figure 1**) and increases the risk of most CVD (2,3). Because overweight and obese patients develop more hypertension and coronary heart disease (CHD), 2 of the major risk factors for heart failure (HF), not surprisingly, these patients also develop HF much more commonly than do the lean counterparts.

Despite the increased prevalence of HF in obesity, many studies have demonstrated a so-called "obesity paradox" in which overweight and at least mildly obese patients with HF often have a better prognosis, during the short-term, compared with lean HF patients (2,4). A recent meta-analysis of 6 studies (n = 22,807) has shown that the highest risk of adverse events, including CV mortality, all-cause mortality, and rehospitalizations, during a mean 2.9-year follow-up, were in those with low body mass index (BMI), whereas the lowest risk occurred in the overweight BMI (**Figure 2**) (5). Another recent study of 6,142 patients with acutely decompensated HF from 12 prospective studies on 4 continents also demonstrated an obesity paradox, but this study found that this was mostly confined to older persons and those with reduced cardiac function, less cardiometabolic illness, and recent-onset HF (6).

In a study reported in this issue of *JACC: Heart Failure*, Vest et al. (7) from the Cleveland Clinic assessed their population with systolic HF (left ventricular ejection fraction [LVEF] <40%; n = 3,811) who had undergone cardiopulmonary stress testing and found that, after adjustment for confounders, the obesity paradox in this population during a mean 6.2-year follow-up was largely confined to women in the overweight BMI range. Other studies have also found an obesity paradox in men or in populations adjusted for sex (6,8,9), but the data by Vest et al. (7) had longer follow-up and a better assessment of potential confounders. The authors estimated body fat (BF) and lean body mass (LBM), which may be seen as a limitation because they did not measure these parameters, but the estimated measures of BF and LBM have been shown to be reliable in a very large database (10,11).

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Cardiorespiratory fitness (CRF) is a strong predictor of prognosis in many populations, including those with HF (9,12). Thus, the obesity paradox can be attributed to better CRF. We demonstrated in 2,066 patients with HF an obesity survival paradox only in those patients with poor CRF (peak oxygen consumption [VO_2] < 14 ml/kg/min), whereas those with a better CRF had a good prognosis regardless of weight (9). These results were subsequently confirmed in an analysis of 1,675 HF patients (13). Although the present study by Vest et al. (7) did not assess patients based on their level of CRF, they did adjust for peak VO_2 in their analyses. As we also demonstrated in patients with CHD (11), these data certainly suggest that CRF alters the relationship

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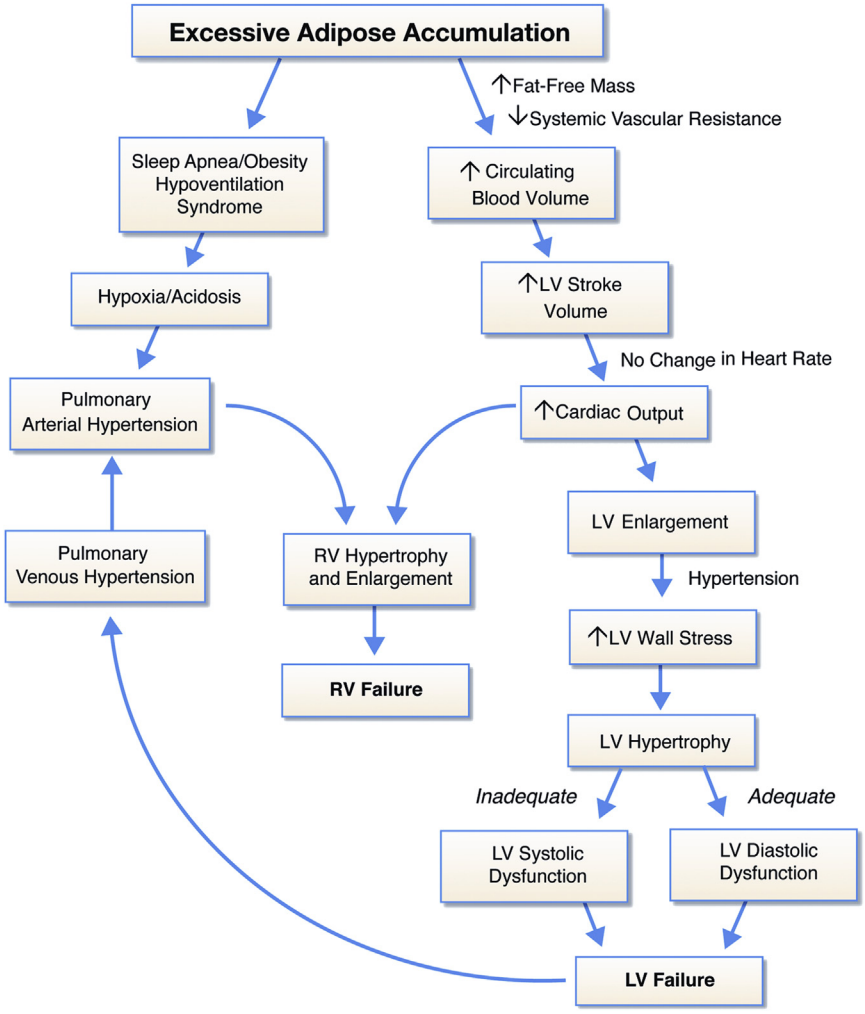
FIGURE 1 Central Hemodynamic, Cardiac Structural Abnormalities, and Alterations in Ventricular Function That May Occur in Severely Obese Patients, Predisposing Them to Heart Failure



Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. In uncomplicated (normotensive) severe obesity, eccentric LV hypertrophy predominates. In severely obese patients with long-standing systemic hypertension, concentric LV hypertrophy is frequently observed and may occur more commonly than eccentric LV hypertrophy. Whether and to what extent metabolic disturbances such as lipotoxicity, insulin resistance, leptin resistance, and alterations of the renin-angiotensin-aldosterone system contribute to obesity cardiomyopathy in humans is uncertain. RV = right ventricular. Reproduced with permission from Lavie et al. (2).

between adiposity and prognosis in patients with HF (12).

One of the limitations of BMI is that this does not differentiate BF from muscle mass, but the obesity paradox in HF has been demonstrated with both BMI and BF (14). More than a decade ago, in a small study of systolic HF, we demonstrated that every 1% increase in BF was associated with a 13% reduction in mortality or urgent transplantation (14). Higher BF has also been proven to be protective in cohorts of CHD (11,12). Although the potential mechanisms for a protective effective BF are numerous and beyond the scope of this discussion, 1 potential mechanism especially applicable to HF is that patients with more BF also have more muscular strength (15). Higher muscular strength is associated with better prognosis in CVD and it prevents frailty and cachexia in HF (16).

Previous studies have shown an obesity paradox in both sexes with HF and in populations that were adjusted for sex (6,8,9). However, it is quite possible