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EDITORIAL COMMENT

Severe Obesity and Acute Decompensated Heart Failure

New Insights Into Prevalence and Prognosis*

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Obesity produces a variety of hemodynamic alterations that predispose to changes in cardiac morphology and impairment of ventricular function that may contribute to the development of heart failure (HF) (1-7). In most obese individuals excess adipose accumulation, in association with increased lean body mass, produces an increase in total and central blood volume (1,5,7). This in turn predisposes to a rise of cardiac output, which is facilitated by a decrease in systemic vascular resistance. Because heart rate changes little, if at all, the augmentation of cardiac output is due predominantly to increased left ventricular (LV) stroke volume (1,2). In uncomplicated obesity, elevation of cardiac output ostensibly predisposes to LV dilation and eccentric LV hypertrophy (LVH) (1,5,7). However, multiple studies have demonstrated that concentric LV geometry occurs as commonly or more commonly than eccentric LVH in obese subjects (1-5,7,8). The reasons for this are uncertain, but they may relate to the presence of comorbidities such as systemic hypertension and neurohormonal and metabolic abnormalities associated with obesity such as activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, insulin resistance with hyperinsulinemia and production of insulin-related growth factors, lipotoxicity and hyperleptinemia due to leptin resistance (2-8). These hemodynamic and morphologic changes are most pronounced in severely obese patients (body mass index [BMI]: ≥40 kg/m^2), but they may occur to a more limited extent in obesity of lesser severity (1,5,7,8). LVH predisposes to LV diastolic dysfunction in severely obese patients. LV systolic dysfunction is observed infrequently and may occur when LVH is inadequate to normalize LV wall stress or in the presence of comorbidities such as coronary artery disease (1-5,7-10). In severely obese patients LV dysfunction may lead to LV failure, pulmonary venous hypertension, and pulmonary arterial hypertension, which in association with hypoxemia from sleep apnea and hypoventilation (common in severely obese patients) contributes to the development of right ventricular failure (1-3,7). HF due predominantly or entirely to severe obesity is referred to as "obesity cardiomyopathy," and in most cases is associated with a preserved LV ejection fraction (1,2,5-7). Excess adiposity has also been identified as a risk factor for heart failure in patients with obesity of lesser severity, due in part to the pathophysiologic alterations previous noted, as well as to the high prevalence of comorbidities such as coronary artery disease and systemic hypertension (1,3,7,9,10).

Although HF is a risk factor for mortality, there is now substantial evidence that HF in patients who are at normal weight (BMI: 25.0 to 29.9 kg/m^2) and those who are underweight (BMI: <18.5 kg/m^2) are at higher risk for all-cause and cardiovascular death than overweight and mildly obese persons (1,7). This phenomenon is known as the obesity paradox (1,7). In studies of chronic HF, the highest risk of all-cause and cardiovascular mortality is incurred by underweight patients, followed by normal weight patients (1-7). Overweight and mildly obese patients consistently have the lowest mortality risk of any BMI group. All-cause and cardiovascular mortality rates begin to rise in moderately obese patients (BMI: 35.0 to 39.9 kg/m^2).

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Severely obese patients have not been as extensively studied as other weight groups with respect to the obesity paradox, but available data suggest that mortality risk continues to rise in such patients (1,7). Thus, in populations with chronic HF, all-cause, and cardiovascular mortality risk forms a U-shaped curve with the highest risk in underweight and severely obese patients and the lowest risk in overweight and mildly obese subjects (1,7). This has been confirmed in diverse HF populations including in female and male subjects, in the elderly, in patients with central and peripheral obesity, and in patients with HF with a reduced and preserved LV ejection fraction (1,7). Lavie et al. (7) have suggested that the following factors may serve as explanations for the obesity paradox: 1) nonvoluntary weight loss due to catabolic diseases; 2) lower prevalence of cigarette smoking; 3) younger age at presentation; 4) higher prevalence of dyspnea resulting in earlier clinical assessment, diagnosis, and treatment; 5) greater metabolic reserves; 6) less frailty and cachexia; 7) higher blood pressure permitting the use of HF medication that may reduce mortality risk; 8) increased muscle mass and muscle strength; 9) better cardiopulmonary fitness in some; 10) attenuated responses to the renin-angiotensin-aldosterone system; 11) differences in etiologies of HF with some associated with better prognosis; and 12) lower natriuretic peptide levels (1,7). Some of these factors, however, do not explain the higher mortality risk in moderately to severely obese patients.

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The study reported by Joyce et al. (11) in this issue of *JACC: Heart Failure* provides information relating to the prevalence, clinical profile, and prognosis of obese patients hospitalized with acute decompensated HF (ADHF) with special emphasis on those who were severely obese. Data were retrospectively derived from 3 randomized controlled trials of patients with ADHF: DOSE (Diuretic Strategies Optimization Evaluation) (12); CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) (13); and ROSE (Renal Optimization Strategies in Acute Heart Failure) (14). In DOSE, 308 patients with ADHF were randomized to receive furosemide at high and low doses via intravenous bolus administration or continuous intravenous infusion (12). In CARRESS-HF, 188 patients with ADHF were randomized to receive stepped pharmacologic therapy or isolated ultrafiltration (13). In ROSE, 360 patients with stages 3 to 4 chronic kidney disease and ADHF were randomized to receive either low dose intravenous dopamine or nesiritide or a placebo (14). All patients in ROSE received high doses of loop diuretics as background therapy (14). The primary clinical outcome of the study by Joyce et al. (11) was a composite endpoint of death, rehospitalization, or unscheduled provider visit within 60 days in normal weight, overweight, mildly to moderately obese, and severely obese subjects (11).

There are several important findings in this study that add to our understanding of the role of obesity in patients with HF. First, there was a very high prevalence of severe obesity (19.7%) in this population of hospitalized patients with ADHF (11). The prevalence of severe obesity in the general population was 6.3% based on the 2009 to 2010 National Health and Nutrition Examination Survey (9). Second, there appears to be an obesity paradox for the composite endpoint of death, rehospitalization, and unscheduled provider visit within 60 days (11). However, unlike most studies demonstrating a nadir in all-cause and cardiovascular mortality in overweight and mildly obese HF patients and a trend toward increasing mortality in those with BMI $\geq$35 kg/m^2 (1,7), this study showed that the lowest risk for the composite endpoint occurred in those with a BMI of approximately 38 to 42 kg/m^2. In a previous study of 108,927 patients with ADHF, there was a linear decline in in-hospital mortality risk with increasing BMI (15). The reasons for these disparities may reflect differences in the outcomes studied and, possibly, differences in the duration of follow-up. Third, there was a progressive, linear decline in plasma natriuretic peptide levels with increasing BMI. This negative correlation has also been reported in patients with chronic HF (1,7). The reasons for this phenomenon are uncertain. It has been postulated that the abundance of natriuretic peptide clearance receptors in adipocytes results in the removal of natriuretic peptides from the circulation (16). Decreased myocardial natriuretic peptide content has been demonstrated in obese humans and adult Zucker rats, thus potentially leading to lower plasma natriuretic peptide levels (16). Although severely obese subjects had lower plasma N-terminal pro-B-type natriuretic peptide levels than normal weight, overweight, and mildly to moderately obese patients did, natriuretic peptides were markedly elevated in all weight classes. Natriuretic peptides have been shown to stimulate lipolysis (16). Reduced circulating levels of natriuretic peptides may contribute to sodium retention and intravascular volume expansion (which are prevalent in obese patients), but also they may reduce breakdown of fat, thus conferring a protective effect by reducing catabolism and increasing metabolic reserves (16).

Several of the baseline clinical and laboratory characteristics of severely obese patients in the study by Joyce et al. (11) differed from patient

characteristics in studies of severely obese patients without HF and in those with chronic HF. The mean age of 63 years was substantially higher than many studies of severely obese subjects (1,5,7). Most previous studies of severely obese patients consisted predominantly of female subjects, whereas the severely obese cohort in this study consisted of 61% male subjects (1,5,7,11). Although LV systolic dysfunction may occur in severely obese patients, it does so infrequently (1,7,10). The mean LV ejection fraction in most studies of severely obese patients is normal, near-normal, or even supranormal (1–5,7). In this study, the mean LV ejection fraction was 43%, and only 40.6% had LV ejection fraction ≥50%. This is likely due to the fact that 52.9% of patients in this study had an ischemic etiology for ADHF. The prevalence values for diabetes mellitus (70%) and systemic hypertension (91.7%) were higher than those reported in severely obese patients without heart failure and those with chronic heart failure (1,7,8,16). Although the prevalence of atrial fibrillation did not differ across BMI strata, it was disproportionately high and may serve as a complication of, and in some case a precipitating factor for ADHF. The clinical significance of the mean troponin elevation in all BMI groups and its decline with increasing BMI in uncertain. Many patients in the core studies suffered from acute kidney injury or chronic kidney disease.

The major limitation of this study, which Joyce et al. (11) acknowledge, is the diverse nature of the interventions for treatment of ADHF. Such heterogeneity could potentially influence outcomes. The use of the composite endpoint of death, rehospitalization, or unscheduled provider visit within 60 days is an innovated approach, but it is also a limitation in that it is difficult to compare the results of this study relating to the obesity paradox to those of other studies that tended to focus on all-cause and cardiovascular mortality. In this study, there were few underweight patients, a group that has consistently demonstrated the highest mortality risk among BMI groups. Although the clinical and laboratory profiles of severely obese patients in this study differed from those of severely obese patients without HF or with chronic HF in previous studies, they are reflective of patients with ADHF in the general population. The results of this study extend those derived from studies of patients with acute coronary syndromes and ADHF. Future studies assessing the prevalence, clinical profile, and prognosis of severe obesity in patients with ADHF should be prospective in nature, should be homogeneous with respect to comorbidities and therapeutic interventions, and should include all-cause and cardiovascular mortality as clinical endpoints.

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REFERENCES

1. Alpert MA, Agrawal H, Aggarwal K, Kumar SA, Kumar A. Heart failure and obesity: pathophysiology, clinical manifestations and management. Curr Heart Fail Rep 2014;11:156–65.

2. Alpert MA, Omran J, Mehra A, Ardhanari S. Impact of obesity and weight loss on cardiac performance and morphology in adults. Prog Cardiovasc Dis 2014;56:391–400.

3. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113:898–918.

4. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiol Rev 2008;88:389–419.

5. Wong C, Marwick TH. Obesity cardiomyopathy: pathogenesis and pathophysiology. Nat Clin Pract Cardiovasc Med 2007;4:436–43.

6. McGavock JM, Victor R, Unger RH, Szczepaniak LS, American College of Physicians and the American Physiological Society. Adiposity of the heart, revisited. Ann Intern Med 2006;144:517–24.

7. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. J Am Coll Cardiol HF 2013;1:93–102.

8. Woodwiss AJ, Norton GR. Obesity and left ventricular hypertrophy: the hypertension connection. Curr Hypertens Rep 2015;17:539.

9. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. Prog Cardiovasc Dis 2014;56:369–81.

10. Alpert MA, Pritchett AM. Bariatric surgery in patients with left ventricular systolic dysfunction: effective, but is it safe? Circ Heart Fail 2016;9:e002960.

11. Joyce E, Lala A, Stevens SR, et al., for the Heart Failure Apprentice Network. Prevalence, profile, and prognosis of severe obesity in contemporary hospitalized heart failure trial populations. J Am Coll Cardiol HF 2016;4:923–31.

12. Felker GM, Lee KL, Bull DA, et al., for the NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805.

13. Bart BA, Goldsmith SR, Lee KL, et al., for the Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296–304.

14. Chen HH, Anstrom KJ, Givertz MM, et al., for the NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA 2013;310:2533–43.

15. Fonarow GC, Srikanthan P, Costanzo MR, et al., for the ADHERE Scientific Advisory Committee and Investigators. An obesity paradox in acute heart failure: analysis of body mass index and inhospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. Am Heart J 2007;153:74–81.

16. Madamanchi C, Alhosaini H, Sumida A, Runge MS. Obesity and natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. Int J Cardiol 2014;176:611–7.

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