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EDITORIAL COMMENT

Disparate Effects of Metabolically Healthy Obesity in Coronary Heart Disease and Heart Failure*

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The conditions of being overweight or obese have been increasing in epidemic proportions in the United States and in much of the Westernized world. At present, more than 70% of the U.S. population is considered to be overweight or obese (1). Even worse, the proportion of severe or morbid obesity, also called "class III obesity" (body mass index [BMI] ≥40 kg/m^2), is increasing more so than obesity per se, and now approximately 3% of the U.S. population meet this level of obesity (2,3). Although welcome declines have been noted in cardiovascular disease (CVD) mortality rates in recent decades, concern has been expressed that the high prevalence of obesity and especially morbid obesity may reverse this trend (1).

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There has been considerable debate on the importance of obesity in U.S. and worldwide mortality levels. A recent high-profile publication by Masters et al. (4) suggested that obesity contributes to approximately 20% of U.S. mortality. In contrast, a large review from Flegal et al. (5) analyzed 97 studies of 2.9 million individuals, including >270,000 deaths, and demonstrated that optimal survival occurred in "overweight" patients (BMI: 25 to 30 kg/m^2), who had a significant 6% lower mortality than the "normal-weight" BMI cohort (BMI: 18.5 to 25 kg/m^2). Although the entire obesity group (class I to III combined) had an increased mortality, the class I obese cohort (BMI: 30 to 35 kg/m^2) had a 5% lower mortality than the normal-weight BMI cohort, which was almost statistically significant.

Obesity adversely affects almost all of the major CVD risk factors, including insulin sensitivity (leading to metabolic syndrome and type 2 diabetes mellitus), blood pressure, dyslipidemia, and systemic inflammation and leads to abnormalities in left ventricular geometry and systolic and especially diastolic dysfunction (1,6). It is not surprising that obesity increases the risk of almost all CVD, including hypertension, coronary heart disease (CHD), heart failure (HF), atrial fibrillation, and peripheral arterial disease. However, prior research has questioned whether obesity without cardiometabolic abnormalities, or "metabolically healthy obesity," has adverse effects on overall CVD risk (7–11). In this regard, prior research regarding both CHD and HF has been conflicting.

In this issue of the *Journal*, Mørkedal et al. (7) assessed a cohort of more than 60,000 people from Norway who were free of CVD and assessed the risk of developing acute myocardial infarction (AMI) and the first HF. After 12 years of follow-up, they report a disparate impact of obesity in the development of CHD and HF. For AMI, the metabolically healthy obese cohort, unlike the metabolically unhealthy cohort, did not seem to have an increased risk of AMI, supporting the premise that the adverse effects of obesity on CHD can be attributed to the adverse effects that obesity has on the various cardiometabolic risk factors and that any adverse effects beyond these metabolic abnormalities are minimal, if any. On the other hand, the impact of obesity on HF is different.

As we have recently reviewed (6), increased adiposity increases total blood volume, stroke volume, cardiac output, and cardiac work and leads to significant abnormalities on both the right and left sides of the heart (Fig. 1). It is not surprising that the risk of HF is significantly increased in obesity. This is probably best demonstrated in the analysis of 5,661 subjects from the Framingham Heart Study, which showed an increased prevalence of HF across the entire spectrum of BMI, with a 5% increase in HF prevalence in men and a 7% increase in HF prevalence in women for every 1 kg/m^2 increase in BMI (12). Other studies have demonstrated that HF particularly increases with the duration of morbid obesity (13). The data in the present large cohort from Norway support the impact of obesity, especially more long-lasting and severe obesity, for increasing the development of first HF, and this impact of obesity in HF appears regardless of the overall cardiometabolic status, healthy or not. These data are in contrast to those reported from a small cohort of 550 patients from Greece, which suggested that metabolic syndrome was more related with HF risk than obesity (14). However, the data from this larger study seem more in line with the pathophysiology of obesity, in which adipose tissue adversely affects the cardiovascular status, including hemodynamic and cardiac

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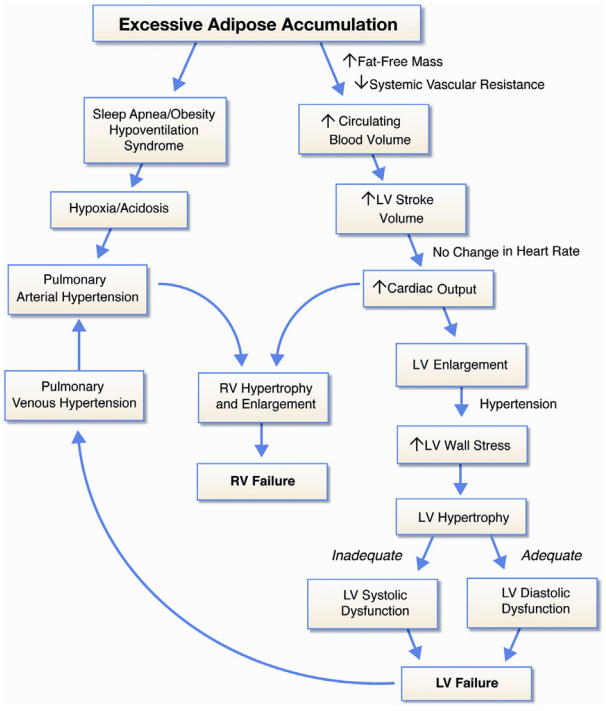

Figure 1 **Pathophysiology of Obesity Cardiomyopathy**

This diagram shows the central hemodynamic, cardiac structural abnormalities, and alterations in ventricular function that may occur in severely obese patients and predispose to heart failure (HF). 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 are uncertain. Adapted with permission from Lavie et al. (6). LV = left ventricular; RV = right ventricular.

structure and function, regardless of the underlying cardiometabolic status (4,5).

Once CHD or HF becomes manifest, similar to other cohorts with CVD, including hypertension and atrial fibrillation, an obesity paradox is apparent because overweight and obese subjects with these conditions seem to have a better prognosis than their leaner counterparts with the same diseases (1). This paradox is present in overweight and obese patients with CHD, despite the fact that obese patients have considerably more cardiometabolic abnormalities, including elevated glucose, lipid, and blood pressure levels, and more inflammation (15,16). Prognosis in both CHD and HF is largely related to baseline cardiorespiratory fitness, with the fitter patients having a good prognosis and no obesity paradox, whereas the worst prognosis is in the leanest patients who are unfit (17,18).

On the basis of these findings and other data, 4 major factors should be emphasized. First, maintaining healthy weight, cardiometabolic status, and overall fitness would be ideal for CVD prevention. Second, if substantial weight gain occurs, preventing and treating cardiometabolic abnormalities seem merited. Third, unlike CHD, for which maintaining a healthy cardiometabolic status seems to protect the obese patients from acute disease, in HF, the risk is increased in obesity regardless of cardiometabolic status. Fourth, overall cardiorespiratory fitness, which may be the strongest of the CVD risk factors, seems to be protective for the overweight and obese patients with CHD or CVD. Finally, measures to prevent being overweight or obese should be emphasized and encouraged. By improving levels of physical activity, and thus an individual's level of fitness, one would prevent both CHD and HF and improve the prognosis in these disorders. However, in our current society, achieving this goal may involve a considerable amount of wishful thinking.

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