Is Subclinical Myocardial Injury the Smoking Gun Linking Obesity With Heart Failure?*

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Although rates of atherosclerotic cardiovascular disease are on the decline, heart failure (HF) is slowly becoming a global epidemic. Recent projections suggest that the prevalence of HF will increase almost 50% from 2012 to 2030 and that 1 in 5 adults will develop HF over their lifetime (1). This emergent HF burden is in part attributable to aging of the population and improved survival from atherosclerotic cardiovascular disease and other chronic cardiovascular diseases. In addition, obesity is increasingly recognized as a key driver of the increase in HF prevalence, due to both staggering increases in rates of obesity and better understanding of the direct and indirect mechanisms through which obesity contributes to HF risk.

In a landmark study of 5,881 participants from the Framingham Heart Study, Kenchaiah et al. (2) demonstrated that for every 1 kg/m² increase in body mass index (BMI), the risk of HF increased by 5% and 7% in men and women, respectively. These epidemiological observations may be partially explained by effects of obesity on intermediate risk factors predisposing to the development of HF, particularly insulin resistance. For example, in a community-based cohort of 1,187 older Swedish men, insulin resistance measured by a 2-h oral glucose tolerance test was associated with a 44% increased relative risk for incident HF independent of other established risk factors, including obesity. When measures of physiologic glucose handling were added to the model, the association between obesity markers and subsequent HF was completely attenuated (3). In contrast, other studies have demonstrated that obesity may increase risk for HF independent of its effects on intermediate risk factors. In a large, prospective cohort of 61,299 Norwegian adults, obesity was associated with a 70% increased relative risk for the development of HF irrespective of metabolic health status, with dose- and time-dependent effects seen, such that severe and long-lasting obesity was associated with a particularly exaggerated hazard (4).

Obesity has myriad effects on cardiac structure, function, and hemodynamics that may contribute to HF risk. Excessive adipose tissue accumulation can lead to increased circulating blood volume that may over time result in eccentric left ventricular hypertrophy (LVH), increased wall stress, and ultimately heart failure with reduced ejection fraction (HFrEF) (5). In the past, eccentric left ventricular (LV) remodeling leading to HFrEF was thought to be the primary pathway of obesity-related HF. However, more modern studies characterizing cardiac remodeling patterns using magnetic resonance imaging (MRI) have shown that increased adiposity may be more closely associated with a concentric LV remodeling phenotype, characterized by increased mass-to-volume ratio, LV wall thickness, and diastolic dysfunction, independent of other known causes of LVH such as hypertension (6,7). These effects may be mediated through a variety of metabolic abnormalities that coexist with or result from obesity such as insulin resistance, elevated leptin levels (or leptin resistance), decreased levels of adiponectin, activation of the renin-angiotensin-aldosterone system, and lipotoxicity (5).
A final common pathway linking multiple HF risk factors, including obesity, with HF appears to be chronic subclinical myocardial injury. In multiple large population-based studies, small elevations in troponin, detectable with high-sensitivity assays, have provided robust incremental prognostic information for incident HF, beyond traditional HF risk factors (8-11). Moreover, small increases in high-sensitivity cardiac troponin T (hs-cTnT) over serial follow-up independently associated with augmented HF risk, suggesting that cardiac injury may represent a potentially modifiable intermediate phenotype in the pathway to HF (10). Two recent studies from the ARIC (Atherosclerosis Risk In Communities) study investigators have provided a preliminary link between insulin resistance, a key consequence of obesity, and subclinical myocardial injury. Increasing hemoglobin A1C levels, even below the threshold for diabetes, were associated with higher hs-cTnT levels (12) as well as a subsequent risk for HF (13), suggesting that associations between dysglycemia and HF risk may be mediated in part through a cardiac injury pathway.

In this issue of JACC: Heart Failure, Ndumele et al. (14), also using data from the ARIC study, contribute important new data to further the understanding of links among obesity, cardiac injury, and HF. They evaluated the cross-sectional association of obesity with hs-cTnT as well as the individual and joint relationships of BMI and hs-cTnT with incident HF among 9,507 ARIC study participants (14). The authors report an independent association between higher BMI and high hs-cTnT levels (≥14 ng/l) that persisted after adjustment for traditional cardiovascular risk factors and confounders. The categorical associations between BMI and high hs-cTnT remained significant only in obese (BMI 30 to 34.9 kg/m²) and severely obese (BMI ≥35 kg/m²) individuals, suggesting a threshold effect. Over a 12-year follow-up period, the authors also found that higher BMI categories associated with incident HF independent of established HF risk factors, with a >2-fold hazard for incident HF among those with severe obesity. Including BMI and hs-cTnT categories in a multivariable model, both higher BMI and higher levels of hs-cTnT were associated with increased HF risk. The individuals with both severe obesity and high hs-cTnT had a >9-fold increased risk of incident HF compared with those with normal weight and undetectable hs-cTnT levels. It is notable that this group at highest relative risk for HF—those with both severe obesity and subclinical cardiac injury—was younger and had a greater proportion of females and African Americans. This finding is particularly striking because this demographic is not traditionally considered to be at high risk for HF and thus may go unrecognized or undertreated.

The Ndumele et al. (14) study combines two seemingly disparate risk factors for HF together based on a plausible pathophysiologic mechanism to show that both obesity and elevated hs-cTnT levels provide important predictive information for HF risk. The study was well performed and provides important new insights into the obesity and HF epidemics. However, several caveats merit mention. First, it is important to note that no statistically significant interaction was seen between BMI and hs-cTnT on the outcome of incident HF. Thus, it is not possible to conclude that cardiac injury modifies the effect of obesity on HF or vice versa. Second, the authors did not account for the potential mediating effects of LVH on the association of obesity with hs-cTnT and HF. It has been demonstrated recently that among individuals without clinical HF or LV dysfunction, the combination of LVH (as measured by either MRI or electrocardiography) and measureable hs-cTnT may represent a malignant LVH phenotype, with markedly increased risk for HF (11). Because obesity clearly predisposes individuals to LVH, it will be important to determine to what extent the associations of obesity with hs-cTnT and HF risk are mediated by LVH. Additionally, given prior ARIC study data linking hyperglycemia with subclinical myocardial injury and HF (12,13), further analyses exploring whether the relationship between obesity and hs-cTnT, and subsequent risk of HF, may be mediated through insulin resistance would be of considerable interest.

Two other aspects relating to the structural phenotype of both the exposure variable (BMI) and outcome variable (HF) need to be addressed. First, BMI is a nonspecific marker of excessive adipose tissue accumulation and incorporates abdominal and nonabdominal adiposity as well as lean muscle mass. Although previous studies demonstrated that standard anthropometric measures of obesity are clearly associated with increased risk for HF in the general population, assessment of obesity-related risk at an individual level is much more challenging because there is significant heterogeneity of cardiovascular and metabolic phenotypes among obese persons that at least in part is related to differences in body fat distribution (15). For example, in a recent study of 2,710 individuals without clinical HF or LV dysfunction, visceral adipose tissue, a marker of central adiposity, was independently associated with
concentric LV remodeling and adverse hemodynamics including higher systemic vascular resistance and lower cardiac output; in contrast, lower body subcutaneous fat was associated with eccentric remodeling, lower systemic vascular resistance, and higher cardiac output (16). Thus, the impact of obesity on LV structure and function may differ based on adipose tissue distribution. The authors of the current study reported analogous results when using waist circumference rather than BMI as a measure of abdominal adiposity. However, simple measures of abdominal fat such as waist circumference and waist-hip ratio provide somewhat redundant information to BMI and include both visceral and subcutaneous abdominal fat depots, which may play very different pathogenic roles among obese individuals (17). More precise measures of abdominal fat distribution (using MRI or computed tomography imaging) may provide further insight into the interplay among obesity, subclinical cardiac injury, and HF risk. Finally, the authors do not subclassify HF into HFrEF and heart failure with preserved ejection fraction (HFpEF). Understanding whether the combination of obesity and elevated hs-cTnT contributes preferentially to HFrEF or HFpEF is an important area for further investigation.

Moving forward, it will be important for other large population-based studies to replicate the observations by Ndumele et al. (14), addressing some of the issues raised previously by including analyses that consider the influences of LVH, insulin resistance, and more sophisticated assessments of body composition. If confirmed, these findings would suggest that preventing or reducing chronic subclinical myocardial injury may emerge as an important strategy to mitigate HF risk among obese individuals. Exploration of the effects of lifestyle, pharmacological, and surgical approaches to obesity management on troponin levels may provide insights as to which strategies are likely to have the greatest impact on HF risk. Additionally, embedding serial measurements of hs-cTnT or high-sensitivity cardiac troponin I within large outcomes trials of novel pharmacological therapies for diabetes or obesity may represent an efficient method of determining whether subclinical cardiac injury represents a modifiable intermediate phenotype in the pathway to HF among obese individuals. Although a single “smoking gun” linking obesity with HF is unlikely to be found, the ARIC study investigators have identified subclinical myocardial injury as one potentially important pathway linking the 2 epidemics. Given the recalcitrant problem of obesity and the markedly elevated risk for HF seen when hs-cTnT is elevated among obese individuals, additional research into this area should be undertaken with high priority.

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