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EDITORIAL COMMENT

Obesity and Cardiovascular Disease: The Hippocrates Paradox?*

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"Sudden death is more common in those who are naturally fat than in the lean."
—*Hippocrates* (1)

Clearly, obesity is a problem that is reaching epidemic proportions in the U.S., with nearly 70% of adults being classified as overweight or obese compared with fewer than 25% 40 years ago (2,3). Although too often obesity is viewed as a cosmetic problem as opposed to a major health concern, there is no question that obesity places a "heavy" burden on the entire cardiovascular system, contributing to considerable overall morbidity and mortality, a fact that was even recognized by Hippocrates centuries ago. In fact, recent evidence indicates that obesity is associated with more morbidity than smoking, alcoholism, and poverty, and if current trends continue will account for over 300,000 deaths annually in the U.S., thus overtaking cigarette abuse as the leading preventable cause of death (2,4,5).

CORONARY RISK

Obesity has adverse effects on several coronary artery disease (CAD) risk factors. Obese patients are more likely to be hypertensive than lean patients, and weight gain is typically associated with increases in arterial pressure (6). However, independent of arterial pressure, obesity increases the risk of left ventricular hypertrophy (LVH), particularly of the eccentric type (7,8). Obesity also adversely affects plasma lipids, especially increasing triglycerides and decreasing the cardioprotective levels of high-density lipoprotein cholesterol, and is the major contributor to adult-onset diabetes mellitus and the insulin resistance syndrome (now called metabolic syndrome), which are associated with high levels of inflammation and overall cardiovascular mortality (9–12). Despite adversely affecting these risk factors, including markedly increasing levels of high sensitivity C-reactive protein (12), data from both the Framingham Heart Study (13) and a large cohort of U.S. nurses (14) have indicated that obesity is an independent risk factor for major CAD events in men and, particularly, in women.

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CARDIAC FUNCTION

In addition to increasing eccentric LVH and the propensity for more complex dysrhythmias (4,5,15–18), obesity also has adverse effects on cardiac function. Diastolic abnormalities occur with all types of LVH (16), with the most marked abnormalities occurring in those with both obesity and hypertension, especially in those with left atrial abnormality by electrocardiogram (19). Although preload dependent indices of systolic function (e.g., ejection fraction) remain preserved early in obesity, preload independent indices (e.g., end-systolic stress/end-systolic volume index) demonstrate reduced contractility early in obesity (20). Alpert et al. (21–23) have confirmed the adverse effects of significant obesity on both diastolic and systolic ventricular function. In a study of 74 morbidly obese patients, Alpert et al. (21) demonstrated that nearly one-third had clinical evidence of heart failure (HF), and the probability of HF increased with increasing duration of morbid obesity. At 20 and 25 years of obesity duration, the probability of HF was 66% and 93%, respectively. A recent epidemiologic study from the Framingham Heart Study indicates that overweightness and obesity are potent predictors of subsequent clinical HF (24).

WEIGHT REDUCTION

Recognizing the adverse effects of obesity, weight reduction has been shown to produce numerous cardiovascular benefits, including reducing arterial pressure, preload, afterload, sympathetic stimulation to the cardiovascular system, and LVH (4,5,25). Alpert et al. (21) demonstrated that New York Heart Association (NYHA) functional class improved in 12 of 14 morbidly obese patients who achieved marked weight loss (<30% of total weight) after gastroplasty—by an average of at least one functional class. Weight loss was also associated with marked improvements in left ventricular (LV) chamber size, LV end-systolic wall stress, and diastolic and systolic ventricular function in these patients. In our cardiac rehabilitation program for patients with CAD, where nearly 40% met criteria for obesity, even small reductions in body weight (e.g., <5% or average 10%) were associated with marked improvements in obesity indices, lipids, and exercise capacity compared with obese patients who did not lose weight (9).

HEART FAILURE PROGNOSIS

Although obesity is clearly associated with more cardiovascular disease, and several studies indicate a progressive increase in all-cause mortality and years of life lost associated with overweightness and, especially, with obesity (26), recent studies have focused on an apparent paradox regarding the relationship between obesity and subsequent cardiovascular prognosis. For example, in a group of patients with

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severe systolic HF, we recently demonstrated a strong inverse relationship between indices of obesity and body composition, including percent body fat and total body fat, as well as body mass indices (BMI), and subsequent clinical prognosis (27). Clearly, in advanced HF, cachexia and wasting appear to be independent predictors of increased mortality (28–30). In addition, recent data indicate that weight loss of more than 6% (presumably non-purposeful) is associated with impaired survival (31). However, in our cohort of HF patients, in the lowest quintiles of body composition parameters, the BMI and percent fat measures were at levels generally considered to be "healthy" and certainly not at levels consistent with a cachectic state. Yet, we found the highest event rates associated with the lowest quintiles of body composition and the lowest event rates associated with the greater obesity. In fact, in our cohort, a higher percent body fat was the strongest independent predictor of better event-free survival—for every 1% increase in percent body fat, clinical events fell by over 13%. Likewise, a study by Horwich et al. (32) demonstrated that in mostly NYHA functional class IV HF patients, various categories of BMI were associated with similar overall survival, but like our study, their study and a study from the Netherlands (33) demonstrated that higher BMI was associated with better overall survival in the multivariate analyses.

We believe that this apparent paradox in HF represents an association and that it is unlikely that the relationship is causal. It is recognized that peak oxygen consumption with exercise is a potent predictor of prognosis in advanced HF. Although, for practical purposes, fat does not consume oxygen or receive substantial perfusion, generally cardiopulmonary parameters are corrected for total body weight as opposed to lean body weight (34–36). We have demonstrated that lean adjusted exercise indices (including peak oxygen consumption, anaerobic threshold, and oxygen-pulse) all predict prognosis better than non-adjusted indices (35,36), which may be particularly applicable to the favorable prognosis in obese HF patients with higher percent body fat who generally have relatively high lean adjusted exercise indices. In addition, none of the above HF studies (27,32,33) have accounted for the effects of non-purposeful weight loss in lean patients, which may be associated with a more advanced form of HF.

CORONARY REVASCULARIZATION

Although obesity may also contribute to CAD risk factors and overall prevalence of CAD, several recent studies also point out the "obesity paradox" after revascularization procedures (37–40). In patients with CAD undergoing percutaneous coronary intervention (PCI), Gruberg et al. (37) demonstrated that underweight and "normal" weight patients had worse short- and long-term outcomes compared with overweight and obese patients. In a multivariate analysis, higher BMI was a weak, but independent, predictor of better one-year survival (37). However, in this study, most of the excess risk seems to be attributed to the groups with the lowest BMI ($\leq$20 kg/m^2, more so in those $<$18.5 kg/m^2). Moreover, in patients who were treated with balloon angioplasty in the Bypass Angioplasty Revascularization Investigation (BARI) trial, a similar obesity paradox was noted—every one unit increase in BMI was associated with a 5.5% lower adjusted risk for major in-hospital events (38). Ellis et al. (39), in a study of over 3,500 patients who underwent PCI, demonstrated that low to normal-weight patients (BMI $<$25 kg/m^2) and severely obese patients (BMI $>$35 kg/m^2) had higher in-hospital mortality compared with overweight and mildly obese patients (BMI 26 to 35 kg/m^2). In a study of over 6,000 patients undergoing PCI at the Mayo Clinic (40), obese patients had similar to lower mortality rates compared with normal-weight patients, whereas underweight patients had the highest mortality. Moreover, underweight and normal-weight patients had higher rates of femoral bleeding, hematoma, and blood loss requiring transfusion compared with obese patients.

Considerable controversy exists regarding the effects of obesity on prognosis after cardiac surgery, with some major systems of classification indicating that obesity is associated with higher perioperative morbidity and mortality (41). The current article by Reeves et al. (42) in this issue of the *Journal* also raises the idea of an apparent "obesity paradox" early after coronary artery bypass grafting (CABG). Although the authors recognize that obese patients may be less likely to be selected for CABG and that, in general, obese patients undergoing CABG may have less high-risk features, particularly less severe CAD and LV dysfunction compared with the lean patients, even when adjusting for these confounding factors, they demonstrated that underweight patients had a higher risk of perioperative complications, whereas the perioperative prognosis was not adversely affected by overweightness and obesity. In fact, these patients generally had similar or even better perioperative prognosis compared with the lean patients. Moreover, they demonstrated that the overweight and obese patients did not have a significant increase in postoperative chest infections, and contrary to popular belief, actually had significantly less postoperative blood loss and need for blood transfusions. On the other hand, recent data from the BARI trial demonstrated that whereas in-hospital complications were not adversely affected by obesity in the CABG patients, five-year mortality progressively increased by up to five-fold with greater obesity (38). Whether or not obesity directly affects prognosis in CAD is still subject to considerable debate. However, certainly all of these data would support the idea that obese patients should not be categorically denied or discouraged to pursue the potential benefits of coronary revascularization, both percutaneous and surgical.

Although the current paper by Reeves et al. (43) may add fuel to the fire regarding an apparent "obesity paradox," we urge caution that a "risk marker" not be confused with a risk factor. Although obesity may clearly be a risk factor for developing CAD and HF, obesity by itself may not necessarily expose patients with these diseases to excess short-term risk, particularly with coronary revascularization. These facts, how-

ever, do not discount the need for more vigorous efforts at obesity prevention and intervention, which may go a long way to prevent these diseases and prevent the morbid complications recognized centuries ago by Hippocrates.

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