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EDITORIAL COMMENT

Cardiac Remodeling in Obesity

Time for a New Paradigm*

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Approximately 70% of people in the U.S. are overweight or obese, nearly twice as many as 30 years ago. Much of the conventional wisdom about obesity and the heart came from small studies performed 30 to 40 years ago (1,2). These studies suggested that obesity produced chronic volume overload due to high cardiac output. This led to eccentric hypertrophy and the eventual development of congestive heart failure (2). The term *cardiomyopathy of obesity* was coined by Alexander (3) in 1985, and the concept that adiposity has an independent causal role in producing cardiac dysfunction is now widely embraced (4). Longer duration of severe obesity has been suggested as the main factor predisposing to cardiac dysfunction (5). Case reports of severely obese patients with heart failure that resolved after significant weight loss seem to support this notion (2).

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In contrast to the paradigm described, several recent studies (6–9) reported that most obese subjects have concentric left ventricular (LV) remodeling or hypertrophy. Increased wall thickness or mass relative to cavity size is usually thought of as a sequela of chronic pressure overload rather than volume overload. Interestingly, concentric LV geometry has been observed in obese patients, even in the absence of documented hypertension (7,9). Although hypertension does not seem to be necessary for LV hypertrophy in obesity, the combination of a higher body mass index (BMI) and hypertension synergistically acts to further increase LV mass (6). Sleep apnea also contributes to LV hypertrophy in obese subjects (6). Additionally, it has been proposed that elevated levels of insulin, insulin-like growth factor 1, or various adipocytokines (e.g., leptin) produce direct trophic effects on the heart (10,11). Whatever the mechanism(s), there is substantial new evidence that most obese people have concentric LV geometry, not dilated, thin-walled hearts.

A distinct cardiomyopathy of obesity is called into question by the findings of several recent studies. First, the mild concentric LV hypertrophy in the majority of obese subjects enrolled in population studies does not fit well with the conventional clinical definition of a cardiomyopathy. Second, even though obese subjects have subclinical LV systolic dysfunction as assessed by mid-wall fractional shortening or tissue Doppler or strain imaging, obese individuals consistently have normal or increased LV ejection fractions (6,8,9,12). Moreover, there is no association between the ejection fraction and the severity of obesity (i.e., LV function is not worse in the most obese subjects). There are no longitudinal studies showing progression of LV dysfunction over time in obese humans. In fact, mild concentric LV hypertrophy and subtle contractile abnormalities have been reported in obese children, adolescents, and adults (6,8,12–14). If obesity commonly causes a cardiomyopathy, one would predict a more consistent pattern of worsening LV function with older age and severity of obesity. The majority of recent reports show, at most, mild diastolic abnormalities in obese individuals (8,9,15,16). Mitral inflow has been normal or has demonstrated a slow relaxation pattern, findings usually associated with normal LV filling pressures. Tissue Doppler imaging and strain imaging have revealed only slight reductions of early diastolic myocardial relengthening velocities (8). No prospective studies have reported significant numbers

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of obese patients with pseudonormal or restrictive LV filling patterns, findings that are expected if these patients had significant diastolic dysfunction.

The aforementioned studies may be criticized because they used echocardiography to assess LV structure and function. Imaging windows become more limited as body weight increases. Thus, echocardiography may be less accurate in the more obese populations. One of the larger studies of echocardiography in obese subjects to date included 851 severely obese subjects (6), but most studies have included fewer than 150 subjects. It may be argued that the relatively small sample sizes might have produced selection bias. These concerns can be largely laid to rest by an impressive new study.

In this issue of *iJACC*, Turkbey et al. (17) report results of cardiac magnetic resonance (CMR) in 5,098 subjects aged 45 to 84 years without apparent cardiac disease who were enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). In the MESA population, 29% were overweight, 41% were obese, ~ 40% had hypertension, and 10% had diabetes. These demographics are reflective of the general population in the U.S. The main findings of the study were that both LV mass and end-diastolic volume were positively associated with measures of obesity. This remained true for both sexes after adjustment for other risk factors. The LV mass-to-volume ratio was positively associated with all measures of obesity including BMI, waist circumference, waist-to-hip ratio, and estimated fat mass. The obese subjects in this study had a high ratio of LV mass to volume, indicating concentric remodeling or hypertrophy. Ejection fractions were normal or increased (mean men, 67%; women, 71%) and showed no significant association with obesity.

The investigators participating in the MESA study are to be commended for the monumental effort involved in performing and analyzing cardiac CMR scans in over 6,000 subjects. This well-designed study used a gold-standard imaging technique in a very large population free of referral bias. The results resoundingly confirm the main findings from most of the recent studies on this topic: LV mass increases out of proportion to cavity size in obese individuals and the degree of concentric remodeling is positively related to BMI and other measures of adiposity. The findings challenge the view that obesity causes a state of chronic volume overload that is predominantly associated with eccentric LV remodeling.

The data from this study do not support the existence of a cardiomyopathy of obesity, at least if cardiac enlargement or reduced ejection fraction are considered as usual components of a cardiomyopathy. Furthermore, 2 findings in this study challenge the hypothesis that longer duration of obesity leads to LV dysfunction. First, the subjects in this study were older (mean age 61 years) than those in previous studies. In most cases, severe obesity requires decades to develop. Even the most obese individuals in the MESA study had changes in cardiac structure and function that were strikingly similar to those reported in much younger populations with lesser degrees of obesity. Second, the absence of any trend toward reduced ejection fraction, even at the highest BMIs, leads to the conclusion that chronicity of the obese condition does not necessarily lead to overt contractile dysfunction. In contrast, it is increasingly clear that obesity is associated with both the premature onset of coronary atherosclerosis (18) and more rapid atherosclerosis progression (19). Thus, comorbid conditions, such as ischemic heart disease, likely explain part of the predilection of obese patients to the development of heart failure (20).

CMR findings in the current study are very similar to those of the most recent studies using echocardiography. Thus, echocardiography is generally a suitable technique for assessment of cardiac structure and function in obesity. This is important because echocardiography is ubiquitous, safe, fast, and less costly than CMR. Furthermore, CMR may be difficult to use in severely obese subjects due to the confining size of the bore on most modern CMR units. The ability to obtain similar data with echocardiography and CMR is a testimony to the steady advances that have been achieved in cardiac ultrasound imaging technology since its inception over 50 years ago.

In summary, it is time to consider a new paradigm regarding the structural and functional impacts of obesity on the heart. Obesity, even when severe and long-standing, is most often associated with concentric LV remodeling, normal LV ejection fraction, and subclinical abnormalities of systolic and diastolic function. There is little evidence that these abnormalities are progressive. With no end in sight to the obesity epidemic, rigorous investigations such as the study by Turkbey et al. (17) will be increasingly important. It is imperative that we gain further understanding of how obesity affects the heart and modulates the cardiovascular responses to lifestyle changes, surgical interventions, and pharmacotherapies.

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