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EDITORIAL COMMENT

Linking Pediatric Obesity to Subclinical Alterations in Cardiac Structure and Function*

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In this issue of *iJACC*, Manger et al. (1) detail preclinical echocardiographic correlates of obesity in children. Specifically, the investigators found that obese children had left ventricular (LV) geometric alterations consistent with concentric remodeling and frank hypertrophy. These obese children also had functional alterations, including reduced longitudinal strain, circumferential strain, and abnormal Doppler diastolic function parameters. This study contributes to a broadening avenue connecting pediatric obesity to pre-clinical anatomic and functional cardiovascular changes that are the underpinnings of future poor cardiovascular health.

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There is general agreement that a substantial portion of obesity-related cardiovascular disease (CVD) risk is mediated through concurrent classic CVD risk factors (2). Although recent reports suggest that there has been a felicitous deceleration in pediatric obesity trends, there are still a large number of children carrying excess weight (3). Unfortunately, early life obesity actually does predict future CVD and premature mortality (4,5). Supporting these observations are data connecting excess weight in early life to atherosclerotic intermediaries such as higher prevalence of high blood pressure and cholesterol; future subclinical atherosclerotic vascular changes; and that life-course improvement in obesity can modify these vascular changes (6–8). The present study adds to this growing body of work demonstrating that pediatric obesity confers presumably deleterious changes on cardiac structure and myocardial function. Although, as the authors point out, direct long-term linkages between these alterations and future CVD events is absent, temporal trends indicate increasing stroke incidence in young adults coincident with higher CVD risk factors (9).

Apropos to this study, obesity is purported to increase intravascular volume through various mechanisms including neurohormonal activation and "insensitivity" to natriuretic hormones (10,11). This excess volume is accommodated by enlarging cardiovascular structures (10). The present study confirms previous investigations suggesting enlarged cardiac chambers, as obese children had larger left atrial, left ventricular, right atrial, and right ventricular chamber sizes. It is important to note that comparisons of cardiac size for obese versus nonobese populations has been enigmatic. Allometric scaling in children is particularly challenging, having to consider physical parameters related to age, pubertal stage, and changes in muscle mass. Weight in kilograms, fat mass, fat-free mass, body mass index, and height all have been used as normalization measures and discrepancies are noted (12). In this study, the authors indexed to body height raised to the 2.7 power and found a differential relation between obesity and chamber sizes. Although larger right atrium, right ventricle, and left atrium persisted after adjustment, LV diameter was not different between obese and nonobese patients. This discrepancy was counterintuitive and was not fully addressed by the authors. As elucidated by the Young-Laplace equation, dilated cardiac chambers will tend to normalize wall tension by increasing wall thickness (13). In this

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study, the investigators noted increased LV mass and relative wall thickness, in the context of relatively smaller LV chamber size. Therefore, it is difficult to attribute the thickened LV to pure volume changes. However, other biochemical processes in obesity may alter myocardial tissue thickness, including local effects of the renin-angiotensin-aldosterone system and the insulin resistance syndrome. These and other biochemical mediators lead to cellular hypertrophy, myocardial fibrosis, and microvascular paucity, which are the key features of pathological hypertrophy.

Initial cardiac responses to obesity may be adaptive, but then progress to a maladaptive phase and contribute to cardiac dysfunction (14). Although there was no difference in LV ejection fraction, reduced tissue Doppler indexes for peak systolic velocity and speckle tracking-derived longitudinal and circumferential strain suggested impaired systolic function in obese children. One important point to note is that studies have shown age-related differences in LV strain (15). Although the 2 groups were matched for age, comparison of strain and strain rate imaging in pediatric studies should consider the potential for age-related differences. Concomitantly, Doppler blood flow and tissue velocity-derived diastolic indexes, including peak mitral E to A, septal and lateral tissue peak E-wave, and E/E′ ratios, were all impaired in the obese children. The authors note that these subtle dysfunctional indexes are consonant with previous studies. The investigators show biologically-plausible univariate correlates to strain abnormalities, including obesity, systolic blood pressure, LV chamber size, wall thickness, triglycerides, high-density lipoprotein cholesterol, homeostasis model assessment-estimated insulin resistance, carotid intima-media thickness, and peripheral reactive hyperemia index. Presumably due to the small size of the study and high degree of collinearity between these factors in a primarily Caucasian cohort, the multivariable model found only obesity and high-density lipoprotein to be associated with strain indexes.

The relation between vascular intermediates and cardiac phenotype underscores the importance of ventricular-vascular interactions. The most commonly measured index of vascular change, blood pressure, is of special mention, as afterload related systolic wall stress can be a potent inducer of LV hypertrophy (16). A recent population-based report in children demonstrated that reorganizing brachial blood pressure into its pulsatile and steady-state components uncovers a dramatic increase in the pulsatile component in parallel with obesity (17,18). As pulsatile load is a strong predictor of cardiac hypertrophy and CVD events, this raises concerns about a future epidemic of CVD (19). The current findings support previous reports linking insulin resistance syndrome features to cardiac remodeling and fibrosis. Cardiac magnetic resonance studies link cardiac fibrosis to decreased strain and diastolic function, which is consistent with the findings presented (20). Additionally, the present study focused on resting cardiac function. Dysfunction under stress usually precedes resting abnormalities. Therefore, in obese children with normal resting function, exercise testing could offer an opportunity for even earlier detection of cardiac dysfunction (21).

The author's important work prompts more questions. First, the linkage from strain and diastolic dysfunction in general pediatric populations to adult CVD events is not yet directly demonstrated. Second, a special mechanistic focus is needed to distinguish the effects of excess weight, higher blood pressure, and cardiotropic biochemical mediators. Third, the longitudinal effects of pediatric obesity on cardiac structure and function deserves more scrutiny (22). Nonetheless, the authors are to be commended for providing more data on the effects of childhood obesity. However, with the global pandemic reaching its third decade (with the earliest cohort now leaving early adulthood), continued attention must now address mechanisms to improve the cardiovascular health of our patients, both young and old.

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