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Impact of obesity on cardiac metabolism, fibrosis, and function

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ABSTRACT

Obesity is a global pandemic with a huge burden on the healthcare system. Obesity is not only linked to the development of risk factors for atherosclerotic vascular disease but also has a strong association with ventricular hypertrophy, heart failure, atrial fibrillation, and stroke. Recent experimental and clinical studies have demonstrated that obesity is associated with cardiac dysfunction, adipokine dysregulation, and activation of the pro-fibrotic signaling pathways leading to cardiac fibrosis, which is a key structural change responsible for atrial fibrillation. Importantly, these also have been shown to be reversible with weight reduction strategies. This review discusses the alterations in cardiac metabolism and function due to obesity. In addition, it addresses the complex and not yet fully understood mechanisms underlying cardiac fibrosis, with a focus on atrial substrate predisposing to atrial fibrillation in obesity.

Introduction

Obesity is a global pandemic with a huge burden on the healthcare systems [1,2]. The prevalence of obesity remains high in developed countries with more than two-thirds of adults being classified as overweight or obese [1–3]. Obesity is not only linked to the development of metabolic risk factors for atherosclerotic vascular disease, it also has strong and independent associations with left ventricular hypertrophy, heart failure, atrial fibrillation, and stroke. Indeed, many studies over the last decades have shown the impact of obesity on cardiac remodeling with structural and functional abnormalities. However, the mechanisms contributing to these changes remain incompletely understood with a complex interplay of hemodynamic, neurohumoral, and metabolic factors as well as inflammation and oxidative stress, contributing to cellular apoptosis, hypertrophy, and interstitial fibrosis. Specifically, concomitant conditions seen frequently in obese individuals such as hypertension, sleep apnea, and diabetes mellitus also have direct cardiac remodeling effects. This review is focused on the cardiac functional, morphological, and metabolic abnormalities due to obesity alone, with specific attention on the underlying signaling pathways underlying cardiac fibrosis seen with increased adiposity.

Cardiac functional and morphological abnormalities due to obesity

Defining the cardiomyopathy due to obesity has proven to be a challenge due to the confounding co-morbid conditions such as hypertension, diabetes, and coronary artery disease that are often present in obese individuals. Conflicting data have been reported in the literature with different imaging

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modalities and indices used for comparisons. Nevertheless, a causal association has been demonstrated in a large longitudinal population-based study whereby a graded increase in the risk of heart failure was observed across all categories of body mass index. There was increase in heart failure risk by 5% in men and 7% in women for each increment of one in the body mass index after adjustments for known risk factors such as age, alcohol consumption, serum cholesterol, diabetes, hypertension, left ventricular hypertrophy, and myocardial infarction [4].

Left ventricular systolic dysfunction

Left ventricular systolic function, as assessed with standard echocardiographic left ventricular ejection fraction, has been shown to be either normal or supranormal in obese subjects. Even in the severely obese, overt systolic dysfunction is uncommon in the absence of concomitant heart disease [5,6]. Despite the variable findings, more recent studies using novel echocardiographic techniques of tissue velocity and deformation imaging have demonstrated the presence of subclinical systolic contractile abnormalities in obese subjects without coronary or structural heart disease. The obese individuals in these studies demonstrate decreased spectral pulsed-wave systolic velocity as well as reduced regional and global strain, although left ventricular (LV) ejection fraction remained in the normal range [7–10]. These tissue Doppler abnormalities, being load-independent, may indicate an inherent abnormality in contractility with obesity not appreciated with load-dependent parameters like LV ejection fraction.

Likewise, variable findings have been reported in different experimental models of obesity including mildly reduced or preserved LV systolic dysfunction [11,12]. Mildly reduced LV systolic function has been demonstrated in obese Zucker diabetic fatty rats, transgenic and chronic high-fat-fed obese insulin-resistant mice and transgenic mice with cardiac steatosis [11,13–16]. The LV systolic function was, however, preserved in leptin-deficient homozygous obese mice despite a slight reduction seen with dobutamine challenge [17]. The significance of these findings in transgenic models of cardiac steatosis and their applicability to humans is not clear. Furthermore, LV systolic function was unchanged or mildly reduced in rats with diet-induced obesity [12,18]. In sheep with high-caloric-diet-induced obesity, LV systolic function as assessed by LV ejection fraction was unaffected [19].

Left ventricular diastolic dysfunction

Although earlier reports on the effect of obesity on LV diastolic dysfunction have been variable, numerous recent studies have reported the presence of mild diastolic dysfunction in obese individuals [7,8,20]. These involved a variety of echocardiographic measures such as prolonged left ventricular relaxation time, increased E/e ratio, and lower E/A ratio, suggestive of diastolic filling abnormalities and elevated filling pressures [7,8]. These have been in keeping with the elevated LV end diastolic and pulmonary wedge pressures reported in obesity [21,22]. The prevalence of diastolic dysfunction appears to increase with increasing severity of obesity [23].

The diastolic dysfunction in obesity has been shown to correlate with left ventricular hypertrophy. However, studies in the severely obese have demonstrated diastolic dysfunction even after adjusting for left ventricular hypertrophy [8,20]. One such study suggested that diastolic dysfunction might be related to cardiotoxicity secondary to elevated free fatty acids [20]. Similarly, diastolic abnormalities have also been shown in leptin-deficient homozygous obese mice, diet-induced obese mice, and diet-induced obese rabbits [12,17,24,25]. Further, persistent diastolic dysfunction has been demonstrated in a transgenic murine model of cardiac steatosis even in the absence of systemic metabolic derangement or weight gain [11]. Elevated right and left atrial and pulmonary artery pressures have also been observed during invasive measurements in an ovine model of diet-induced obesity [19]. As with humans, elevated atrial pressures in presence of normal left ventricular pressure suggested diastolic dysfunction in this obese ovine model.

Left ventricular hypertrophy

Recent data from a meta-analysis of 22 echocardiographic studies confirmed a consistent relationship between obesity and left ventricular hypertrophy [26]. Specifically, the overall prevalence of left ventricular hypertrophy was 56% in obesity, with a significant relationship between body mass index and left ventricular hypertrophy. There was an odds ratio of 4.19 for developing left ventricular hypertrophy with obesity [26]. Likewise, several smaller studies on younger healthy obese patients without co-morbid conditions have also demonstrated a positive relationship between obesity and left ventricular hypertrophy [7,8]. Furthermore, a higher prevalence of eccentric rather than concentric left ventricular hypertrophy (66% vs. 34%) has been observed with obesity in an echocardiographic study [26]. However, a recent cardiac magnetic resonance study in patients without identifiable cardiac risk factors suggested a predominant concentric hypertrophic pattern in obese men and both concentric and eccentric hypertrophy in obese women [27]. The cardiac remodeling process due to obesity is likely to be progressive with more ventricular hypertrophy seen with longer duration and larger amount of weight gain (Fig. 1) [19].

Left atrial enlargement

Left atrial enlargement has been associated with obesity in both children [28] and adults [8,29]. The echocardiographic measures of the left atrium from different planes suggested an oval-shaped left atrium in obese individuals. The anterior–posterior (parasternal long-axis view) and longitudinal diameters (apical four-chamber view) were increased without a significant change in the transverse apical four-chamber measure [30]. In addition, an echocardiographic imaging study has demonstrated a lower atrial peak systolic strain rate indicative of atrial dysfunction in obese individuals [28]. The Framingham observational cohort study has further highlighted the strong association between left atrial enlargement in obese individuals and incident atrial fibrillation [29]. In keeping with clinical observations, cardiac magnetic resonance imaging has also demonstrated increased bi-atrial and pericardial fat volume in an ovine model of diet-induced obesity (Fig. 1) [19]. Indeed, increased left atrial epicardial