Published in final edited form as:

Trends Cardiovasc Med. 2015 February ; 25(2): 127–128. doi:10.1016/j.tcm.2014.09.010.

Obesity-Related Cardiomyopathy is an Adipocyte-Mediated Paracrine Disease

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Keywords

adipocyte; cardiomyopathy; fibrosis; obesity

Obesity is associated with an increased burden of chronic diseases, including diabetes mellitus, hypertension, and coronary atherosclerosis, all of which contribute to higher rates of morbidity and mortality in obese patients. This was confirmed in a prospective study that demonstrated a 2–3-fold increase in mortality in obese as compared to normal weight individuals [1]. The World Health Organization currently estimates that by 2015, approximately 700 million adults worldwide will be obese (body mass index $> 30 \text{ kg/m}^2$) with another 2.3 billion adults being categorized as overweight (body mass index 25–29 kg/m^2) [2]. Based on this prediction, it is expected that there will be an attendant increase in obesity-related cardiovascular disorders.

It is increasingly recognized that cardiac remodeling and dysfunction that occurs as a consequence of obesity cannot be attributed solely to the comorbidities associated with excess weight. In fact, the Coronary Artery Risk Development in Young Adults (CARDIA) study found that over a 25-year follow-up period obesity was highly related to left ventricular dysfunction even after adjusting for baseline and interval changes in other risk factors [3]. In this issue of *Trends in Cardiovascular Medicine*, Mahajan *et al* review cardiac dysfunction in obesity with a focus on cardiac metabolism and fibrosis [4]. They present an overview of left ventricular remodeling, systolic dysfunction and diastolic dysfunction; discuss changes in metabolism as a contributor to decreased myocardial performance; and, review mediators of fibrosis that are upregulated in obesity and participate in cardiac remodeling.

There are several interesting points raised by this review. The first is that there is no consensus opinion on what defines the obesity-related cardiomyopathy. Evidence presented suggests that this cardiomyopathy includes left heart remodeling (i.e., left atrial dilation and left ventricular hypertrophy) as well as abnormalities in left ventricular contractile and relaxation functions. The second is that the obesity-related cardiomyopathy may be a paracrine disorder owing to factors secreted by dysfunctional adipocytes in close apposition to atrial and ventricular cardiomyocytes. Third, despite differences in etiology, obesity-

related cardiomyopathy appears to have the same aberrant shifts in metabolism as other cardiomyopathies. Finally, like other chronic diseases, obesity facilitates cardiac fibrosis, which may predispose to cardiac dysfunction and adverse cardiovascular outcomes.

The confusion as to what features comprise the cardiomyopathy of obesity may have occurred, in part, from conflicting data reported by prior studies. One potential explanation for these discordant results is that obesity is not a uniform disorder and individuals enrolled in clinical studies may represent a heterogeneous group. For example, obesity is typically determined by body mass index, a metric that doesn't take into account body fat distribution. Although excess visceral adipose tissue is associated with adverse cardiac events, subcutaneous obesity with minimal visceral fat has a lower cardiac risk profile [5]. This suggests that studies that enroll patients based on body mass index plus other measures of adipose tissue distribution, such as waist circumference and waist-to-hip ratios, will likely lead to more reproducible findings and aid in defining obesity-related cardiomyopathy [6].

The concept that obesity-related cardiomyopathy is manifested as left ventricular hypertrophy with predominantly diastolic dysfunction and that this occurs as a result of an adipocyte paracrine effect is not surprising. This is based on observations made in congenital or acquired generalized lipodystrophy, which is characterized by increased extra- and intra-cardiac ectopic adipose deposition [7]. In patients with this lipotoxic cardiomyopathy, cardiac magnetic resonance imaging studies have confirmed an increase in myocardial triglyceride content, pericardial fat, and concentric left ventricular hypertrophy similar to what is observed in obesity-related cardiomyopathy [8].

Analogous to lipodystrophy, obesity may be considered an energy storage disorder with expansion of adipose tissue in both the epicardial and intracardiac spaces [3]. As discussed in the review, adipocyte hypertrophy in obesity is associated with tissue hypoxia that reprograms the adipocytes to a proinflammatory phenotype. This transition is accompanied by increased levels or expression of factors that promote ventricular dysfunction. For example, tissue Doppler studies identified subclinical systolic dysfunction in obesity, detected as a decrease in longitudinal strain and strain rate, suggesting a possible intrinsic abnormality in obesity cardiomyocytes [9]. However, this could also be explained by the fact that obesity is associated with increased oxidant stress and mitochondrial dysfunction [10]. Oxidant stress, in turn, can oxidize and decrease activity of sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA). Downregulation of SERCA has been observed in obesity and likely contributes to aberrant excitation-contraction coupling in the obese heart [10] [11]. Other possible mechanisms of systolic dysfunction include the direct cardiodepressant effects of factors secreted by dysfunctional adipocytes, including the adipocyte fatty acid binding protein A-FABP and resistin [12].

While the authors provide a concise review of signaling pathways involved in cardiac fibrosis in the obese heart, it is not clear if these pathways are activated and operative in adipocytes, cardiomyocytes and/or fibroblasts. There is, however, clear evidence implicating epicardial adipose tissue as a mediator of cardiac fibrosis. *In vitro* studies that incubated human atrial myocytes with conditioned medium from human epicardial adipose tissue samples demonstrated increased fibrosis of the atrial tissue. Moreover, the profibrotic

secretome of these adipocytes was determined and they were found to secrete the profibrotic factors activin A, transforming growth factor- β 1, and matrix metalloproteinases 1,2,3,8,9, and 13 [13]. Thus, dysfunctional adipocytes stimulate extracellular matrix remodeling and fibrosis in the myocardium. This may also underlie the relationship between obesity and atrial fibrillation, which may occur as a result of atrial fibrosis or the direct effects of adipocyte-derived factors on the pulmonary veins. This is plausible as studies have shown that atrial myocytes extend back into the pulmonary veins [14].

The most encouraging aspect of obesity-related cardiomyopathy discussed in the review is that it is reversible with dietary or surgical weight loss. It will be interesting to note if there are any characteristics, such as the degree of fibrosis that will identify a timepoint when reversibility is no longer possible. In this case, continuing to understand the paracrine relationship between dysfunctional adipocyte depots adjacent to the myocardium and cardiac structure and function will be important. It will also be equally important to understand if obesity mediates right heart dysfunction and remodeling. This is an area of interest as autopsy and noninvasive studies have confirmed that right ventricular hypertrophy is present in patients with obesity [9]. Taken together, the studies outlined in the review and future comprehensive studies in the field may yield modifiable targets for small molecule or gene transfer therapies that could be delivered locally to extracardiac fat depots.

Acknowledgments

This work was funded by NIH/NHLBI R01 HL105301 and U01 HL125215 (JAL).

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