

Effects of Obesity and Adiposity on Cardiac Mechanical Properties

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ABSTRACT

Metabolic abnormalities accompanied by excessive body fat and systemic inflammation can lead to higher incidence of heart failure. Obesity is associated with altered cardiac remodeling, possibly due to increased hemodynamic load, neurohormonal activation, and increased cytokine production. Through direct quantification of visceral adipose tissues surrounding vital organs, especially the epicardial adipose tissue, investigators have demonstrated the link between its activity and adverse cardiovascular events.

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Key words: Obesity, Epicardial fat, Cardiac Dysfunction, Inflammation

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INTRODUCTION

The long-term deleterious consequences of excessive adiposity have great clinical importance. In recent years, increasing interest has been raised regarding the impact of body fat composition or distribution to alterations in cardiac structure and function^[1,2]. A number of studies have shown that measures of central adiposity such as waist circumference are superior to measures of global adiposity such as weight and body mass index (BMI) in assessing the risk of cardiovascular disease^[3](CVD) and all-cause and cardiovascular-specific mortality^[4]. Central obesity is also independently associated with left ventricular (LV) diastolic dysfunction^[5-7].

PATHOPHYSIOLOGY OF ADIPOCYTE-MEDIATED SYSTEMIC INFLAMMATION

Obesity is a state of chronic systemic inflammation resulting from interactions between adipocytes and the macrophages recruited to adipose tissue. As a hallmark of obesity, adipose tissue inflammation may play as a central factor in mediating subsequent metabolic derangements and clinical disorders^[8-10]. More and more data had indicated that the regulation of immune cells infiltration and pro-inflammatory cytokines production as a consequence of altered inflammatory signaling by macrophages may modulate adipose tissue inflammation to a degree^[11,12], which in part helps to explain the transition of excessive visceral adiposity deposition to several unfavorable biological effects. In this regard, more recent studies had demonstrated that M1-type macrophages may serve as a link to lipodystrophy by their infiltrate into adipose tissues of obese individuals via MCP1, where they are activated by saturated fatty acids, leading to low-grade inflammation by producing various pro-inflammatory cytokines^[13,14]. Instead, the differentiation of tissue-resident M2-like macrophages by *trib1* gene in the bone marrow may play a major role in maintaining the homeostasis of adipose and the hepatic tissue in response to IL-4 and IL-13 from eosinophils via a PPAR- γ - and PPAR- δ -dependent mechanisms, respectively^[15-17]. A

recent report also revealed that Trib1 gene may play as critical role in the differentiation of M2-like macrophage and several other forms of circulating white blood cells via the ubiquitin-binding domain, another form of macrophage other than M1, had a central role in regulating insulin resistance, triglyceride level, as well as mediating pro-inflammatory cytokines levels^[18].

In this regard, through measurement of excessive visceral adipose tissue surrounding vital organs, investigators have demonstrated that visceral fat is biologically active and could be a key mediator of various metabolic derangements, systemic inflammation process^[19] with cytokine effects leading to adverse cardiovascular events or progressive heart failure^[20,21]. Most studies have used high-sensitivity C-reactive protein (hs-CRP) to represent the extent of vascular and systemic inflammation response^[22]. It has also been widely advocated as a novel risk factor of CVD^[23]. For instance, the JUPITER trial demonstrated that statin can reduce CVD incidence in overweight subjects with normal lipid profile and elevated Hs-CRP levels^[24]. One interpretation of the study results was that Hs-CRP is not only an inflammatory marker, but also plays a direct role in the pathogenesis of atherosclerosis and thrombosis^[25].

EFFECTS OF EPICARDIAL FAT ON CARDIAC STRUCTURAL REMODELING AND DYSFUNCTION

Our team has reported previously that epicardial fat was independently associated with metabolic derangements and systemic inflammation^[26,27]. The specific effects of epicardial fat on LV structural remodeling in terms of greater concentricity and functional disturbances that may be mediated by various mechanisms including mechanical, paracrine, and systemic processes have been suggested^[28,29]. Furthermore, direct compression of the heart by this enveloping fat deposit may cause impaired LV diastolic filling, leading to atrial remodeling and enlargement^[30].

Importantly, the association between regional adiposity and cardiac structural or functional remodeling is not limited to the ventricle, and may also involve left atrium (LA) which was evidenced by the Framingham Heart Study^[31]. In that study, the authors reported their findings in that larger pericardial fat volume was independently associated with greater LA size in men, with such relationship remained significant after adjustment for body weight and total visceral fat volume. The fact that LA enlargement may be independent of conventional anthropometrics suggests a possible biological role for local pericardial fat on LA remodeling beyond systemic obesity. LA enlargement has long been regarded as one of the strongest predictors for the development of atrial fibrillation (AF). Pericardial fat has also been observed to be independently associated with AF incidence beyond traditional risk factors, including LA size^[32,33]. It may also have predictive value for recurrent paroxysmal AF after ablation^[34]. This further provided insights about the possible role of pericardial adipose burden in the pathophysiological link to AF development.

The differential effects of total visceral fat, epicardial and intrathoracic fat on the cardiovascular system have been compared in previous literature, especially in the Framingham Heart Study^[35,36]. This may be attributed to their different origins of blood supply. Abdominal visceral fat shares the same circulation with the hepatic portal system, so it may be associated with hepatocytic insulin resistance and systemic effects on atherosclerosis^[37,38]. On the other hand, the inflammatory effect of epicardial fat was suggested to be more local than systemic, owing to its proximity to the surrounding

coronary arteries and myocardium^[35,39,40]. As for intrathoracic periaortic or mediastinal fat, their association with CVD is weak because of small volume and lack of anatomical proximity.

BIOCHEMICAL AND GENETIC MECHANISMS

Interestingly, the exact pathophysiological role of epicardial adiposity remains controversial so far^[40-43]. As a potential source of pro-atherogenic adipokines and inflammatory mediators^[44], epicardial fat may exert its toxic effect by either local secretion or systemic inflammation^[45]. Due to its proximity to the myocardium and the same coronary blood supply, epicardial fat may have stronger correlations with coronary vasculopathy^[46], cardiac structure and function than other measures of adiposity, such as total visceral fat or subcutaneous fat tissue^[47].

The linear relationship between intra-myocardial lipids and typical adipose tissue locations^[48] in subjects with excessive fat depots remains to be clarified. Indeed, certain kinds of myocardial steatosis and dysfunction in a more extreme clinical scenario, namely cardiac lipotoxicity^[49,50], may happen with long-term exposure to circulating free fatty acid (FFA) level in subjects with diabetes^[51,52], leading to obviously increased intra-myocardial triglyceride (TG) deposition and impaired cardiac function^[53]. Re-esterification to TG formation rather than classical oxidation of the over-influx of cardiac FFA has thus been proposed as the main mechanism underlying, in part may be further driven and aggravated by FFA high turn-over process generating potentially noxious intermediate metabolites (eg. ceramide), causing mitochondrial and myocardial functional decline^[54] (Figure 1).

Recent large scale genome-wide association studies have identified genomic loci for indices of body fat distribution that are independent of BMI^[55-57], further suggesting the possible existence of unique genetic variants associated with pericardial fat independent of other body fat depots. In one large meta-analysis^[58] of the Framingham Heart Study (FHS) and the Multi-Ethnic Study of Atherosclerosis (MESA), through single nucleotide polymorphism (SNP) genotyping in more than 5000 individuals, a genome-wide significant signal was identified near TRIB2 gene. This SNP was not associated with visceral fat or body mass index. TRIB2 gene expression was also observed in the pericardial fat of mice. This association was limited to pericardial fat, not measures of generalized or visceral adiposity. These findings suggest that unique genetic signatures may be specifically linked to different ectopic fat depots.

THE OBESITY PARADOX

The paradoxical protective effect of central obesity has been widely explored in current literature^[59-61]. Under normal physiologic conditions, epicardial fat may act as a local energy reservoir or a buffer against excessive free fatty acids (FFA) to protect the myocardium from their toxic effects^[62]. On the other hand, it can also release energy rapidly in the form of FFAs to meet increased myocardial energy demands, particularly during myocardial ischemia^[63]. Besides energy storage, the epicardial adipose tissue is also an active source of circulating adipokines (eg: interleukins, tumor necrosis factors) that can profoundly affect energy metabolism as well as systemic inflammation^[45,64]. Although these inflammatory reactions are mostly detrimental to the cardiovascular system, some positive effects may exist, such as the angiogenesis of collateral circulation in patients with coronary artery disease^[45]. This implies more evidence that such regional adipose tissues can be beneficial by preserving myocardial energy under certain circumstances.

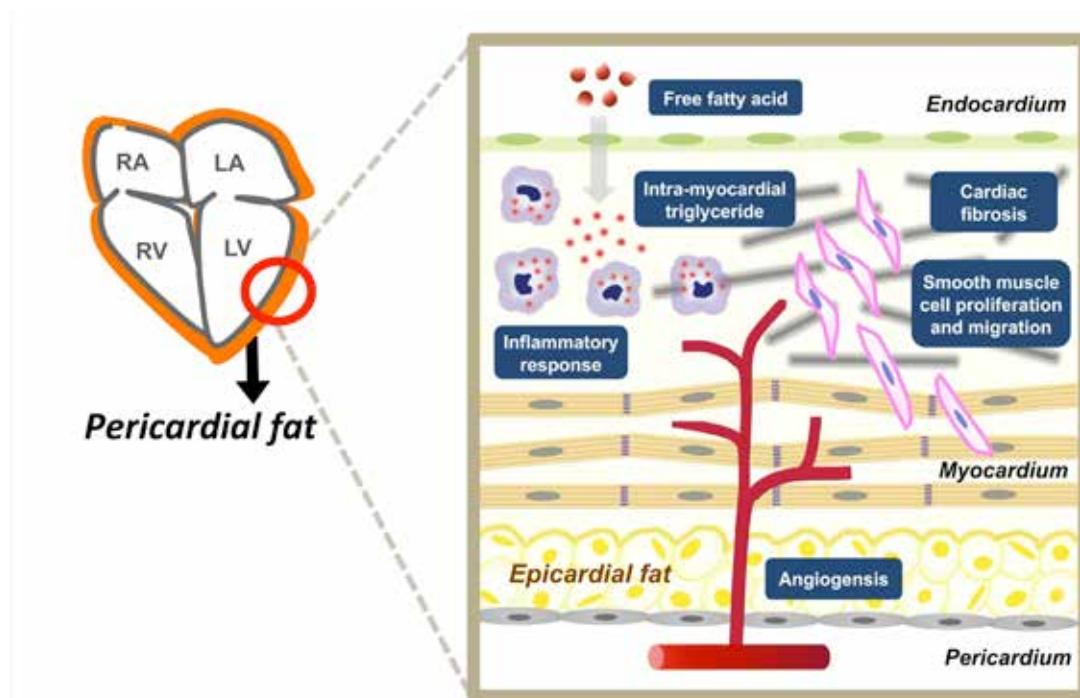


Figure1 Illustration of cardiac steatosis and proposed mechanisms underlying excessive visceral adiposity depots. Free fatty acids (FFA) from the bloodstream were absorbed into the endocardium and synthesized into triglyceride (TG). Excessive depots of myocardial TG may lead to higher oxidative stress, inflammatory response and fibrosis of myocardium. High turnover of FFA can generate potentially toxic intermediate metabolites. Since the epicardium shares the same blood supply as the myocardium and coronary vessels, cardiac steatosis may also promote adipocyte proliferation along the epicardial border. (LA: left atrium; LV: left ventricle).

CONCLUSION

In conclusion, we reviewed the adverse effects of systemic obesity and regional adipose tissue burden on cardiac function from various aspects, including biochemical components, mechanics and genetic issues. Accumulating evidence has supported the hypothesis that epicardial and pericardial fat should be regarded as an independent novel risk factor for cardiovascular disease. The concept that it is a key factor in modulating the process of cardiac structural and functional derangements is becoming more and more widely recognized, and further research on pathophysiologic signaling, pathways and potential therapeutic interventions are warrant in the era of high prevalence of obesity and related metabolic abnormalities.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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