JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 71, NO. 20, 2018

JACC STATE-OF-THE-ART REVIEW

Epicardial Adipose Tissue May Mediate Deleterious Effects of Obesity and Inflammation on the Myocardium

Milton Packer, MD

ABSTRACT

Epicardial adipose tissue has unique properties that distinguish it from other depots of visceral fat. Rather than having distinct boundaries, the epicardium shares an unobstructed microcirculation with the underlying myocardium, and in healthy conditions, produces cytokines that nourish the heart. However, in chronic inflammatory disorders (especially those leading to heart failure with preserved ejection fraction), the epicardium becomes a site of deranged adipogenesis, leading to the secretion of proinflammatory adipokines that can cause atrial and ventricular fibrosis. Accordingly, in patients at risk of heart failure with preserved ejection fraction, drugs that promote the accumulation or inflammation of epicardial adipocytes may lead to heart failure, whereas treatments that ameliorate the proinflammatory characteristics of epicardial fat may reduce the risk of heart failure. These observations suggest that epicardial adipose tissue is a transducer of the adverse effects of systemic inflammation and metabolic disorders on the heart, and thus, represents an important target for therapeutic interventions. (J Am Coll Cardiol 2018;71:2360–72) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

People with obesity are at increased risk of heart failure (1), and bariatric surgery reduces the likelihood of developing heart failure (2,3). Although it has long been believed that the effect of obesity is mediated through hemodynamic stresses related to an exaggerated demand on the ventricles imposed by excess body mass, an increase in loading conditions is not likely to be the primary determinant of heart failure (4). Varying degrees of sodium retention and plasma volume expansion are seen in most people with obesity (5), but only those who are morbidly obese develop a volume overload phenotype (i.e., high-output heart failure). Patients with high-output heart failure have markedly enlarged ventricles with heightened levels of circulating natriuretic peptides and glomerular hyperfiltration (6). In contrast, the heart failure phenotype in most obese patients is characterized by only modestly increased cardiac volumes, comparatively low levels of natriuretic peptides, and impaired renal function (7). These features cannot be readily explained by postulating that excessive hemodynamic stresses are the primary cause of heart failure in obese people.

The most common disorder of the myocardium in obese people is heart failure with preserved ejection fraction (HFpEF) (8). Although these patients exhibit an expansion of plasma volume that is proportional to their body mass, their primary pathophysiological abnormality appears to be a decrease in ventricular distensibility (7). The capacity of the left ventricle to dilate in response to an increase in blood volume is impaired, and thus, even modest degrees of volume overload lead to cardiac overfilling and disproportionate increases in cardiac filling pressures. Regardless of the underlying cause of HFpEF, the primary mechanism that limits ventricular distensibility appears to be cardiac microvascular rarefaction and fibrosis (9–11); the quantity of fibrosis is closely

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From the Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, Texas. Dr. Packer has served as a consultant for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Celyad, Daiichi-Sankyo, Gilead, Novo Nordisk, Novartis, Relypsa, Sanofi, Takeda, Teva, and ZS Pharma.

Manuscript received January 5, 2018; revised manuscript received February 20, 2018, accepted March 18, 2018.

ISSN 0735-1097/$36.00

https://doi.org/10.1016/j.jacc.2018.03.509

related to abnormalities of cardiac diastolic filling, functional capacity, and outcomes (12–14). When obesity is the primary cause of this syndrome, it is assumed that adiposity drives the development of the microcirculatory derangements and myocardial fibrosis (7,8). Yet, it is worth asking: how does obesity lead to these abnormalities (**Central Illustration**)?

OBESITY AS A SYSTEMIC INFLAMMATORY STATE AND EPICARDIAL ADIPOSE TISSUE AS A LOCAL TRANSDUCER OF SYSTEMIC INFLAMMATION

Obesity promotes systemic inflammation (15,16), and its presence adds to the inflammatory burden of many chronic noncardiovascular inflammatory disorders; this augmentation explains why obesity adversely affects the clinical course of rheumatoid arthritis, human immunodeficiency virus infection, and psoriasis (17–19). It is well established that the systemic inflammatory response in each of these disorders can adversely influence the coronary arteries. Obesity, rheumatoid arthritis, human immunodeficiency virus infection, and psoriasis are all accompanied by accelerated coronary atherosclerosis and an increased risk of myocardial infarction (20–22). However, the mechanism by which systemic inflammation enhances coronary atherogenesis has not been defined.

Yet, it is noteworthy that the presentation of coronary artery disease in these illnesses is similar to the common classical disorder that is related to hypercholesterolemia; it is a highly localized event that typically affects multiple short segments of the coronary vasculature (23). This pattern is distinctly different from the diffuse coronary artery lesions seen in transplanted heart, which are undoubtedly the result of a systemic inflammatory response (24). The existence of allograft vasculopathy indicates that systemic inflammation is capable of attacking the entire span of the coronary arteries and causing diffuse disease; yet, the coronary artery lesions that are aggravated by obesity, rheumatoid arthritis, human immunodeficiency virus infection, and psoriasis are focal and manifest as typical atherosclerotic plaques. Therefore, given the fact that systemic inflammation promotes the formation of canonical atherosclerotic lesions in patients with obesity and other inflammatory disorders, some mechanism must exist that transduces this localized effect.

Interestingly, the chronic systemic inflammation that is seen in obesity, rheumatoid arthritis, human immunodeficiency virus infection, psoriasis, and other disorders is accompanied by the significant accumulation of epicardial adipose tissue (24–28). Inflammation can drive adipogenesis, presumably acting as an adaptive mechanism that prevents the deposition of proinflammatory fatty acids in cells other than adipocytes (29). Interestingly, the epicardium appears to be more sensitive to lipogenesis than other types of visceral adipose tissue (30), possibly because it is replete with mobile and developmentally plastic mesenchymal cells that are the source of progenitor cardiomyocytes during fetal development but give rise to adipocytes in adulthood (31,32). Systemic inflammation also adversely influences the biology of epicardial fat (particularly the perivascular adipose tissue that surrounds the coronary arteries) (33–35), promoting the expression of a proinflammatory phenotype (35,36). It is therefore noteworthy that in chronic inflammatory states, the accumulation of epicardial adipose tissue is closely associated with the presence, severity, and progression of coronary artery disease, both in obese and nonobese people, in a manner that is independent of visceral adiposity (37–41). Cessation of the stimulus for systemic inflammation is accompanied by lessening of epicardial fat inflammation (33,42), and experimentally, surgical resection of the epicardial fat depot is followed by amelioration of coronary atherosclerosis (43,44).

Importantly, the distribution of epicardial fat is focally asymmetric (45,46), and thus, the action of epicardial adipose tissue to promote atherogenesis is highly localized, with focal obstructive lesions residing in the coronary arterial segments that are immediately adjacent to areas of epicardial fat with the greatest thickness (47–50). These observations strongly support the hypothesis that the inflammation of epicardial fat can act in a paracrine manner to influence the structure and function of neighboring tissues (51,52). Furthermore, the release of proinflammatory adipocytokines from epicardial (and other visceral) fat into the general circulation may contribute to the systemic inflammatory state; systemic inflammation (in turn) promotes the accumulation of epicardial adipose tissue, which promotes local and systemic inflammation and end-organ dysfunction, thereby creating a positive feedback loop (53–58). Hence, epicardial fat appears to be the transducer that mediates the influence of systemic inflammation on adjacent tissues (e.g., the underlying coronary arteries) (59). It is the accumulation and inflammation of epicardial adipose tissue that is responsible for the ability of obesity to aggravate the cardiovascular complications of many systemic inflammatory disorders that are triggered by a noncardiovascular source (**Figure 1**) (60–64).

ABBREVIATIONS AND ACRONYMS

HFpEF = heart failure with preserved ejection fraction