EPICARDIAL FAT IN THE MAINTENANCE OF CARDIOVASCULAR HEALTH

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Abstract

Epicardial fat is a unique adipose tissue located between the myocardium and the visceral layer of pericardium. This tissue is characterized by highly active fatty acid metabolism and highly expressed thermogenic genes. Epicardial fat and the underlying myocardium share the same microcirculation, suggesting a close and strong interaction between these two structures. Under physiological conditions, epicardial fat protects and supports the heart to exert its normal function. Many clinical studies have shown significant associations between increased amounts of epicardial fat and coronary artery disease (CAD). In patients with CAD, increased epicardial fat becomes inflammatory and may promote plaque development through secretion of proinflammatory cytokines and other mechanisms. Therefore, epicardial fat is a biomarker of cardiovascular risk and a potential therapeutic target for cardiovascular disease. Weight loss and pharmaceuticals can reduce epicardial fat and improve its protective physiological functions.

Introduction: Location and Morphology of Epicardial Fat

Epicardial fat is defined as visceral fat that deposits within the heart.[1] In the embryo stage, epicardial fat develops from brown adipose tissue. In adults, the macroscopic anatomy of epicardial adipose shows that it is situated between the myocardium and visceral layer of pericardium and commonly exists in the atrioventricular and interventricular grooves, whereas in juveniles it is found around the atrial free wall and two atrial appendages.[1,2] Pericardial fat is located outside the visceral pericardium and on the external surface of the parietal pericardium. Although close in proximity, these two fat depots are very different (Table 1).[3] Epicardial fat is vascularized by branches of the coronary arteries, while pericardial fat is vascularized by noncoronary arteries. Epicardial fat originates from splanchnopleuric mesoderm, while pericardial adipose is derived from the primitive thoracic mesenchyme. Notably, epicardial adipose has no fascia layer separating it from the underlying myocardium. This means these two essential components of the heart share the same microcirculation, suggesting a close and strong interaction between the two structures.[3] Massive increases of epicardial fat could fill up the space between the visceral pericardium and myocardium surface and even cover the whole epicardium surface. Small amounts of epicardial fat can also grow inside myocardium and usually accompany the intramyocardial branch of coronary artery.[4]

Physiological Functions of Epicardial Fat

The functional complexity of human epicardial fat is not fully elucidated. However, the role of epicardial fat within the heart can be generally distinguished by mechanical, metabolic, thermogenic, and endocrine/paracrine functions.

Mechanical Functions

Since epicardial fat commonly accompanies the main branches of coronary artery and is located in the atrioventricular or interventricular groove as a cushion, it has the compressibility and elasticity that can mechanically protect the coronary artery against excessive distortion caused by artery pulse and myocardial contraction.[5]

Metabolic Functions

Epicardial fat has a higher rate of free fatty acid (FFA) release and uptake compared to subcutaneous and other visceral fat depots.[6] It is well known that energy production in the heart is highly dependent on FFA oxidation. Epicardial fat is rich in saturated fatty acids, and this enrichment and increased metabolism of FFAs in epicardial fat sustains myocardium energy supplies, especially during periods of high demand. FFAs in epicardial fat might diffuse through the interstitial fluid into the myocardium. They also flow into the coronary artery bloodstream and are delivered to myocardium. Although epicardial fat was thought to be an energy supplier for myocardium, the exact degree of its contribution is unknown.

Thermogenic Functions

Brown adipose tissue contains mitochondria with large amounts of uncoupling protein-1 (UCP1) to generate heat in response to cold exposure. Sacks et al.[7] found that expressions of UCP1 and its related genes are higher in epicardial fat than fat depots in other parts of the body, such as the abdomen, thighs, and subcutaneous tissue. These results suggested that epicardial fat could function similarly to brown adipose tissue, producing heat to protect the myocardium and coronary artery from hypothermia damage.

Protective Secreting Factors

Growing evidence demonstrates that human epicardial fat can produce multiple bioactive cytokines. The secretomes are so multitudinous that they make epicardial fat uniquely different from other fat depots. These cytokines are involved in the regulation of endothelial function, coagulation, and inflammation. In fact, a number of bioactive molecules secreted from epicardial fat can ei-

	Epicardial Fat	Pericardial Fat
Origin	Splanchnopleuric mesoderm	Primitive thoracic mesenchyme
Location	Situated between myocardium and visceral layer of pericardium, commonly found in atrioventricular and interventricular grooves, or directly within myocardium	Situated on the external surface of parietal pericardium
Relation to Myocardium	No fascia, contiguity with adventitia and myocardium	No compact relation to myocardium
Blood Supply	Branch of coronary artery	Mostly branch of mammary artery
Adipocytes	Generally smaller, more preadipocytes, high energy consuming metabolism	Mature adipocytes

Table 1. Differences between epicardial and pericardial fat.

ther protect or adversely affect the myocardium and coronary arteries (Table 2).[1] Under normal physiological conditions, epicardial adipose produces anti-inflammation or antiatherosclerotic cytokines, such as adiponectin and adrenomedullin, to exert its cardioprotective functions.[8,9] Adiponectin is a secreting factor produced only by adipocytes and has been described as having antidiabetic, antiatherogenic, antioxidative, and anti-inflammatory properties.[8] Adiponectin activates the adenosine monophosphate-activated protein kinase (AMPK) pathway, leading to increased fatty acid oxidation and reduced lipid deposits in cardiac muscle.[9] In addition, adiponectin inhibits production of inflammatory factors and maintains an anti-inflammatory microenvironment in the cardiovascular system.[10] Unlike adiponectin, adrenomedullin is produced in a variety of organs including the kidneys, lungs, and heart, and it exerts many cardioprotective actions including vasodilation, natriuresis, antiapoptosis, and stimulation of nitric oxide production.[11] In disease conditions, epicardial fat can be harmful, producing inflammatory factors that are discussed later in this review.

Clinical Implication of Epicardial Fat

Epicardial Fat Measurement

Detection and quantification of epicardial fat require a variety of useful imaging techniques, including 2-dimensional (2D) echocardiography, magnetic resonance imaging (MRI), and noncontrast computed tomography (CT).[12,13] Though the epicardial fat volume is superior to thickness as a clinical index, it is technically more difficult to measure. The thickness of epicardial fat tissue can be visualized and calculated with standard 2D echocardiographic methods that are noninvasive and reliable. Epicardial fat is generally identified as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium, and its thickness is measured between the epicardial surface and the parietal pericardium in at least two locations on the right ventricular free wall. There is some controversy over which stage in the cardiac cycle is most suitable for echocardiographic measurement. Some recommend that measurement be taken during systole to prevent possible deformation by epicardial fat compression during diastole, while others suggest measurement in diastole to coincide with other imaging modalities (CT and MRI).[12,14,15]

Since fat tissue generates a strong MRI signal, both thickness and volume of epicardial fat can be easily measured with this modality. At the end of diastole, the epicardial fat is contoured in each short axis; therefore, it is in this stage that the thickness and total volume of epicardial fat can be measured and calculated manually using the modified Simpson method.[15,16]

Noncontrast CT provides a more sensitive and accurate measurement of epicardial fat thickness and volume, but it is more expensive and cumbersome.[12,14] Epicardial fat measurements are taken in the right ventricular free wall and around the main coronary arteries, and the acquired images are reconstructed in 3D slices with 2-mm to 3-mm thickness.[15,17,18] These higher-resolution images provide more detail but need more technical care and require longer radiation exposure for the patient. Several studies used the semiautomated technique for measuring the volume of epicardial fat, and software has been developed more recently to automate this process.[17-20]

Factor	Regulation in CAD	Major Functions
Adiponectin	Down-regulated	Increasing FFA oxidation; anti-inflammation
Adrenomedullin	Down-regulated	Vasodilation; stimulation of NO synthesis; inhibition of heart hypertrophy and fibrosis
Leptin	Up-regulated	Activation of multiple immunocytes
Resistin	Up-regulated	Insulin resistance; thrombosis
TNF-α	Up-regulated	Inhibition of adiponectin production; lipolysis induction; NF-κB activation
IL-1	Up-regulated	
IL-6	Up-regulated	
MCP-1	Up-regulated	Recruitment of inflammatory immunocytes
CAD: coronary artery disease; FFA: free fatty acid; NO: nitric oxide; NF-κB: nuclear factor-κB; TNF: tumor necrosis factor; IL: interleukin		

Table 2. Major bioactive secreting factors released from epicardial fat.

Clinical Correlations among Epicardial Fat, Obesity, and Heart Disease

Epicardial fat has a direct relationship with obesity and body mass index.[19] Most studies report an association between increased amounts of epicardial fat and metabolic syndrome, which is characterized by inflammation, hypertension, and disturbances in insulin sensitivity.[16] Epicardial fat thickness and volume have subsequently been associated with multiple independent cardiac risk factors, such as high fasting glucose, high levels of C-reactive protein, low HDL, carotid intima-media thickness, and others.[21] However, when adjusted for visceral adipose tissue, many of these associations are diminished or absent; even so, epicardial fat thickness and volume are still directly associated with coronary artery disease and some cancers.[15] The magnitude of the association is quite variable, even nonexistent in some studies, which could be attributed to differences in coronary artery disease severity among individuals and to the research methods used.[22]

Studies have found epicardial fat to be 22% thicker in patients ages 65 years and older, implying that it increases with age.[20] There is no consensus in the literature on the impact of gender on epicardial fat. Some literature has suggested that epicardial fat is more associated with risk factors in women than in men.[23] While data is lacking with regard to epicardial fat volume and ethnicity, there is speculation of an association; for example, African American men have less central obesity than Caucasian men and have been shown to have less epicardial fat, although they are more insulin resistant.[18,24]

Epicardial Fat in the Pathogenesis of Heart Diseases

The mechanism by which epicardial fat can influence heart function and structure continues to be an active research topic. Increased epicardial fat leads to additional mass on both ventricles that can increase the work demands on the heart and result in left ventricular hypertrophy.[25] Moreover, epicardial fat thickness is positively correlated with myocardial lipid content and may affect cardiomyocyte function.[26] In addition to these mechanical and metabolic mechanisms, fat tissue-derived secreting factors were recently identified as major players linking abnormal epicardial fat to heart dysfunction. Like other visceral adipose tissue, epicardial fat serves as an endocrine and paracrine organ and plays an important role in regulating myocardial function. In this section, we will focus on the inflammatory processes and factors in epicardial fat and their roles in CAD.

The first evidence indicating the inflammatory state of human epicardial fat was provided in 2003 by Mazurek et al.[27] Since then, many studies have shown elevated inflammation with epicardial fat in terms of leukocyte infiltration and inflammatory gene expression. Macrophages are one of the major effector cells mediating adipose inflammation. Hirata et al. found that patients with advanced CAD have more inflammatory M1 (classically activated) macrophages but fewer anti-inflammatory M2 (alternatively activated) macrophages in epicardial fat compared to subjects without CAD.[28] The transition of macrophages from an anti-inflammatory M2 state to an activated M1 state suggests a macrophage-mediated inflammation in epicardial fat.

In addition to macrophages, other immunocytes, including T lymphocytes and mast cells, have been identified in epicardial fat and may be associated with inflammatory states in patients with CAD.[27] These infiltrated leukocytes respond to innate inflammatory signals through Toll-like receptors (TLRs) and produce inflammatory factors. TLRs recognize endogenous ligands such as lipopolysaccharide and saturated fatty acids, leading to translocation of nuclear factor-κB into the nucleus and activation of c-Jun N-terminal kinase with subsequent transcription of inflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor alpha, and monocyte chemoattractant protein-1.[29] In obese patients with critical CAD, expression and secretion of these factors are upregulated in epicardial fat and are associated with infiltration of leukocytes.[27,30,31]

Under obese conditions, adipocytes also produce inflammatory adipokines and can be viewed as integral components of the immune system.[32] For example, obesity induces overexpression of major histocompatibility complex class II molecules in adipocytes and makes them act as antigen-presenting cells to instigate T-cell activation in adipose tissue.[33] Adipocytes possess machinery including TLRs to produce inflammatory cytokines. They also release inflammatory adipokines, such as resistin and leptin, to promote epicardial adipose inflammation in patients with CAD.[34] Parallel to the inflammatory state of epicardial fat, secretion of anti-inflammatory adipokines from epicardial fat is decreased in patients with CAD,[35] further suggesting increased epicardial adipose inflammation in CAD development. Thus, the inflammatory process within epicardial fat results in paracrine or vasocrine secretion of epicardial inflammatory cytokines, in turn creating the metabolic and inflammatory milieu that promotes CAD.

In addition to inflammation, oxidative stress also plays a significant role in the development and progression of CAD. Epicardial fat in subjects with CAD shows higher mRNA expression of genes involved in oxidative stress and higher levels of reactive oxygen species (ROS) products than subcutaneous fat,[36] suggesting a higher oxidative stress in epicardial fat. Since ROS induces chronic inflammation, the higher oxidative stress could activate inflammatory signals in epicardial fat and contribute to the development and progression of CAD.

Conclusions: Therapeutic Implications and Future Directions

Epicardial fat is a special visceral fat depot with unique anatomical and functional features. It is a primary source of biomolecules that act as a local gland to regulate the heart through paracrine or vasocrine mechanisms. The thickness and volume of epicardial fat can be measured by using echocardiography, CT, or MRI. It is well established that epicardial fat volume and thickness is significantly associated with the degree and severity of metabolic syndrome and CAD. This association and the simplicity of imaging techniques have enabled the use of epicardial fat measurements as a predictive biomarker of cardiometabolic diseases.

The pharmaceutical value of epicardial fat in cardiovascular diseases is still unclear. Despite strong clinical correlations, there is still no direct evidence that inflammatory epicardial fat exacerbates CAD. Since mice have no epicardial fat, the vast majority of studies on epicardial fat have been performed in humans. These clinical studies are cross-sectional and correlative and have not yet clarified the causative role of epicardial fat in CAD. A larger mammalian animal model of epicardial fat must be developed to investigate whether and how increased epicardial adipose fat promotes CAD. Studies focusing on the detailed mechanisms associated with epicardial fat and its causative role will also provide direct evidence to support the idea that epicardial fat is a valuable cardiovascular therapeutic target.

Many factors, including weight loss and pharmaceutical treatments, can decrease the thickness of epicardial fat. Weight loss by caloric restriction,[37] exercise,[38] or bariatric surgery[39] in obese

patients leads to significant reductions (9%-32%) in epicardial fat thickness. Pharmaceutical treatments associated with thinner epicardial fat target either lipid metabolism or glucose homeostasis. In a 2-year study of 145 patients with coronary artery stenosis, statins were shown to improve lipid profiles and also significantly decrease epicardial fat thickness.[40] Another study performed in type 2 diabetes patients showed that insulin replacement therapy resulted in a reduction of epicardial fat thickness.[41] It is still unknown whether the decrease of epicardial fat volume following weight loss or pharmaceutical treatment is associated with changes in the inflammatory state of epicardial fat. Future studies that determine the effect of these interventions on epicardial fat-related inflammatory cells and molecules are warranted.

Key Points:

1. Epicardial fat has multiple functions to support a healthy heart.
2. An increased amount of epicardial fat is associated with both obesity and coronary artery disease.
3. Inflammatory epicardial fat promotes the development of coronary artery disease.

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Keywords: epicardial fat, adipokine, inflammation, myocardium, coronary artery disease

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