

## Editorial

## Epicardial Fat, Metabolic Dysregulation, and Cardiovascular Risk: Putting Things Together



## Grasa epicárdica, mala regulación metabólica y riesgo cardiovascular: cómo encajar las piezas

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For several decades, pathologists observed that coronary atherosclerosis is generally limited to subepicardial segments and that intramyocardial coronary segments rarely show atherosclerosis.<sup>1</sup> They also observed that pericardial fat is primarily located along the main coronary branches.<sup>2,3</sup> These 2 observations led investigators to suspect and confirm a relationship between pericardial fat and coronary atherosclerosis.

Obesity or excessive adipose tissue has long been related to cardiovascular disease and mortality. Epidemiologic studies have demonstrated that visceral fat, perhaps more than total fat, is implicated in atherosclerosis by indirect mechanisms—such as metabolic dysregulation—and obesity-related risk factors—such as systemic hypertension and dyslipidemia.<sup>4–6</sup> Studies have also shown direct mechanisms linking obesity and cardiovascular disease, such as an increased free fatty acid circulation and cytokine production.<sup>7–9</sup> More contemporary studies have demonstrated that pericardial fat, a type of ectopic visceral fat located around the heart either as subepicardial adipose tissue (intrapericardial) or outside the pericardium, has a high level of inflammatory markers and is metabolically active.<sup>10,11</sup> Other studies have demonstrated that the pericardial fat of patients with atherosclerosis is more metabolically active than the fat of people without atherosclerotic coronary disease.<sup>12,13</sup> Cross-sectional studies have shown an association between pericardial fat measured with echocardiography, computed tomography, or magnetic resonance and the presence and extent of coronary atherosclerosis,<sup>14–16</sup> as well as an association between pericardial fat and decreased myocardial perfusion using nuclear stress tests.<sup>17</sup> The epicardial fat in ventricles is related to myocardial mass not only in normal hearts, but also in hypertrophic or ischemic hearts.<sup>18</sup> Studies have also shown that atrial septum thickness, which is mainly determined by the amount of subepicardial fat, is associated with coronary disease.<sup>19</sup> Some reports, however, have failed to show an association between pericardial fat and coronary disease. A study published by

Chaowalit et al<sup>20</sup> on 180 consecutive patients who underwent echocardiography and coronary angiography found no significant correlation between subepicardial adipose tissue thickness (measured on the free wall of the right ventricle) and any angiographic variables ( $P > .05$ ). In that study, neither the proportion of patients with significant coronary artery disease or any coronary artery disease nor the severity score was significantly associated with subepicardial adipose tissue thickness. Additionally, the same study found no significant correlation between epicardial fat and dyslipidemia, diabetes mellitus, smoking, or obesity, but epicardial fat was correlated with age. To strengthen the hypothesis linking pericardial fat and coronary disease, prospective studies have demonstrated an association between pericardial fat and cardiovascular events, supporting the notion that pericardial fat is implicated in the genesis and progression of atherosclerotic coronary disease.<sup>21</sup>

The association between pericardial fat and coronary disease has been attributed in part to paracrine mechanisms due to the proximity of the pericardial adipose tissue and the coronary arteries.<sup>22</sup> It has also been suggested that pericardial fat could be implicated in the overall metabolic dysregulation associated with visceral fat,<sup>14</sup> although this hypothesis is questionable because the volume of pericardial fat is very small compared with the volume of other deposits of visceral fat. Therefore, the association between pericardial fat and metabolic dysregulation is most likely explained by the association between pericardial fat and total visceral fat, acting as a confounding effect from the statistical standpoint. This point has been demonstrated in some studies where the association between pericardial fat and metabolic dysregulation and coronary disease is generally lost or significantly attenuated after adjusting for measures of noncardiac visceral fat.<sup>14</sup>

In the article published in *Revista Española de Cardiología*, Fernández-Muñoz et al<sup>23</sup> have tested the hypothesis that pericardial fat is associated with visceral fat, metabolic syndrome, and insulin resistance in postmenopausal women, testing 34 women aged 50 to 65 years who underwent a transthoracic echocardiogram and measurements of pericardial fat. These authors have shown that epicardial fat has a strong correlation with body mass index, waist circumference, and visceral fat, and also with the presence of metabolic syndrome. This study is the first to test this association in postmenopausal women and adds an

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important piece of information to the literature by proving that pericardial fat is strongly correlated with other visceral fat deposits and with clinical measures of insulin resistance in postmenopausal women. Although this study provides additional information to better understand the complex association between obesity, metabolic dysregulation and cardiovascular disease, there are still several questions that will need to be answered in the next few years by similar studies. Those questions relate to the role of pericardial fat in the pathophysiology of cardiovascular disease and the potential role of measuring pericardial fat as a clinical tool.

### **QUESTION 1: DOES PERICARDIAL FAT PLAY A CAUSAL ROLE IN THE GENESIS AND PROGRESSION OF CARDIOVASCULAR DISEASE?**

Most of the evidence testing the association between pericardial fat and cardiovascular disease is cross-sectional, limiting any conclusions about directionality and causality. There is a need for more prospective studies assessing the association between pericardial fat and clinical outcomes. It has been pointed out that pericardial fat could be a hazardous component or may be just a para-phenomenon signaling the presence of other cardiovascular risk factors.<sup>24</sup> Because pericardial fat is strongly correlated with total visceral fat, and especially with abdominal visceral fat, it is not clear whether the association between pericardial fat and metabolic dysregulation is actually independent or is—as previously mentioned—merely a confounding effect. The main problem is that pericardial fat is so strongly correlated with other fat deposits that it is difficult to separate the effect of each fat deposit on metabolic dysregulation.

### **QUESTION 2: WHAT CAUSES THE ACCUMULATION OF PERICARDIAL FAT?**

Several studies have shown only a modest association between general obesity as measured by body mass index and pericardial fat,<sup>25,26</sup> suggesting that pericardial fat deposition may not be fully explained by an imbalance between energy consumption and expenditure, as is the case with general obesity. Because pericardial fat may play a role as a handy source of fatty acids for myocardial consumption, it is possible that pericardial fat accumulation may be driven at least in part by compensatory or protective mechanisms. For example, in type 2 diabetic patients treated with pioglitazone for 24 weeks, there was an increase in pericardial fat volume, compared with the control group treated with metformin, with simultaneous improvement of diastolic function.<sup>27</sup> It has also been proposed that the accumulation of pericardial fat may be a compensatory, protective mechanism for a myocardium that may otherwise be at risk for ischemia. For example, macrophage infiltration into adipose tissue can promote angiogenesis.<sup>28</sup> Studies helping to better understand the etiology of pericardial fat will help us determine whether pericardial fat is a therapeutic target or not.

### **QUESTION 3: WHAT IS THE INCREMENTAL DIAGNOSTIC OR PROGNOSTIC VALUE OF MEASURING PERICARDIAL FAT?**

Determining the incremental diagnostic or prognostic value of a test is complex. To provide added value, a new test should demonstrate that it identifies people at risk who would otherwise not be labeled as such by using standard tests. Mathematical ways to provide added value include testing the increase in the area under the receiver operator characteristics curve or assessing the net reclassification rate. Unfortunately, no clinical study has

specifically focused on testing the incremental diagnostic or prognostic value of measuring pericardial fat to identify people at risk for coronary disease or with cardiovascular events. Given the very strong correlation between pericardial fat and other visceral fat depositions, and also with simple methods to measure adiposity such as waist circumference, it is unlikely that measuring pericardial fat will provide any additional value above and beyond measurement of waist circumference or fat distribution using the waist-to-hip ratio. Clinical studies testing the incremental diagnostic and prognostic value of measuring pericardial fat will answer this question.

Finally, it is important to recognize that a better understanding of the biology, etiology, and associated risk of pericardial fat will help us to better understand the complex association between adiposity and cardiovascular disease. Recent studies have demonstrated a strong correlation between pericardial fat and atrial fibrillation<sup>29</sup> and other studies suggest that pericardial fat is only the tip of the iceberg related to cardiac accumulation of fat. Steatosis of myocardial tissue may have an even more significant role on cardiovascular conditions than pericardial fat, but studies simultaneously measuring cardiac steatosis and pericardial fat in cohort studies are lacking. Myocardial triglyceride content represents a promising tool to identify and quantify cardiac steatosis.<sup>30</sup> Cardiac steatosis may indeed be a major predictor of heart failure and cardiac arrhythmias, although this is yet to be proven. The nature, roles and causes of epicardial fat accumulation will be better clarified by genetic studies. Preliminary results show a unique locus for ectopic fat, not related to general or visceral fat.<sup>31</sup> Future studies simultaneously assessing different forms of cardiac adiposity will elucidate the independent or synergistic role of fat around or within the myocardium. For now, the undoubted results of multiple studies support the idea that cardiac obesity, or fat accumulation in and around the heart, is a major risk factor for cardiovascular disease.

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### **CONFLICTS OF INTEREST**

None declared.

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