

## Epicardial Fat: Definition, Measurements and Systematic Review of Main Outcomes

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### Abstract

Epicardial fat (EF) is a visceral fat deposit, located between the heart and the pericardium, which shares many of the pathophysiological properties of other visceral fat deposits. It also potentially causes local inflammation and likely has direct effects on coronary atherosclerosis. Echocardiography, computed tomography and magnetic resonance imaging have been used to evaluate EF, but variations between methodologies limit the comparability between these modalities.

We performed a systematic review of the literature finding associations of EF with metabolic syndrome and coronary artery disease. The summarization of these associations is limited by the heterogeneity of the methods used and the populations studied, where most of the subjects were at high cardiovascular disease risk.

EF is also associated with other known factors, such as obesity, diabetes mellitus, age and hypertension, which makes the interpretation of its role as an independent risk marker intricate. Based on these data, we conclude that EF is a visceral fat deposit with potential implications in coronary artery disease. We describe the reference values of EF for the different imaging modalities, even though these have not yet been validated for clinical use. It is still necessary to better define normal reference values and the risk associated with EF to further evaluate its role in cardiovascular and metabolic risk assessment in relation to other criteria currently used.

### Introduction

Epicardial fat (EF) has been proposed as a marker of cardiovascular risk. This review shows the anatomical and pathophysiological characteristics of EF, its measurement methods, its main determinants and clinical associations. We systematically reviewed the literature for articles

### Keywords

Abdominal Fat; Metabolic Syndrome; Echocardiography; Magnetic Resonance Imaging; Computed Tomography.

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describing the associations between EF and the major related outcomes: Metabolic Syndrome (MS) and coronary artery disease (CAD).

### Anatomy and Nomenclature

Fat deposits are often found around the heart. This fat can be separated into different compartments. Epicardial fat is the adipose tissue accumulated between the visceral pericardium and the myocardium, without a structure or fascia separating it from the myocardium and the epicardial vessels. EF has a variable distribution, being more prominent in the atrioventricular and interventricular grooves and right ventricular lateral wall<sup>1</sup>. Adipocyte infiltration into the myocardium wall as well as triglyceride infiltration into myocytes may also occur.

The fat located on the outer surface of the fibrous pericardium differs from EF in their biochemical, molecular and vascular nutrition properties. It is nourished by the pericardiophrenic artery, a branch of the internal thoracic artery<sup>2</sup>, while EF is nourished by the coronary arteries. The structure that delimitates these layers is the pericardium, seen on imaging tests as a thin layer around the heart, between 1.0 and 4.0 mm, of which visualization is sometimes difficult<sup>3</sup>. This extrapericardial fat deposit nomenclature varies according to different authors, being called intrathoracic<sup>4,5</sup>, paracardial<sup>6</sup>, mediastinal<sup>7</sup> or pericardial<sup>8</sup>. Some groups treat these different fat deposits as a single compartment, calling it paracardial or pericardial fat<sup>9</sup>. Due to discrepancies and ambiguities in the definition and nomenclature of fatty deposits among several authors, we used a common name in the reviewed articles, according to Table 1.

### Pathophysiology

Small fat deposits are naturally found outside the subcutaneous adipose tissue, including epicardial fat. EF has the same embryological origin of omental and mesenteric adipose tissues and produces cytokines with a standard comparable to abdominal visceral adipose tissue<sup>2,10</sup>.

Among the several physiological roles of EF are: local distribution and regulation of vascular flow by vasocrine mechanisms<sup>11</sup>; immune barrier, protecting the myocardium and coronary arteries from inflammatory and pathogenic substances<sup>12</sup>; mechanical protection of the coronary arteries, providing space for the arterial wall expansion in the early stages of atherosclerosis; local source of fatty acids for the myocardium during of high-demand moments<sup>13</sup>, and thermogenic effects related to brown adipose tissue<sup>14</sup>.

**Table 1 - Nomenclature of body fat deposits**

Epicardial fat	Visceral intrapericardial fat contiguous with the myocardial surface (delimited between the epicardium and the visceral pericardium)
Paracardial fat	Fat deposits in the mediastinum outside the parietal pericardium, also called intrathoracic fat
Pericardial fat	The sum of epicardial and paracardial fat deposits
Perivascular fat	Adipose tissue with different characteristics around vessels, with potential vascular paracrine activity without anatomic delineation
Ectopic fat	Triglyceride deposits of non-adipose tissue cells, such as myocytes and hepatocytes
Visceral fat	Adipose tissue around the viscera and organs

EF increases in states of positive energy balance, when the free fatty acids in the blood are converted into triglycerides and accumulated initially in adipocytes and then in nonfat cells<sup>15</sup>. Magnetic resonance and spectroscopy have demonstrated the strong correlation ( $r = 0.79$ ,  $p < 0.01$ ) between EF volume and triglyceride concentration in the myocardium<sup>16</sup>. Not only the accumulation of triglycerides, but also disorders of glucose-insulin metabolism and low-grade chronic inflammation, with production of pro- and anti-inflammatory cytokines by adipocytes<sup>10</sup> are associated with metabolic syndrome<sup>17,18</sup> and are phenomena also identified in EF<sup>19</sup>.

Adipokines are cytokines mainly produced by adipose tissue that have a role in the regulation of other cytokines and in the metabolism of glucose-insulin and lipids. Leptin and resistin are associated with increased cardiovascular risk<sup>10,20</sup> and show greater concentration in EF<sup>21</sup>.

Adiponectin is an anti-inflammatory cytokine that increases insulin sensitivity, decreasing circulating free fatty acids and intracellular triglyceride content in the liver and muscle. Adiponectin levels are lower in obese individuals<sup>10</sup> and in those with increased cardiovascular risk<sup>22-24</sup> and are inversely associated with deposits of abdominal visceral, epicardial and intrathoracic fat<sup>25</sup>.

In addition to these systemic effects shared with other fat deposits, it is possible that EF has paracrine effects. Due to the anatomical proximity with the coronary arteries and heart, cytokines and fatty acids are disseminated locally through microcirculation and vasa vasorum. The perivascular cytokine concentration is higher than that in subcutaneous fat<sup>26</sup> and can locally accelerate the atherosclerotic process by endothelial dysfunction, local proliferation of smooth muscle cells<sup>27</sup>, increased oxidative stress (leptin) plaque instability via apoptosis (TNF- $\alpha$ ) and neovascularization (MCP-1)<sup>28</sup>. A recent study investigating coronary arteries through optical coherence tomography found an association between the amount of pericoronary fat and markers of plaque instability<sup>29</sup>.

## Measurement and Imaging Methods

Echocardiographic allows adequate assessment of pericardial space in most clinical situations and it has been used to measure EF, mainly by Iacobellis et al<sup>30</sup>, since 2003. Computed tomography (CT) and magnetic resonance imaging (MRI) have been traditionally used as adjuvants to echocardiography, but their role is increasing due to high spatial resolution and the possibility of volumetric assessment.

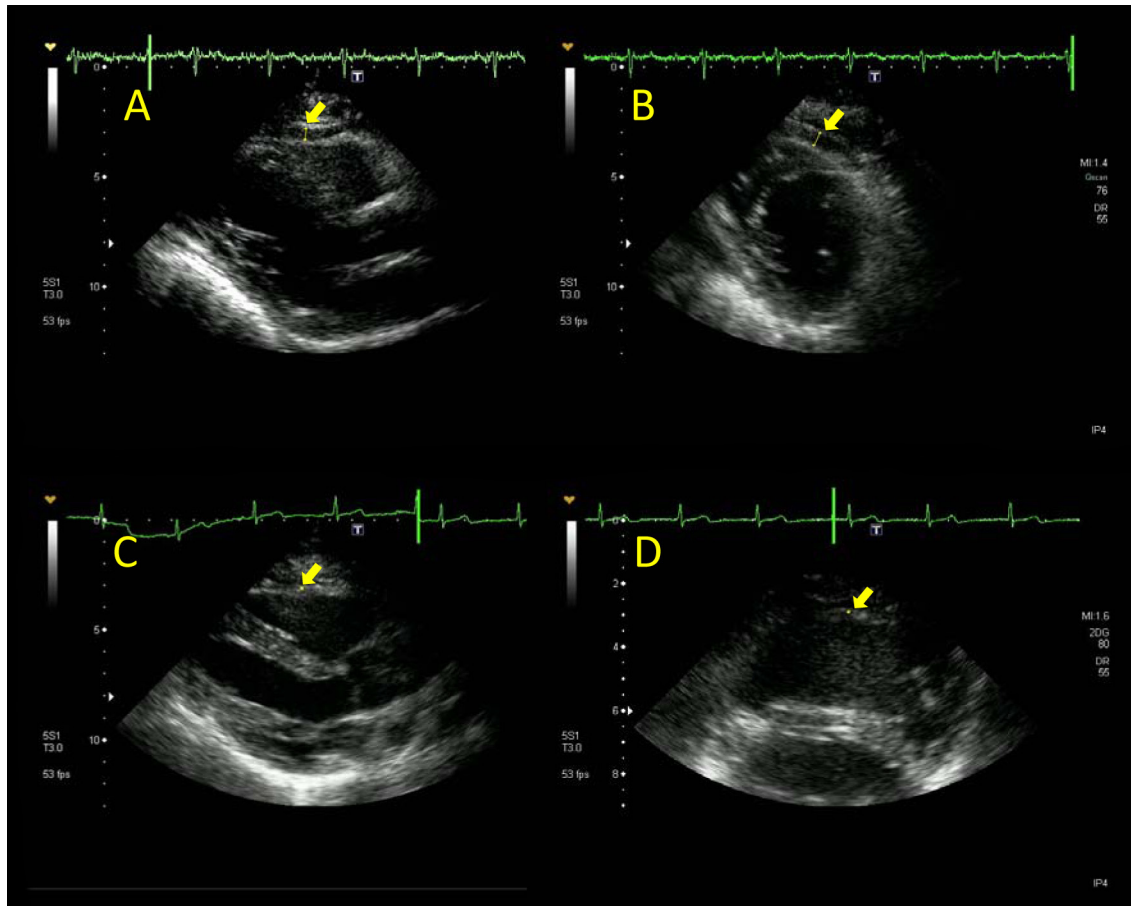
## Two-Dimensional echocardiography

There is no consensus regarding its use in clinical practice, but some recommendations are suggested for EF measurement by echocardiography<sup>1</sup>. Epicardial fat thickness should be measured on the right ventricular free wall in at least two locations, from both parasternal longitudinal and transverse parasternal views (Figure 1), using the mean of three consecutive beats. These measurements show good correlation with the values found on MRI ( $r = 0.91$ ,  $p = 0.001$ )<sup>31</sup>. EF is identified as a hypochoic space anteriorly to the right ventricular wall and its thickness is measured between the epicardial surface and the parietal pericardium, identified by the sliding between these two layers. Epicardial fat should not be confused with pericardial fluid. On the other hand, paracardial fat is difficult to delimit by echocardiography. A critical issue in EF measurement is the inconsistency in the measurement location due to spatial variations the echocardiographic window, especially along the great vessels and the right ventricle. Anatomical landmarks should always be used for the measurements, such as the position of the interventricular septum and the aortic annulus<sup>32</sup>.

Another controversial point is which time in the cardiac cycle is the most suitable for measuring EF thickness in echocardiography. Some recommend the measurement during systole to prevent possible deformation by EF compression during diastole<sup>1</sup> and others in diastole, to coincide with other imaging modalities (CT and MRI)<sup>6,33</sup>. The mean values described for EF thickness in systole by Iacobellis et al<sup>34</sup> during the investigation of cardiovascular risk were 6.8 mm (1.1 to 22.6 mm) and 9.5 mm (7.0 to 20.0 mm) for men and 7.5 mm (6.0 -15.0 mm) for women in a sample of obese and overweight patients<sup>35</sup>. When measured in diastole, Jeong et al<sup>36</sup> found a mean value of 6.4 mm (1.1 to 16.6 mm) in more than 200 individuals submitted to coronary angiography and Nelson et al<sup>37</sup> found a mean of  $4.7 \pm 1.5$  mm in 356 asymptomatic patients. Even though some of these studies have suggested higher cutoffs, measurements  $> 5$  mm should represent a relevant cutoff to define increased EF, especially in low-risk populations.

## Magnetic Resonance Imaging

MRI is considered the gold standard for the assessment of total body fat and reference modality for the analysis of ventricular volumes and mass<sup>38,39</sup>, thus making it a natural choice for the detection and quantification of EF<sup>31</sup>.



**Figure 1** – Epicardial fat measurement by echocardiography in the parasternal longitudinal and transverse parasternal views. Epicardial fat (indicated by arrows) with increased thickness (1A and 1B) and minimum epicardial fat (1C and 1D).

EF evaluation by MRI usually includes structural assessment with sequences that allow the characterization of the fat (black blood sequences) and functional sequences (bright blood sequences). Once characterized, EF is manually delimited to calculate the volume or measure its thickness<sup>40,41</sup> (Figure 2).

Epicardial fat the total volume can be estimated using the modified Simpson method, in which the epicardial tissue is contoured in each short axis at the end of diastole. The interobserver reproducibility of EF volume measurement seems to be superior to the EF thickness measurement (coefficient of variability of 5.9% for the volumetric method and 13.6% for EF thickness at the long axis); however, it is technically more difficult. The measurement of maximum EF thickness is more feasible, without significant accuracy decrease. Flutter et al<sup>42</sup> evaluated EF thickness by MRI using the mean of maximum EF thickness at several points of the right ventricular free wall and found mean values comparable to those found by Schejbal et al<sup>43</sup> in 200 autopsies (mean thickness:  $4.12 \pm 1.4$  mm).

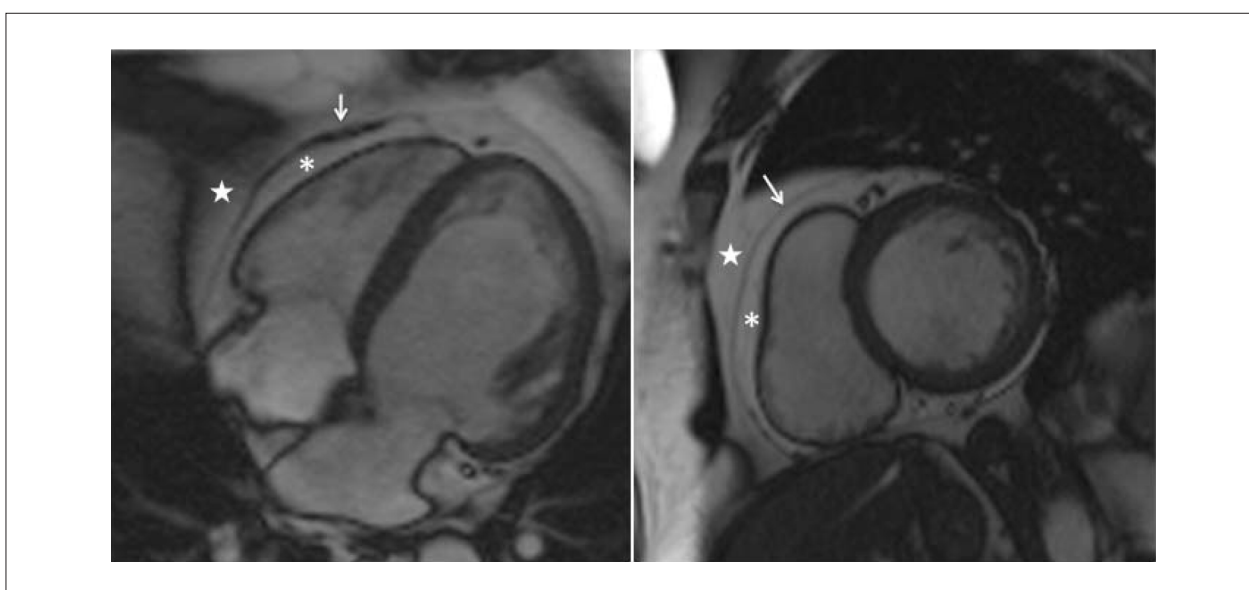
The MRI and EF studies published to date have evaluated small samples of patients, of which population representativeness is questionable to define reference values.

### Computed Tomography

It is possible to measure the EF with CT scanners with 16 or more detectors using acquisitions used for coronary calcium score evaluation coronary angiography<sup>44</sup>. In coronary calcium score examinations, the images are prospectively collected using the electrocardiographic tracing. Radiation exposure occurs at a predetermined phase of the cardiac cycle (65-85% of RR interval). There is no need to use contrast. The acquired images are reconstructed in slices with 2-3 mm thickness<sup>45</sup> (Figure 3).

CT angiography examinations allow the reconstruction of images with greater detail, with slices < 1.0 mm, but which require contrast use and greater technical care in image acquisition to minimize radiation exposure<sup>46</sup>.

Epicardial fat thickness, volume and total area can be accurately measured by CT. It has been demonstrated an independent association between pericardial fat and cardiovascular risk factors, coronary calcification and the presence of CAD. Epicardial and paracardial/intrathoracic fat deposits are individualized outlining the parietal pericardium, however, some of these



**Figure 2** – Characterization of the pericardium (white arrow), epicardial fat (asterisk) and paracardial fat (star) by magnetic resonance. Left frame shows long-axis four-chamber and the right, basal short-axis view at end-diastole (SSFP cine sequence - bright blood).



**Figure 3** – Measurement of epicardial fat volume by computed tomography. In the figure, acquired slices are used for evaluation of coronary calcium score (3-mm thickness). The area of interest is defined by the manual delineation of the pericardium and the volume calculated in a semi-automatic way by specific software.

studies did not differentiate between epicardial and pericardial fat, raising doubts about the relevance of paracardial fat measurement in this context. Even with different properties, the measurement of pericardial fat as a surrogate marker of EF would be operationally simpler and faster by dispensing pericardial delineation, having as rationale the strong correlation between the two measurements (Spearman correlation coefficient = 0.92,  $p < 0.001$ )<sup>9</sup>.

#### Epicardial Fat Thickness by computed tomography

EF thickness can be measured in the right ventricular free wall and around the main coronary arteries<sup>21,47</sup>, the latter limited by the slice thickness, usually higher in tests assessing coronary calcium score. The measurement of pericoronary fat is performed in the axial view, perpendicular to the heart surface at the level of the three main coronary arteries (right, left anterior descending and circumflex arteries). Fat thickness can also be measured



in different regions of the heart surface, such as the right ventricular free wall and the inter- and atrioventricular grooves. The difficulty in standardizing measurement locations limits the determination of EF thickness reference values by CT.

### Epicardial Fat Volume at computed tomography

Similarly to echocardiography, EF thickness assessment by CT seems to be more susceptible to interobserver variability, a fact that seems to be minimized by performing the measurement of EF volume (intraclass correlation coefficient of 0.95)<sup>4,47</sup>. Several studies have been published using the semi-automated technique for measuring the amount of EF<sup>44,47-50</sup>. This technique requires an adequate tool at the workstation to determine the volume of fat. The chest area where EF is visualized must be delimited by the operator, including slices 1 cm above the emergence of the left main coronary artery to the cardiac apex. The pericardium must be outlined manually by the operator at each cross-section, thus determining the area of interest. There may be difficulties to recognize the pericardium in lean individuals<sup>9</sup>. Studies assessing the pericardial fat (epicardial and paracardial) consider the chest wall as the anterior limit and the aorta and bronchi as the posterior limit, without pericardium delineation. At the end, the software recognizes in the delimited area, the content with density between -30 and -200 HU, characteristic of fatty tissue. The sum of the volume of all sections provides the overall EF volume. More recently, proprietary software have been used aiming the automation of the EF measurement<sup>51</sup>.

The mean volume of EF found in population-based studies ranges from  $68 \pm 34$  mL to  $124 \pm 50$  mL<sup>5,52</sup>. In a study including patients from the Framingham cohort, the mean EF volume was  $110 \pm 41$  mL in women and  $137 \pm 53$  mL in men<sup>8</sup>. In 2011, Shmilovich et al<sup>53</sup> published a study that aimed to determine the upper limit of normal EF volume by tomography in a population at low cardiovascular risk. In this cohort of 226 patients, the 95<sup>th</sup> percentile of EF volume indexed to body surface area was 68.1 mL/m<sup>2</sup>.

## Determinants of Epicardial Fat

In addition to methodological factors, there is a broad individual variation in the amount and distribution of EF, attributable to their clinical and demographic characteristics.

### Obesity

The association between obesity and EF has been described<sup>34,49</sup>; moreover, reduction in body weight (mean reduction of  $40 \pm 14$  kg) in patients undergoing bariatric surgery decreased the EF thickness from  $5.3 \pm 2.4$  mm to  $4.0 \pm 1.6$  mm ( $p < 0.001$ )<sup>54</sup>.

### Age

Epicardial fat seems to increase with age<sup>4,50,55</sup>, being 22% thicker in individuals older than 65 years<sup>44</sup>. During the aging process, there is a decrease in lean body mass and increase in fat mass, with fat tissue redistribution to the trunk and viscera<sup>56</sup>.

These changes seem to occur at a different rate and intensity between men and women, with a greater redistribution seen in older women<sup>57</sup>.

### Gender

There is no consensus in the literature on the impact of gender on the amount of epicardial fat. Based on the data from the Framingham cohort, Rosito et al<sup>6</sup> suggest that EF is more associated with risk factors in women than in men; however, two other studies of the same cohort did not find this association<sup>5,53</sup>. Taking this into consideration, it is not possible to attribute these differences to the gender or to other concomitant characteristics.

### Ethnicity (genetics)

Ethnicity may also contribute to the amount of EF. In general, individuals with black skin color have less central obesity than whites, although they are more insulin-resistant<sup>58</sup>, suggesting that in those with black skin color, the adiposity has a more diabetogenic than atherogenic nature, by mechanisms not yet clearly understood<sup>59</sup>.

There are little data on ethnicity and EF, but these are consistent with those found for visceral fat, where it is lower in individuals with black skin color<sup>60</sup>.

## Clinical Associations

Associations between EF and several outcomes have been reported, particularly with metabolic syndrome and coronary artery disease. To investigate these associations, we performed a systematic review of the literature (details in Appendix). The results shown in the following text and in Tables 2 (MS) and 3 (CAD) expose the diversity of methods used and the populations studied, which prevented the summarization of the results in the form of meta-analysis.

### Metabolic Syndrome and Diabetes Mellitus

Most studies<sup>8,21,31,34,61-64</sup> described a higher amount of EF in individuals with metabolic syndrome (MS), across different clinical characteristics and prevalences of MS (Table 2).

Inflammation<sup>21,22,24,28</sup>, derangements in insulin sensitivity<sup>31,65</sup> and arterial hypertension<sup>50,63,66</sup>, which characterize MS, have been associated with EF. In general, there is a moderate association between EF and MS, but most of these effects can be explained by obesity.

Epicardial fat is also moderately associated with glycemic levels<sup>67</sup> and with the prevalence of DM<sup>68</sup>.

### Coronary Artery Disease

Overall, observational studies in patients undergoing coronary angiography identified a direct association between the amount of EF and the presence/severity of coronary artery disease (CAD). The magnitude of the association is quite variable, being even non-existent in some studies<sup>37,69</sup>, a which could be attributed to differences in CAD severity among individuals and to the research methods used.

Table 2 – Associations between Epicardial Fat (EF) and Metabolic Syndrome

	Author	Patient source	Characteristics	N	MS Prevalence	EF measurement	Mean values of EF	Association or Mean
EF THICKNESS AT ECHOCARDIOGRAPHY	Iacobellis et al. <sup>31</sup> , 2003	Referred to echocardiography	BMI between 22 and 47 kg/m <sup>2</sup>	72	Not informed	EF in systole	M: 7.6 ± 3.6 mm F: 6.9 ± 3.7 mm	Men with MS: 9.9 ± 2.6 mm Without MS: 4.1 ± 1.7 mm Women with MS: 7.6 ± 3.0 mm Without MS: 3.1 ± 1.9 mm (p < 0.01)
	Ahn et al. <sup>61</sup> , 2008	Referred to Cath	Suspected CAD	527	23%	EF Median in diastole (CO = 3.0 mm)	3,2 ± 2,5 mm	With MS: 3.5 mm Without MS: 1.6 mm r = 0.32; (p < 0.001)
	Okuy et al. <sup>62</sup> , 2008	Referred to echocardiography	Patients with MS and controls	246	Case:control 1:1	EF in diastole	Not informed	With MS: 5.1 ± 1.7 mm Without MS: 3.4 ± 1.6 mm (p < 0.001)
	Iacobellis et al. <sup>34</sup> , 2008	Referred to echocardiography	Mean BMI = 32 kg/m <sup>2</sup>	246	58%	Median EF in systole	M: 7.0 mm F: 6.5 mm	With MS M: 9.5 mm F: 7.5 mm ROC Area = 0.79
	Lai et al. <sup>75</sup> , 2011	Referred for coronary artery disease screening	Asymptomatic	359	23%	EF thickness (CO = 8.0 mm)	7,6 ± 1,4 mm	OR = 3.65 (95%CI: 2.62-5.09)* ROC Area = 0.80
	Momesso et al. <sup>76</sup> , 2011	Outpatients with Type 1 DM	Women with Type 1 DM (mean age 37 years)	45	45%	EF in diastole	Not informed	With MS: 6.1 ± 0.4 mm Without MS: 4.9 ± 0.3 mm (p = 0.006)
	Pierdomenico et al. <sup>77</sup> , 2011	Referred to echocardiography	Hypertensive Caucasians	174	12%	EF in diastole	Not informed	With MS 4.0 ± 0.8 mm Without MS 2.5 ± 0.9 mm (p < 0.01)*
EF THICKNESS AT CT	Wang et al. <sup>21</sup> , 2009 <sup>21</sup>	Referred to CT and Cath	Stable angina	148	Not informed	EF thickness at left AV groove. > 12.4mm	Left AV groove = 12.7 ± 3,2 mm RV = 4.3 ± 1.8 mm	ROC area = 0.80 (p = 0.004)*
	Yorgun et al. <sup>64</sup> , 2011	Referred to CT	Suspected CAD	83	48%	EF thickness	Not informed	With MS 8.5 ± 1.4 mm Without MS 7.4 ± 2.1 mm (p < 0.001)*
VOLUME DE EF AT CT	Rosito et al. <sup>8</sup> , 2008	Population-based sample	Participants of Framingham Offspring Study free of CVD	1.155	~30%	Increase of 1 SD in EF volume	M: 137 ± 53 mL F: 110 ± 41 mL	Men: OR = 1.85 (1.49 - 2.29)* Women: OR = 2.13 (1.74 - 2.61)*
	Gorter et al. <sup>49</sup> , 2008	Referred to Cath	Unstable angina or stable angina	60	37%	EF Volume	Not informed	0.70 SD (95%CI: 0.18 - 1.23)
	Dey et al. <sup>45</sup> , 2010	Referred to CT	Coronary risk factors but without known CAD	201	30%	EF Volume	87,3 ± 43,7 mL	With MS: 111 mL Without MS: 77 mL (p < 0.001) OR = 6.1; p < 0.01

AV – atrioventricular; Cath: cardiac catheterization; CAD: coronary artery disease; CVD: cardiovascular disease; SD: standard deviation; HR: hazard ratio; OR: odds ratio; 95% CI – 95% confidence interval; BMI: body mass index; CO: cutoff; ROC: Receiver Operating Characteristic; CT: computed tomography; RV: right ventricle; M: male; F: female; \* Risk assessment is adjusted for age, sex and body weight (body mass index, and waist circumference) and other confounding variables.

Two studies found a moderate association between EF and clinical outcomes. Cheng et al<sup>70</sup>, in a case-control study of incident cases during a four-year follow-up, compared 58 patients with major adverse cardiac events with 174 controls free of events, matched by sex and a propensity risk score that included age, risk factors and coronary calcium score. The researchers found a higher risk of events (OR = 1.74, 95% confidence interval [95% CI]: 1.03-2.95) with a two-fold increase in EF volume. Ding et al<sup>9</sup> performed a case-cohort study in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, investigating a random sample of 998 participants and the 147 individuals who developed coronary events. EF was associated with CAD (relative risk for increase of one standard deviation in EF = 1.26, 95% CI: 1.01-1.59) even after adjustment for cardiovascular risk factors.

Coronary artery calcification (CAC) has been used as a marker of subclinical atherosclerosis in representative population samples. Associations between EF and CAC were found both in the Framingham<sup>8</sup> and in the MESA studies<sup>52</sup>.

#### Other associations

It is speculated that the increase in EF and fatty infiltration in the myocardium may cause other deleterious effects, such as interfering with diastolic relaxation, affecting the cardiac conduction system and predisposing to AF<sup>71,72</sup>. EF is inversely associated with ejection fraction and left ventricular mass<sup>33,73</sup>. Additionally, EF may be a manifestation of lipodystrophy associated with subclinical atherosclerosis

in patients with HIV, particularly after the introduction of highly active antiretroviral therapy<sup>74</sup>.

## Conclusions

The epicardial fat is a visceral fat deposit that partially shares its systemic metabolic and inflammatory effects. In addition, there is a rationale for the local atherosclerotic effect of EF on the coronary artery walls. EF is consistently associated with metabolic syndrome and coronary artery disease, although the magnitude of these associations is probably lower than previously expected. Inconsistencies in the nomenclature and measurement methods are limitations to its implementation. According to current knowledge, EF thicknesses > 5 mm, or a volume > 125 mL or 68 mL/m<sup>2</sup> might be considered abnormal.

Despite the availability of different methods to assess EF, there is no rationale for the primary indication of examinations for its measurement. However, the identification of abundant amounts of EF in patients clinically referred for cardiac imaging may raise concerns about cardiometabolic conditions of the patient.

## Appendix

### Systematic Review Methodology

Search strategy: Two reviewers searched independently in PubMed database, additional references were identified

**Table 3 – Associations between Epicardial Fat (EF) and Coronary Artery Disease (CAD)**

	Author	Patients source	Characteristics	n	Exposure (CO – when reported)	Outcome (CO – when reported)	Association and/or Distribution
EF THICKNESS IN ECHOCARDIOGRAPHY	Chaowalit et al. <sup>69</sup> , 2006	Referred to echocardiography and Cath	Not informed	139	CO 1 - EF: 0-1mm CO 2 - EF > 1mm	CAD (stenosis ≥50%)	EF Medians: 0-1mm:1.5 > 1mm:1
	Jeong et al. <sup>36</sup> , 2007	Referred to Cath	Patients with diagnosis of AMI or angina	203	EF ≥ 7.6mm in diastole	CAD (stenosis ≥ 50%)	OR: 10.53 (95%CI: 2.2 – 51.2)*
	Ahn et al. <sup>61</sup> , 2008	Referred to Cath	Suspected angina	527	EF ≥ 3mm in diastole	CAD (stenosis ≥50%)	OR: 3.36 (95%CI: 2.2 – 5.2)
	Eroglu et al. <sup>63</sup> , 2009	Referred to Cath	Suspected angina	150	EF thickness ≥ 5.3 mm in diastole	CAD (stenosis ≥20%)	OR: 4.57 (95%CI: 2.7 – 7.8)*
	Yun et al. <sup>7</sup> , 2009	Referred to Cath	Chest pain assessment	153	EF thickness ≥ 2.6 mm in diastole	CAD (stenosis ≥50%)	OR: 11.53 (95%CI: 3.61 - 36.8)*
	Nelson et al., 2011 <sup>37</sup>	Referred to cardiovascular risk assessment	Low pretest probability of CAD	356	EF thickness ≥ 5 mm in diastole	Coronary calcium score	r: 0.01 (p = 0.873)
	Mustelier et al. <sup>76</sup> , 2011	Referred to Cath	Suspected angina	250	EF thickness ≥ 5.2 mm in systole	CAD (stenosis ≥50%)	OR: 1.27 (95%CI: 1.1 - 1.5)*
	Shemirani and Khoshav, 2012 <sup>79</sup>	Referred to Cath	Unstable angina or stable angina	315	EF thickness	Presence of CAD vs. Absence of CAD	5.4 ± 1.9 mm vs. 4.4 ± 1.8 mm* (p = 0.001)

## Continuation

EF VOLUME AT CT	Djaberi et al. <sup>48</sup> , 2008	Referred to CT	Suspected angina	190	EF Volume > 75mL	Presence of coronary plaque	OR: 1.03 (95%CI: 1.01-1.05)*
	Ueno et al. <sup>80</sup> , 2009	Referred to CT and Cath	Suspected angina	71	EF Volume indexed for TBS $\geq 50\text{cm}^3/\text{m}^2$	Chronic coronary occlusion	OR: 4.64 (95%CI: 1.21 - 17.72)*
	Alexopoulos et al. <sup>50</sup> , 2010	Referred to CT	Suspected angina	214	EF Volume > 71cm <sup>3</sup>	Presence of coronary plaque	OR: 3.9 (95%CI: 1.1 - 13.8)*
	Sarin et al. <sup>81</sup> , 2008	Referred to CT	Low pretest probability of CAD	151	EF Volume $\geq 100\text{mL}$	Coronary calcium score	CCS EF $\geq 100\text{mL}$ : 216 $\pm$ 39 EF < 100mL: 67 $\pm$ 155 (p = 0.03)
	Rosito et al. <sup>8</sup> , 2008	Population-based sample	Participants of Framingham Offspring Study free of CVD	1155	Increase of 1 SD in EF volume	Coronary calcium score	OR: 1.21 (95%CI: 1.005 - 1.46)*
	Ding et al. <sup>52</sup> , 2008	Population-based sample	Participants of MESA study	398	Increase of 1 SD in EF volume	Calcified coronary plaque by CT	OR: 1.38 (95%CI: 1.04 - 1.84)*
	Ding et al. <sup>9</sup> , 2009	Population-based sample	Participants of MESA study	998	Increase of 1 SD in EF volume	Incident CAD	HR: 1.26 (95%CI: 1.01 - 1.6)*
	Mahabadi et al. <sup>5</sup> , 2009	Population-based sample	Participants of Framingham Offspring Study free of CVD	1267	Increase of 1 SD in EF volume	Presence of CAD	OR: 1.92 (95%CI: 1.23 - 3.02)*
	Cheng et al. <sup>70</sup> , 2010	Referred to CT	Low pretest probability of CAD	232	EF Volume > 125cm <sup>3</sup>	Major adverse cardiac event in 4 years	OR: 1.74 (95%CI: 1.03 - 2.95)*
	Wang et al. <sup>82</sup> , 2010	Referred to CT and Cath	Stable angina	224	EF Volume	CAD (stenosis $\geq 50\%$ )	EF Volume: 113 $\pm$ 42 mL vs. 102 $\pm$ 36 ml (p = 0.04)
	Iwasaki et al. <sup>83</sup> , 2011	Referred to CT	Suspected angina	197	EF Volume $\geq 100\text{ mL}$ vs. < 100 mL	CAD (stenosis $\geq 50\%$ )	40.2% vs. 22.7%; (p = 0.008)
	Oka et al. <sup>84</sup> , 2011	Referred to CT	Suspected CAD	357	EF Volume $\geq 100\text{ mL}$	Presence of low-density plaque and positive remodeling at CT (components of vulnerable plaque)	OR: 2.56 (95%CI: 1.38 - 4.85)* (p = 0.003)
	Bettencourt et al. <sup>68</sup> , 2011	Referred to CT	No previous diagnosis of CAD	215	EF Volume	Coronary calcium score	Increase of 3.7% of CCS/10mL of EF*
	Harada et al. <sup>85</sup> , 2011	Acute coronary syndrome	ACSWSTE and ACSSTE	170	EF Volume > 100mL	Presence of acute coronary syndrome	OR: 2.8 (95%CI: 1.2 - 6.9)*
	Shmilovich et al. <sup>53</sup> , 2011	Patients referred to CCS	Patients with (cases) and without (controls) major adverse cardiac events	232	EF volume indexed for total body surface > 68.1cm <sup>3</sup> /m <sup>2</sup>	Major adverse cardiac event in 4 years	OR: 2.8 (95%CI: 1.3 - 6.4)*
	Yerramasu et al. <sup>86</sup> , 2012	Risk Stratification for CAD	Type II diabetic patients	333	EF Volume	Coronary calcium score (presence vs. absence)	85.8 vs. 69.3 cm <sup>3</sup> (p < 0.001) OR: 1.13 (95%CI: 1.04 - 1.22))
Nakazato et al. <sup>87</sup> , 2012	Risk stratification for CAD	Suspected CAD	92	EF Volume indexed for total body surface > 68.1cm <sup>3</sup> /m <sup>2</sup>	Presence of ischemia at PET CT and stenosis $\geq 50\%$ at coronary angiography	OR: 6.18 (95%CI: 1.73 - 22.01*)	
Schlett et al. <sup>88</sup> , 2012	Referred to CT	Patients treated at ER with chest pain	358	EF Volume	Presence of high-risk coronary plaque vs. Absence of coronary plaque	151.9 (109 - 179) cm <sup>3</sup> vs. 74.8 (58 - 112) cm <sup>3</sup> * (p < 0.0001)	

Cath: cardiac catheterization; CAD: coronary artery disease; CVD: cardiovascular disease; SD: standard deviation; CCS: coronary calcium score; HR: hazard ratio; AMI: acute myocardial infarction; 95% CI: 95% confidence interval; MESA: Multi-Ethnic Study of Atherosclerosis; OR: odds ratio; CO: cutoff; r: correlation (Pearson or Spearman); CT: computed tomography; \* Measurements of risk assessment are adjusted for age, sex, body weight measurements (body mass index, waist circumference) and other confounding variables.



by reviewing bibliographic references of these articles. The following key words were used (epicardial or pericardial or subepicardial) AND (fat or adipose) for the title and summary of the article, restricted to articles in Portuguese and English published between January 1990 and April 2012.

**Article selection:** Initially, 771 articles were found. Reviews (51) were excluded, as well as editorials and correspondence (31), meta-analyses (1) and society consensus (1), and articles in experimental models or the ones that evaluated only laboratory variables. The outcome selection criteria were restricted to the key words: metabolic syndrome, coronary artery disease, coronary calcium score. At the end, 37 original articles were identified describing the association between epicardial fat / pericardial measurement and MS, CAD or coronary calcium score.

**Data extraction and summarizing:** The two reviewers extracted the following data from the articles: sample size, demographic characteristics (gender, age, body mass index, cardiovascular risk) study inclusion criteria (convenience sample or population study), exposure factor and method employed (CT, MRI, echocardiography), measurement assessed (thickness or volume), outcome of interest (MS, CAD, calcium score) and mean values and measurements of association between groups. Due to the heterogeneity of methods employed in the studies as well as the populations studied, we considered inappropriate to summarize the

results in the form of meta-analysis. The results of the systematic review are described in Tables 2 (MS) and 3 (CAD) of the article.

### Author contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Bertaso AG, Bertol D, Duncan BB, Foppa M; Acquisition of data: Bertaso AG, Bertol D, Foppa M; Statistical analysis: Bertaso AG, Bertol D.

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## References

- Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. *J Am Soc Echocardiogr.* 2009;22(12):1311-9.
- Verhagen SN, Visseren FL. Perivascular adipose tissue as a cause of atherosclerosis. *Atherosclerosis.* 2011;214(1):3-10.
- Wang ZJ, Reddy GP, Gotway MB, Yeh BM, Hetts SW, Higgins CB. CT and MR imaging of pericardial disease. *Radiographics.* 2003;23 Spec No:S167-80.
- Fox CS, Gona P, Hoffmann U, Porter SA, Salton CJ, Massaro JM, et al. Pericardial fat, intrathoracic fat, and measures of left ventricular structure and function: the Framingham Heart Study. *Circulation.* 2009;119(12):1586-91.
- Mahabadi AA, Massaro JM, Rosito GA, Levy D, Murabito JM, Wolf PA, et al. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. *Eur Heart J.* 2009;30(7):850-6.
- Nelson AJ, Worthley MI, Psaltis PJ, Carbone A, Dundon BK, Duncan RF, et al. Validation of cardiovascular magnetic resonance assessment of pericardial adipose tissue volume. *J Cardiovasc Magn Reson.* 2009;11:15.
- Yun KH, Rhee SJ, Yoo NJ, Oh SK, Kim NH, Jeong JW, et al. Relationship between the echocardiographic epicardial adipose tissue thickness and serum adiponectin in patients with angina. *J Cardiovasc Ultrasound.* 2009;17(4):121-6.
- Rosito GA, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS, et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation.* 2008;117(5):605-13.
- Ding J, Hsu FC, Harris TB, Liu Y, Kritchevsky SB, Szklo M, et al. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr.* 2009;90(3):499-504.
- Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS, et al. Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. *Cardiovasc Diabetol.* 2006;5:1.
- Yudkin JS, Eringa E, Stehouwer CD. "Vasocrine" signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet.* 2005;365(9473):1817-20.
- Schäffler A, Schölmerich J. Innate immunity and adipose tissue biology. *Trends Immunol.* 2010;31(6):228-35.
- Sacks HS, Fain JN, Cheema P, Bahouth SW, Garrett E, Wolf RY, et al. Inflammatory genes in epicardial fat contiguous with coronary atherosclerosis in the metabolic syndrome and type 2 diabetes: changes associated with pioglitazone. *Diabetes Care.* 2011;34(3):730-3.
- Yao X, Shan S, Zhang Y, Ying H. Recent progress in the study of brown adipose tissue. *Cell Biosci.* 2011;1:35.
- Gastaldelli A, Basta G. Ectopic fat and cardiovascular disease: what is the link? *Nutr Metab Cardiovasc Dis.* 2010;20(7):481-90.
- Malavazos AE, Di Leo G, Secchi F, Lupo EN, Dogliotti G, Coman C, et al. Relation of echocardiographic epicardial fat thickness and myocardial fat. *Am J Cardiol.* 2010;105(12):1831-5.
- Schmidt MI, Duncan BB. Diabetes: an inflammatory metabolic condition. *Clin Chem Lab Med.* 2003;41(9):1120-30.
- Britton KA, Fox CS. Ectopic fat depots and cardiovascular disease. *Circulation.* 2011;124(24):e837-41.

19. Cheng KH, Chu CS, Lee KT, Lin TH, Hsieh CC, Chiu CC, et al. Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease. *Int J Obes (Lond)*. 2008;32(2):268-74.
20. Jung HS, Park KH, Cho YM, Chung SS, Cho HJ, Cho SY, et al. Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. *Cardiovasc Res*. 2006;69(1):76-85.
21. Wang CP, Hsu HL, Hung WC, Yu TH, Chen YH, Chiu CA, et al. Increased epicardial adipose tissue (EAT) volume in type 2 diabetes mellitus and association with metabolic syndrome and severity of coronary atherosclerosis. *Clin Endocrinol (Oxf)*. 2009;70(6):876-82.
22. Teijeira-Fernandez E, Eiras S, Grigorian-Shamagian L, Fernandez A, Adrio B, Gonzalez-Juanatey JR. Epicardial adipose tissue expression of adiponectin is lower in patients with hypertension. *J Hum Hypertens*. 2008;22(12):856-63.
23. Duncan BB, Schmidt MI, Pankow JS, Bang H, Couper D, Ballantyne CM, et al. Adiponectin and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*. 2004;53(9):2473-8.
24. Iacobellis G, Pistilli D, Gucciardo M, Leonetti F, Miraldi F, Brancaccio G, et al. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. *Cytokine*. 2005;29(6):251-5.
25. Jain SH, Massaro JM, Hoffmann U, Rosito GA, Vasan RS, Raji A, et al. Cross-sectional associations between abdominal and thoracic adipose tissue compartments and adiponectin and resistin in The Framingham Heart Study. *Diabetes Care*. 2009;32(5):903-8.
26. Hirata Y, Kurobe H, Akaike M, Chikugo F, Hori T, Bando Y, et al. Enhanced inflammation in epicardial fat in patients with coronary artery disease. *Int Heart J*. 2011;52(3):139-22.
27. Rajsheker S, Manka D, Blomkalns AL, Chatterjee TK, Stoll LL, Weintraub NL. Crosstalk between perivascular adipose tissue and blood vessels. *Curr Opin Pharmacol*. 2010;10(2):191-6.
28. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation*. 2003;108(20):2460-6.
29. Ito T, Nasu K, Terashima M, Ehara M, Kinoshita Y, Ito T, et al. The impact of epicardial fat volume on coronary plaque vulnerability: insight from optical coherence tomography analysis. *Eur Heart J Cardiovasc Imaging*. 2012;13(5):408-15.
30. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. *Obes Res*. 2003;11(2):304-10.
31. Iacobellis G, Ribaudo MC, Assael F, Vecchi E, Tiberti C, Zappaterreno A, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. *J Clin Endocrinol Metab*. 2003;88(11):5163-8.
32. Natale F, Tedesco MA, Mocerino R, de Simone V, Di Marco GM, Aronne L, et al. Visceral adiposity and arterial stiffness: echocardiographic epicardial fat thickness reflects, better than waist circumference, carotid arterial stiffness in a large population of hypertensives. *Eur J Echocardiogr*. 2009;10(4):549-55.
33. Mookadam F, Goel R, Alharthi MS, Jiamsripong P, Cha S. Epicardial fat and its association with cardiovascular risk: a cross-sectional observational study. *Heart Views*. 2010;11(3):103-8.
34. Iacobellis G, Willens HJ, Barbaro G, Sharma AM. Threshold values of high-risk echocardiographic epicardial fat thickness. *Obesity (Silver Spring)*. 2008;16(4):887-92.
35. Iacobellis G, Singh N, Wharton S, Sharma AM. Substantial changes in epicardial fat thickness after weight loss in severely obese subjects. *Obesity (Silver Spring)*. 2008;16(7):1693-7.
36. Jeong J, Jeong MH, Yun KH, Oh SK, Park EM, Kim YK, et al. Echocardiographic epicardial fat thickness and coronary artery disease. *Circ J*. 2007;71(4):536-9.
37. Nelson MR, Mookadam F, Thota V, Emami U, Al Harthi M, Lester SJ, et al. Epicardial fat: an additional measurement for subclinical atherosclerosis and cardiovascular risk stratification? *J Am Soc Echocardiogr*. 2011;24(3):339-45.
38. Ross R, Shaw KD, Martel Y, de Guise J, Avruhc L. Adipose tissue distribution measured by magnetic resonance imaging in obese women. *Am J Clin Nutr*. 1993;57(4):470-5.
39. Machann J, Thamer C, Schnoedt B, Haap M, Haring HU, Claussen CD, et al. Standardized assessment of whole body adipose tissue topography by MRI. *J Magn Reson Imaging*. 2005;21(4):455-62.
40. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E; Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. *J Cardiovasc Magn Reson*. 2008;10:35.
41. Doesch C, Haghi D, Flüchter S, Suselbeck T, Schoenberg SO, Michaely H, et al. Epicardial adipose tissue in patients with heart failure. *J Cardiovasc Magn Reson*. 2010;12:40.
42. Flüchter S, Haghi D, Dinter D, Heberlein W, Kühl HP, Neff W, et al. Volumetric assessment of epicardial adipose tissue with cardiovascular magnetic resonance imaging. *Obesity (Silver Spring)*. 2007;15(4):870-8.
43. Schejbal V. [Epicardial fatty tissue of the right ventricle-morphology, morphometry and functional significance]. *Pneumologie*. 1989;43(9):490-9.
44. Abbara S, Desai JC, Cury RC, Butler J, Nieman K, Reddy V. Mapping epicardial fat with multi-detector computed tomography to facilitate percutaneous transeptal ablation. *Eur J Radiol*. 2006;57(3):417-22.
45. Dey D, Wong ND, Tamarappoo B, Nakazato R, Gransar H, Cheng VY, et al. Computer-aided non-contrast CT-based quantification of pericardial and thoracic fat and their associations with coronary calcium and metabolic syndrome. *Atherosclerosis*. 2010;209(1):136-41.
46. Budoff MJ, Shinbane JS. *Cardiac CT imaging diagnosis of cardiovascular disease*. London: Springer-Verlag London Limited: Springer e-books; 2010.
47. Gorter PM, de Vos AM, van der Graaf Y, Stella PR, Doevendans PA, Meijis MFL, et al. Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography. *Am J Cardiol*. 2008;102(4):380-5.
48. Djaber R, Schuijff JD, van Werkhoven JM, Nucifora G, Jukema JW, Bax JJ. Relation of epicardial adipose tissue to coronary atherosclerosis. *Am J Cardiol*. 2008;102(12):1602-7.
49. Gorter PM, van Lindert AS, de Vos AM, Meijis MF, van der Graaf Y, Doevendans PA, et al. Quantification of epicardial and peri-coronary fat using cardiac computed tomography; reproducibility and relation with obesity and metabolic syndrome in patients suspected of coronary artery disease. *Atherosclerosis*. 2008;197(2):896-903.
50. Alexopoulos N, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. *Atherosclerosis*. 2010;210(1):150-4.
51. Dey D, Suzuki Y, Suzuki S, Ohba M, Slomka PJ, Polk D, et al. Automated quantitation of pericardial fat from noncontrast CT. *Invest Radiol*. 2008;43(2):145-53.
52. Ding J, Kritchevsky SB, Hsu FC, Harris TB, Burke GL, Detrano RC, et al. Association between non-subcutaneous adiposity and calcified coronary plaque: a sub-study of the Multi-Ethnic Study of Atherosclerosis. *Am J Clin Nutr*. 2008;88(3):645-50.
53. Shmilovich H, Dey D, Cheng VY, Rajani R, Nakazato R, Otaki Y, et al. Threshold for the upper normal limit of indexed epicardial fat volume: derivation in a healthy population and validation in an outcome-based study. *Am J Cardiol*. 2011;108(11):1680-5.
54. Willens HJ, Byers P, Chirinos JA, Labrador E, Hare JM, de Marchena E. Effects of weight loss after bariatric surgery on epicardial fat measured using echocardiography. *Am J Cardiol*. 2007;99(9):1242-5.
55. Silaghi A, Piercecchi-Marti M-D, Grino M, Leonetti G, Alessi MC, Clement K, et al. Epicardial adipose tissue extent: relationship with age, body fat distribution, and coronaropathy. *Obesity (Silver Spring)*. 2008;16(11):2424-30.

56. Dey DK, Rothenberg E, Sundh V, Bosaeus I, Steen B. Height and body weight in the elderly. I. A 25-year longitudinal study of a population aged 70 to 95 years. *Eur J Clin Nutr.* 1999;53(12):905-14.
57. Perissinotto E, Pisent C, Sergi G, Grigoletto F. Anthropometric measurements in the elderly: age and gender differences. *Br J Nutr.* 2002;87(2):177-86.
58. Duncan BB, Chambless LE, Schmidt MI, Szklo M, Folsom AR, Carpenter MA, et al. Correlates of body fat distribution. Variation across categories of race, sex, and body mass in the atherosclerosis risk in communities study. The Atherosclerosis Risk in communities (ARIC) Study Investigators. *Ann Epidemiol.* 1995;5(3):192-200.
59. Ferris WF, Crowther NJ. Once fat was fat and that was that: our changing perspectives on adipose tissue. *Cardiovasc J Afr.* 2011;22(3):147-54.
60. Willens HJ, Gómez-Marín O, Chirinos JA, Goldberg R, Lowery MH, Iacobellis G. Comparison of epicardial and pericardial fat thickness assessed by echocardiography in African American and non-Hispanic White men: a pilot study. *Ethn Dis.* 2008;18(3):311-6.
61. Ahn SG, Lim H-S, Joe DY, Kang SJ, Choi BJ, Choi SY, et al. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. *Heart.* 2008;94(3):e7.
62. Okyay K, Balcioglu A, Tavil Y, Tacoy G, Turkoglu S, Abacı A. A relationship between echocardiographic subepicardial adipose tissue and metabolic syndrome. *Int J Cardiovasc Imaging.* 2008;24(6):577-83.
63. Eroglu S, Sade LE, Yildirir A, Bal U, Ozbicer S, Ozgul AS, et al. Epicardial adipose tissue thickness by echocardiography is a marker for the presence and severity of coronary artery disease. *Nutr Metab Cardiovasc Dis.* 2009;19(3):211-7.
64. Yorgun H, Canpolat U, Hazirolan T, Ateş AH, Sunman H, Dural M, et al. Increased epicardial fat tissue is a marker of metabolic syndrome in adult patients. *Int J Cardiol.* 2011 Sep 16. [Epub ahead of print].
65. Sironi AM, Pingitore A, Ghione S, De Marchi D, Scattini B, Positano V, et al. Early hypertension is associated with reduced regional cardiac function, insulin resistance, epicardial, and visceral fat. *Hypertension.* 2008;51(2):282-8.
66. Nakazato R, Rajani R, Cheng VY, Shmlovich H, Nakanishi R, Otaki Y, et al. Weight change modulates epicardial fat burden: A 4-year serial study with non-contrast computed tomography. *Atherosclerosis.* 2012;220(1):139-44.
67. Iacobellis G, Barbaro G, Gerstein HC. Relationship of epicardial fat thickness and fasting glucose. *In J Cardiol.* 2008;128(3):424-6.
68. Bettencourt N, Toschke AM, Leite D, Rocha J, Carvalho M, Sampaio F, et al. Epicardial adipose tissue is an independent predictor of coronary atherosclerotic burden. *Int J Cardiol.* 2012;158(1):26-32.
69. Chaowalit N, Somers VK, Pellikka PA, Rihal CS, Lopez-Jimenez F. Subepicardial adipose tissue and the presence and severity of coronary artery disease. *Atherosclerosis.* 2006;186(2):354-9.
70. Cheng VY, Dey D, Tamarappoo B, Nakazato R, Gransar H, Miranda-Peats R, et al. Pericardial fat burden on ECG-gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. *JACC Cardiovasc Imaging.* 2010;3(4):352-60.
71. Thanassoulis G, Massaro JM, O'Donnell CJ, Hoffmann U, Levy D, Ellinor PT, et al. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. *Circ Arrhythm Electrophysiol.* 2010;3(4):345-50.
72. Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol.* 2011;57(17):1745-51.
73. Liu J, Fox CS, Hickson DA, May WL, Ding J, Carr JJ, et al. Pericardial fat and echocardiographic measures of cardiac abnormalities: the Jackson Heart Study. *Diabetes Care.* 2011;34(2):341-6.
74. Guaraldi G, Scaglioni R, Zona S, Orlando G, Carli F, Ligabue G, et al. Epicardial adipose tissue is an independent marker of cardiovascular risk in HIV-infected patients. *AIDS.* 2011;25(9):1199-205.
75. Lai YH, Yun CH, Yang FS, Liu CC, Wu YJ, Kuo JY, et al. Epicardial adipose tissue relating to anthropometrics, metabolic derangements and fatty liver disease independently contributes to serum high-sensitivity c-reactive protein beyond body fat composition: a study validated with computed tomography. *J Am Echocardiogr.* 2012;25(2):234-41.
76. Momesso DP, Bussade I, Epifanio MA, Schettino CD, Russo LA, Kupfer R. Increased epicardial adipose tissue in type 1 diabetes is associated with central obesity and metabolic syndrome. *Diabetes Res Clin Pract.* 2011;91(1):47-53.
77. Pierdomenico SD, Pierdomenico AM, Neri M, Cucurullo F. Epicardial adipose tissue and metabolic syndrome in hypertensive patients with normal body weight and waist circumference. *Am J Hypertens.* 2011;24(11):1245-9.
78. Mustelier JV, Rego JO, González AG, Sarmiento JC, Riverón BV. Echocardiographic parameters of epicardial fat deposition and its relation to coronary artery disease. *Arq Bras Cardiol.* 2011;97(2):122-9.
79. Shemirani H, Khoshavi M. Correlation of echocardiographic epicardial fat thickness with severity of coronary artery disease-an observational study. *Anadolu Kardiyol Derg.* 2012;12(3):200-5.
80. Ueno K, Anzai T, Jinzaki M, Yamada M, Jo Y, Maekawa Y, et al. Increased epicardial fat volume quantified by 64-multidetector computed tomography is associated with coronary atherosclerosis and totally occlusive lesions. *Circ J.* 2009;73(10):1927-33.
81. Sarin S, Wenger C, Marwaha A, Qureshi A, Go BD, Woomert CA, et al. Clinical significance of epicardial fat measured using cardiac multislice computed tomography. *Am J Cardiol.* 2008;102(6):767-71.
82. Wang TD, Lee WJ, Shih FY, Huang CH, Chen WJ, Lee YT, et al. Association of epicardial adipose tissue with coronary atherosclerosis is region-specific and independent of conventional risk factors and intra-abdominal adiposity. *Atherosclerosis.* 2010;213(1):279-87.
83. Iwasaki K, Matsumoto T, Aono H, Furukawa H, Samukawa M. Relationship between epicardial fat measured by 64-multidetector computed tomography and coronary artery disease. *Clin Cardiol.* 2011;34(3):166-71.
84. Oka T, Yamamoto H, Ohashi N, Kitagawa T, Kunita E, Utsunomiya H, et al. Association between epicardial adipose tissue volume and characteristics of non-calcified plaques assessed by coronary computed tomographic angiography. *Int J Cardiol.* 2012; 161(1):45-9.
85. Harada K, Amano T, Uetani T, Tokuda Y, Kitagawa K, Shimbo Y, et al. Cardiac 64-multislice computed tomography reveals increased epicardial fat volume in patients with acute coronary syndrome. *Am J Cardiol.* 2011;108(8):1119-23.
86. Yerramasu A, Dey D, Venuraju S, Anand DV, Atwal S, Corder R, et al. Increased volume of epicardial fat is an independent risk factor for accelerated progression of sub-clinical coronary atherosclerosis. *Atherosclerosis.* 2012;220(1):223-30.
87. Nakazato R, Dey D, Cheng VY, Gransar H, Slomka PJ, Hayes SW, et al. Epicardial fat volume and concurrent presence of both myocardial ischemia and obstructive coronary artery disease. *Atherosclerosis.* 2012;221(2):422-6.
88. Schlett CL, Ferencik M, Kriegl MF, Bamberg F, Ghoshhajra BB, Joshi SB, et al. Association of pericardial fat and coronary high-risk lesions as determined by cardiac CT. *Atherosclerosis.* 2012;222(1):129-34.