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 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. 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, while EF is nourished by the coronary arteries. The structure that delimits 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. This extrapericardial fat deposit nomenclature varies according to different authors, being called intrathoracic, paracardial or mediastinal or pericardial. Some groups treat these different fat deposits as a single compartment, calling it paracardial or pericardial fat. 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.

Among the several physiological roles of EF are: local distribution and regulation of vascular flow by vasocrine mechanisms; immune barrier, protecting the myocardium and coronary arteries from inflammatory and pathogenic substances; 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, and thermogenic effects related to brown adipose tissue.
Table 1 - Nomenclature of body fat deposits

| Fat Deposit                  | Description                                                                 |
|-----------------------------|-----------------------------------------------------------------------------|
| Epicardial fat              | Visceral intrapericardial fat contiguous with the myocardial surface         |
| Visceral intrapericardial   | (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                                 |

Table 1 - Nomenclature of body fat deposits

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. Magnetic resonance and spectroscopy have demonstrated the strong correlation (r = 0.79, p < 0.01) between EF volume and triglyceride concentration in the myocardium. 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 are associated with metabolic syndrome and are phenomena also identified in EF.

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 and show greater concentration in EF.

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 and in those with increased cardiovascular risk and are inversely associated with deposits of abdominal visceral, epicardial and intrathoracic fat.

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 and can locally accelerate the atherosclerotic process by endothelial dysfunction, local proliferation of smooth muscle cells, increased oxidative stress (leptin) plaque instability via apoptosis (TNF-α) and neovascularization (MCP-1). A recent study investigating coronary arteries through optical coherence tomography found an association between the amount of pericoronary fat and markers of plaque instability.

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, 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. 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). EF is identified as a hypoechoic 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.

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 and others in diastole, to coincide with other imaging modalities (CT and MRI). The mean values described for EF thickness in systole by Iacobellis et al 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. When measured in diastole, Jeong et al 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 found a mean of 4.7 ± 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, thus making it a natural choice for the detection and quantification of EF.
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.\(^{40,41}\) (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. Flutcher et al\(^{42}\) 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\(^{43}\) in 200 autopsies (mean thickness: 4.12 ± 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.\(^{44}\) 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\(^{45}\) (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.\(^{46}\)

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
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).\(^9\)

**Epicardial Fat Thickness by computed tomography**

EF thickness can be measured in the right ventricular free wall and around the main coronary arteries\(^{21,47}\), 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

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**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.
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)\(^4,47\). Several studies have been published using the semi-automated technique for measuring the amount of EF\(^4,47-50\). 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\(^5\). 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\(^51\).

The mean volume of EF found in population-based studies ranges from 68 ± 34 mL to 124 ± 50 mL\(^5,52\). In a study including patients from the Framingham cohort, the mean EF volume was 110 ± 41 mL in men\(^5\). In 2011, Shmilovich et al\(^51\) 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\(^{th}\) percentile of EF volume indexed to body surface area was 68.1 mL/m\(^2\).

**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\(^34,49\); moreover, reduction in body weight (mean reduction of 40 ± 14 kg) in patients undergoing bariatric surgery decreased the EF thickness from 5.3 ± 2.4 mm to 4.0 ± 1.6 mm (p <0.001)\(^64\).

**Age**

Epicardial fat seems to increase with age\(^4,50,55\), being 22% thicker in individuals older than 65 years\(^66\). 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\(^66\). These changes seem to occur at a different rate and intensity between men and women, with a greater redistribution seen in older women\(^52\).

**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\(^5\) 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\(^5,52\). 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\(^56\), suggesting that in those with black skin color, the adiposity has a more diabetogenic than atherogenic nature, by mechanisms not yet clearly understood\(^57\).

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\(^56\).

**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\(^8,21,31,34,61-64\) described a higher amount of EF in individuals with metabolic syndrome (MS), across different clinical characteristics and prevalences of MS (Table 2).

Inflammation\(^21,22,24,28\), derangements in insulin sensitivity\(^31,65\) and arterial hypertension\(^50,63,66\), 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\(^67\) and with the prevalence of DM68.

**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\(^57,69\), 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 |
|-------------------------|---------------------------------|-----------------------------------------------------|------|---------------|-----------------|-------------------|---------------------|
| Iacobellis et al. [1],  | Referred to echocardiography   | BMI between 22 and 47 kg/m²                          | 72   | Not informed  | EF in systole   | M: 7.6 ± 3.6 mm   | F: 6.9 ± 3.7 mm     |
| 2003                    |                                 |                                                     |      |               |                 |                   |                     |
| Ahn et al. [2], 2008    | Referred to Cath                | Suspected CAD                                        | 527  | 23%           | EF Median in    | 3.2 ± 2.5 mm      | With MS: 5.3 mm     |
|                         |                                 |                                                     |      |               | diastole       |                   | Without MS: 1.6 mm  |
|                         |                                 |                                                     |      |               | (CO = 3.0 mm)   |                   | (r = 0.32; p < 0.001) |
| Okyay et al. [3], 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. [4],  | Referred to echocardiography   | Mean BMI = 32 kg/m²                                  | 246  | 58%           | Median EF in    | M: 7.0 mm         | With MS: 2.8 ± 1.6 mm |
| 2008                    |                                 |                                                     |      |               | systole         | F: 6.5 mm         | F: 5.7 mm ROC Area  = 0.79 |
| Lai et al. [5], 2011    | Referred for coronary artery    | Asymptomatic                                         | 359  | 23%           | EF thickness    | 7.6 ± 1.4 mm      | With MS: 6.1 ± 0.4 mm |
|                         | disease screening               |                                                     |      |               | (CO = 6.0 mm)   |                   | Without MS: 4.9 ± 0.3 mm (p = 0.006) |
| Momesso et al. [6], 2011| Outpatients with Type 1 DM      | Women with Type 1 DM (mean age 37 years)             | 45   | 45%           | EF in diastole   | Not informed      | With MS: 4.0 ± 0.8 mm |
|                         |                                 |                                                     |      |               |                 |                   | Without MS: 2.5 ± 0.9 mm (p < 0.001)* |
| Pierdomenico et al. [7],| Referred to echocardiography   | Hypertensive Caucasians                               | 174  | 12%           | EF in diastole   | Not informed      | With MS: 8.5 ± 1.4 mm |
| 2011                    |                                 |                                                     |      |               |                 |                   | Without MS: 7.4 ± 2.1 mm (p < 0.001)* |
| Wang et al. [8], 2009  | Referred to CT and Cath         | Stable angina                                        | 148  | Not informed  | EF thickness at left AV groove. > 12.4 mm | Left AV groove = 12.7 ± 3.2 mm | Right V = 4.3 ± 1.8 mm |
|                         |                                 |                                                     |      |               |                 | ROC area = 0.80   | (p = 0.004)*       |
| Yorgun et al. [9], 2011 | Referred to CT                  | Suspected CAD                                        | 83   | 48%           | EF thickness    | Not informed      | With MS: 111 mL     |
|                         |                                 |                                                     |      |               |                 |                   | Without MS: 77 mL   |

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.

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Two studies found a moderate association between EF and clinical outcomes. Cheng et al., 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. 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 and in the MESA studies.

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. EF is inversely associated with ejection fraction and left ventricular mass. 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.

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/m² 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

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 |
|------------------|-----------------------------------------|----------------------------------|----|-----------------------------|-----------------------------|---------------------------------|
| Chaowalit et al., 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., 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., 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., 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., 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 - 36.6)* |
| Nelson et al., 2011 | 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., 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 | 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

| Authors               | Year | Referred to | Diagnosis                     | EF Volume | Event                          | OR (95% CI)      |
|-----------------------|------|-------------|-------------------------------|-----------|--------------------------------|------------------|
| Djaberi et al.        | 2008 | Referred to CT | Suspected angina              | 190       | EF Volume > 75mL              | Presence of coronary plaque | OR: 1.03 (95% CI: 1.01-1.05)* |
| Uno et al.            | 2009 | Referred to CT and Cath | Suspected angina              | 71        | EF Volume indexed for TBS ≥ 50cm²/m² | Chronic coronary occlusion | OR: 4.64 (95% CI: 1.21 - 17.72)* |
| Alexopoulos et al.    | 2010 | Referred to CT | Suspected angina              | 214       | EF Volume > 71cm³             | Presence of coronary plaque | OR: 3.9 (95% CI: 1.1 – 13.8)* |
| Sarrin et al.         | 2008 | Referred to CT | Low pretest probability of CAD | 151       | EF Volume ≥ 100mL             | Coronary calcium score | EF ≥ 100mL: 216 ± 39 EF < 100mL: 67 ± 155 (p = 0.03) |
| Rosito et al.         | 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.           | 2009 | 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.           | 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.       | 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.          | 2010 | Referred to CT | Low pretest probability of CAD | 232       | EF Volume > 125cm³           | Major adverse cardiac event in 4 years | OR: 1.74 (95% CI: 1.03 – 2.95)* |
| Wang et al.           | 2010 | Referred to CT and Cath | Stable angina                 | 224       | EF Volume                     | CAD (stenosis ≥ 50%) | EF Volume: 113 ± 42 mL vs. 102 ± 36 ml (p = 0.04) |
| Iwasaki et al.        | 2011 | Referred to CT | Suspected angina              | 197       | EF Volume ≥ 100 mL vs. < 100 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) |
| Oka et al.            | 2011 | Referred to CT | Suspected CAD                 | 357       | EF Volume ≥ 100 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.    | 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.         | 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.     | 2011 | Patients referred to CCS | Patients with (cases) and without (controls) major adverse cardiac events | 232       | EF volume indexed for total body surface > 68.1cm²/m² | Major adverse cardiac event in 4 years | OR: 2.8 (95% CI: 1.3 - 6.4)* |
| Yerramasu et al.      | 2012 | Risk Stratification for CAD | Type II diabetic patients     | 333       | EF Volume                     | Coronary calcium score (presence vs. absence) | 85.8 vs. 69.3 cm³ (p < 0.001) OR: 1.13 (95% CI: 1.04 - 1.22) |
| Nakazato et al.       | 2012 | Risk stratification for CAD | Suspected CAD                 | 92        | EF Volume indexed for total body surface > 68.1cm²/m² | Presence of ischemia at PET CT and stenosis ≥ 50% at coronary angiography | OR: 6.18 (95% CI: 1.73 - 22.01)* |
| Schlott et al.        | 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) cm³ vs. 74.8 (58 - 112) cm³ (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 consensuses (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.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article contains parts of the theses of master submitted by Angela Gallina Bertaso and Daniela Bertol, from Universidade Federal do Rio Grande do Sul.

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