

Epicardial adipose tissue: far more than a fat depot

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Abstract: Epicardial adipose tissue (EAT) refers to the fat depot that exists on the surface of the myocardium and is contained entirely beneath the pericardium, thus surrounding and in direct contact with the major coronary arteries and their branches. EAT is a biologically active organ that may play a role in the association between obesity and coronary artery disease (CAD). Given recent advances in non-invasive imaging modalities such as multidetector computed tomography (MDCT), EAT can be accurately measured and quantified. In this review, we focus on the evidence suggesting a role for EAT as a quantifiable risk marker in CAD, as well as describe the role EAT may play in the development and vulnerability of coronary artery plaque.

Keywords: Epicardial adipose tissue (EAT); epicardial fat; coronary artery disease (CAD); multidetector computed tomography (MDCT)

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Introduction

Cardiovascular disease is the largest cause of death in the world, and coronary artery disease (CAD) makes up the greatest proportion of those deaths (1). Considerable time and effort has been invested identifying cardiovascular risk factors that may contribute to early stages of CAD, and the search continues for novel factors that may enable more sensitive measures for risk stratification, or offer novel therapeutic targets for the prevention and treatment of coronary vascular disease.

Excess adiposity has long been associated with increased cardiovascular disease (2). There are many plausible mechanisms that could account for this, including changes in blood pressure, blood glucose regulation, lipid metabolism and overall systemic inflammation (3). Furthermore, adipose tissue secretes multiple exocrine and paracrine factors that may directly influence vessel wall homeostasis by altering the function of endothelial cells, arterial smooth muscle cells and macrophages, leading to the development of atherosclerotic plaques in the vessel wall (4).

There is substantial evidence that visceral adipose tissue (VAT), defined as fat in the trunk and abdomen, confers a much higher cardiovascular risk than peripheral adiposity [subcutaneous adipose tissue (SCAT)] that is present on hips and thighs (4-6). Thus measurement of waist-to-hip ratio is favoured as a better predictor of cardiovascular disease than the traditionally used BMI (6). A limitation of waist-to-hip measurements is that population studies indicate that general obesity is not necessarily associated with cardiovascular disease, and that not all obese patients present a similar risk profile (7). For example, a large waist circumference may not necessarily be indicative of a large amount of abdominal visceral fat but rather may be due to substantial accumulation of subcutaneous fat, which is often associated with a benign cardiometabolic profile (8). It is becoming increasingly evident that cardiovascular risk is not simply linked to the quantity of adipose tissue, but more importantly the location in which it accumulates. Regional fat distribution appears to play a significant role in cardiovascular disease and recent work has shown that regional fat deposits have a variety of functions other than

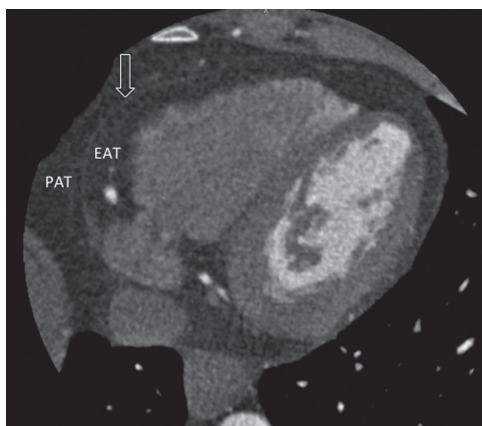


Figure 1 Epicardial adipose tissue (EAT) and paracardial adipose tissue (PAT) separated by a clearly visible parietal pericardium (open arrow) on axial computed tomography images of the heart. Pericardial fat is made up of the combination of EAT plus PAT.

simply a storage depot for fat.

Adipose tissue that directly surrounds the heart, which is in direct contact with the coronary vasculature, is of particular interest. This fat deposit is known as epicardial adipose tissue (EAT). Rapid advancement in non-invasive imaging techniques such as multidetector computed tomography (MDCT), echocardiography and cardiac magnetic resonance (CMR) imaging has allowed for the accurate measurement and quantification of this local fat depot. This review will focus on evidence suggesting a role for epicardial fat as a quantifiable independent risk marker for cardiovascular disease, as well as describing the role it may have as an active player in the development and vulnerability of coronary artery plaque in the arteries that it surrounds.

Discussion

Definition of cardiac fat deposits

A variety of terms including ‘epicardial’, ‘pericardial’, ‘paracardial’ and ‘intra-thoracic’ have been used to describe adipose tissue deposits in proximity to the heart or within the mediastinum. The use of these terms appears to be a point of confusion, as there is vast variation and inconsistency with their use within the literature. Of particular confusion is the term used to describe the adipose tissue that is found between the outer wall of the myocardium and the visceral layer of the pericardium, thus describing the fat that is fully enclosed within the pericardial

sac. This has previously been described in the literature as “pericardial fat” (9-12), while other groups have referred to this same fat deposit as “epicardial fat” (13-18). These terms are not simply interchangeable, as others use the term “pericardial fat” to describe the fat that is contained within the pericardial sac combined with the fat found on the external surface of the parietal pericardium (19-22).

As illustrated in *Figure 1*, the most accurate term for the adipose tissue—between the epicardial surface of the heart and the visceral surface of the pericardium—that is fully enclosed by the pericardial sac and directly surrounds the coronary arteries is “EAT”. Fat that is present on the external surface of the parietal pericardium is known as paracardial fat or mediastinal fat, and the term pericardial describes the combination of the adipose tissue within the pericardium and the paracardial adipose tissue that surrounds the external surface of the parietal pericardium.

Difference between epicardial and paracardial adipose tissue

It is very important to differentiate adipose tissue within the pericardium as “epicardial” and adipose tissue outside the pericardium as “paracardial” as they are quite different, not only anatomically, but also embryologically and biochemically. Under physiological conditions EAT constitutes approximately 20% of cardiac weight (23). It is found to be most concentrated in the atrioventricular and interventricular grooves, and as a consequence the coronary arteries and their major branches are often embedded within this tissue. Smaller fat foci are also found along the free walls of the atria and around the two atrial appendages, and a small amount often extends into the myocardium following branches of the coronary arteries (24). As the amount of epicardial fat increases, it begins to cover the walls of the ventricles, and in extreme cases may even cover the entire epicardial surface of the heart.

EAT is derived from the splanchnopleuric mesoderm associated with the gut, and is of the same embryologic origin as mesenteric and omental fat cells, having evolved from brown adipose tissue during embryogenesis (24-26). EAT is composed of far more than simply adipocytes; also containing nervous and nodal tissue, as well as inflammatory, stromal and immune cells within it (27).

The coronary arteries perfuse the EAT and also supply the myocardium (28). They are in direct contact with one another given there is no fascia or similar structure that separates EAT from the adventitial surface of the coronary arteries or the myocardium. This facilitates an environment

Table 1 Imaging modalities to measure epicardial adipose tissue

Imaging modality	Spatial resolution	Variables that can be measured	Reproducibility	Cost	Limitations	Strengths
Echocardiography	+	Thickness	Good Reproducibility. Interobserver and intraobserver intraclass coefficient of correlation 0.90 and 0.98 respectively (30)	+	Variable imaging quality—particularly in obese subjects; unable to quantify total volume or area	Does not use ionizing radiation; low cost; non-invasive; readily available
Cardiac computer tomography	++	Thickness, volume, total area	Highly reproducible correlation coefficient $r \geq 0.98$ (31,32)	++	Radiation exposure	High spatial resolution; can simultaneously assess coronary artery disease
Cardiovascular magnetic resonance	+++ (gold standard)	Thickness, volume, total area	Highly reproducible; low intra and interobserver variability (33,34)	+++	Accessibility; high cost	High spatial resolution; does not use ionizing radiation

for a local interaction between EAT and the coronary arteries that it directly opposes.

Paracardial adipose tissue (PAT) on the other hand refers to the fat depot that is superficial to the pericardium. Under physiologic conditions it covers 80% of the heart and constitutes between 20-50% of the cardiac mass (23). In contrast to EAT, PAT originates from the primitive thoracic mesenchyme, which splits to form the parietal pericardium and the outer thoracic wall (20,24). PAT is not perfused by the coronary arteries but rather supplied by branches of the internal mammary artery such as the pericardiophrenic artery (20,24). These are clearly two vastly different cardiac fat depots, and as Iacobellis *et al.* has rightly pointed out, it is imperative to differentiate between them (29).

Quantifying EAT

EAT can be relatively easily measured by a variety of different imaging techniques (Table 1). EAT fat thickness was first visualized by and measured with Transthoracic Two-dimensional (2D) Echocardiography. EAT is visible as an echo free space between the outer wall of the myocardium and the visceral layer of the pericardium. The thickness of this space is measured on the right ventricular free wall in the parasternal long and short axis views where EAT is thought to be thickest (35). Using this technique Iacobellis *et al.* reported excellent interobserver and intraobserver agreement with an intraclass coefficient

of 0.90 and 0.98, respectively (30). Another study found the echocardiographic concordance of EAT to be poor with an intraobserver intraclass correlation of 0.625 and an interobserver intraclass correlation of 0.605 (36). Echocardiographic measurement of EAT thickness is a cheap and readily available non-invasive measurement. It does, however, have the limitation of not being truly volumetric, as it is a linear measure at a single location. Therefore it does not reflect variability in fat thickness or provide information about the total fat volume. Whether echocardiographic EAT thickness measured at a single point is an accurate surrogate marker for total EAT volume is doubtful considering the significant inter-individual differences in EAT distribution. Three-dimensional echocardiography may be able to provide more accurate volumetric assessment of EAT in the future.

Computed tomography (CT) has also been used to measure EAT (Figure 2). Given the high spatial resolution of CT and that adipose tissue has distinct attenuation values, EAT is readily identified allowing for accurate volumetric measurement. Volumetric quantification of EAT involves identification of the limits of the heart and the pericardium, followed by tracing of the pericardium to exclude any extra-cardiac fat. This can be done manually or via a semi-automated process. Software is readily available that can be used to identify and quantify EAT on the basis of thresholds for CT attenuation.

Nakazato *et al.* demonstrated excellent interscan

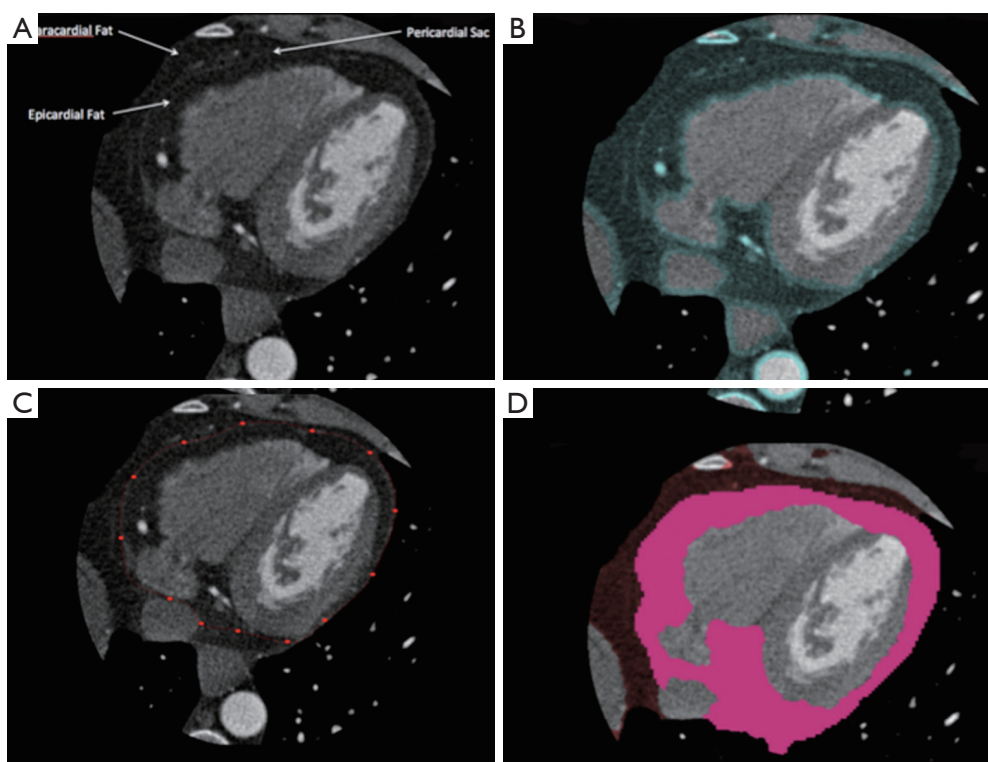


Figure 2 Figure illustrating epicardial and pericardial fat quantification. (A) On an axial view the pericardial sac is easily identified as a thin band enveloping the heart. Epicardial fat is the fat contained between the pericardium and the heart. (B) Total thoracic fat (epicardial fat plus paracardial fat). (C) The pericardial sac is traced by an expert observer in 10–20 axial slices between the upper and lower borders of the heart. (D) Semi-automated software calculates all epicardial fat (pink overlay), separated from paracardial fat (red overlay).

reproducibility using a semi-automated method with a correlation coefficient of ≥ 0.98 (31). CT disadvantages include exposure to ionizing radiation and a relatively high cost, making it somewhat poorly accessible and impractical for daily practice.

CMR imaging can also be used to measure EAT, with excellent image resolution it is considered the ‘gold standard’ modality for imaging adipose tissue (37,38). Similar to CT, a tracing is obtained of the pericardial sac and the adipose tissue voxels in each slice are added to calculate the total volume of this tissue. The use of CMR has been validated as an accurate and reproducible modality for the assessment of EAT (33). While the image resolution and accuracy of CMR is greater than CT, it is also far more costly and less accessible at this stage, which significantly limits its utility.

As has been described, EAT can be quantified by measuring either the thickness at a single point or volumetric quantification of total EAT volume. Using cardiac dual source CT, Bastarrika *et al.* performed a

comparison between the two methods to determine which was the most reproducible and which correlated best with the extent of CAD. They found using automated volumetry is more reproducible than a manual bidimensional approach which is based on thickness measurements. In addition, using automated volumetry, patients with significant coronary artery stenosis had significantly greater EAT volumes (154.58 ± 58.91 mL) than those without significant coronary artery stenosis (120.94 ± 81.85 mL) ($P=0.016$). Yet, epicardial distance measurements failed to show any significant difference between these two groups (39). Thus, volumetric quantification of total EAT is not only more reproducible but also correlates better with extent of CAD.

EAT—biologically active organ

It has become evident that adipose tissue is far more than simply a fat storage depot, but rather a biologically active organ that may play a central role in the association between obesity and cardiovascular disease (3). The

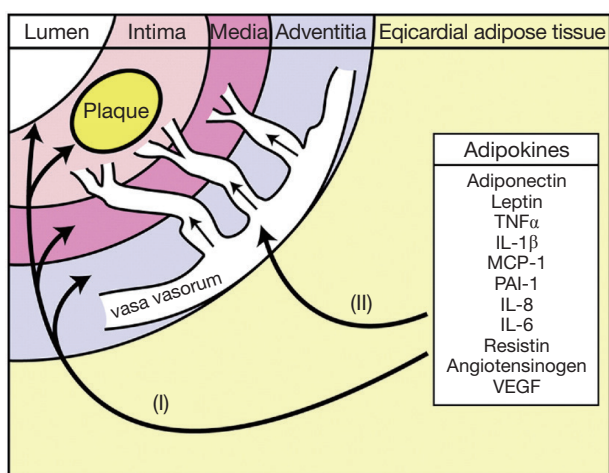


Figure 3 Proposed mechanisms in which epicardial adipokines may access underlying atheroma to play a role in coronary atherogenesis. (I) Paracrine signalling: adipokines directly diffuse through layers of the arterial wall; (II) vasocrine signalling: adipokines transverse through the vessel into adventitial vasa vasorum lumen and are transported downstream to react with cells in the intima and media around atherosclerotic plaques (20). Reproduced with permission from Elsevier Limited.

metabolic profile of EAT is dependent on the metabolic context of the patient. EAT and PAT are normally present in humans, and under normal conditions EAT is thought to serve a number of physiologic functions, including acting as an energy source to the myocardium. EAT has a greater capacity for the uptake and release of free fatty acids (FFAs) and has a lower rate of glucose utilization than other visceral fat depots (40). Fatty acids are the major energy source for the contractile function in a healthy heart (41), and FFA oxidation is responsible for about 50-70% of the energy production of the heart. The myocardium sources these FFAs via the coronary arteries, which the EAT surrounds. Given that EAT has such high rates of FFA synthesis, incorporation, and breakdown, it is thought that EAT may actually act as a buffer between the myocardium and the local vasculature, scavenging excess FFAs and thus protecting the heart from lipotoxicity (25). In addition, the high lipolytic activity of EAT suggests that it may also play a role as a ready source of FFAs to meet increased myocardial energy demand through the β -oxidation of FFAs (42). EAT has also been shown to be a source of many putatively beneficial adipokines with anti-atherogenic and anti-inflammatory effects, of which adiponectin appears to be most important with its anti-atherosclerotic properties (43,44). Anatomically EAT

provides mechanical protection of the coronary arteries, buffering them against the torsion induced by the arterial pulse wave and cardiac contraction (45).

EAT is, however, a visceral fat deposit and as such has the capacity to secrete a number of cytokines and chemokines, known collectively as adipokines. These are biologically active molecules that are secreted by mature adipocytes themselves, as well as stromal preadipocytes, macrophages, fibroblasts, mast cells and lymphocytes that are located within the adipose tissue (46). Interleukin (IL)-1 β , -6, -8 and -10, tumor necrosis factor α (TNF- α), monocyte chemoattractive protein 1 (MCP-1), adiponectin, leptin and plasminogen activator inhibitor 1 (PAI-1) are all examples of adipokines (47). Adipokines can have both endocrine and paracrine functions that influence the development of cardiovascular disease, and in particular CAD (47). For example, elevated IL-6, TNF- α , MCP-1 and decreased adiponectin have been correlated with the development of atherosclerosis (48).

Adipokines produced by EAT are thought to gain access and thus influence underlying atherosclerotic plaque development via two main mechanisms: paracrine and vasocrine action (Figure 3). In paracrine signalling, it is hypothesised that adipokines produced by EAT surrounding the coronary vessels could diffuse directly through the layers of the vessel wall via the interstitial fluid to interact with the vasa vasorum, vascular smooth muscle cells, endothelium and the cellular components of the plaque leading to the initiation of inflammation, the development of atherosclerosis and changes in plaque phenotype. An alternative vasocrine signalling mechanism has been proposed in which it is hypothesized that adipokines secreted from the EAT directly enter the lumen of closely opposed adventitial vasa vasorum and thus are transported downstream into the arterial wall where they may act on cells in and around the atherosclerotic plaques (20,40).

EAT—mediator of local inflammation

While at normal quantities, there are many putative physiologic functions of EAT. In obesity however, many changes occur as EAT volumes substantially increase. These changes are often characterized by hypertrophy, failure to store triglycerides, increased lipolysis and inflammation (43). As EAT expands it becomes hypoxic and dysfunctional (49) and is invaded by increased numbers of macrophages and T lymphocytes, resulting in a shift in its metabolic profile. The result is increased secretion of pro-inflammatory cytokines

such as TNF- α , MCP-1, IL-1 β , IL-6 and many others that contribute to the inflammatory environment characteristic of atherogenesis (27), as well as reduced secretion of anti-atherosclerotic adipokines such as adiponectin (50). In this setting, the beneficial paracrine effects of EAT are lost, and such dysfunctional changes may play a causative role in local inflammation, with the potential to influence the development and progression of coronary artery plaque.

EAT—development of CAD

Atherosclerosis has long been recognised as an inflammatory disease (51), involving an ongoing inflammatory response that has been shown to play a fundamental role in mediating all stages of atherosclerotic plaque, from initiation through to progression, and ultimately in the thrombotic complications of atherogenesis (48). Many studies have linked long-term cardiovascular risk in both healthy populations and those with established CAD with circulating levels of inflammatory cytokines such as IL-6 and TNF- α (52-54) and raised high-sensitivity C-reactive Protein (55,56). Systemic inflammation and the production of adipokines by adipose tissue are considered important mechanistic contributors to the atherogenic process (4,57). Inflammation from within the vessel wall and from remote extravascular structures such as adipose tissue contributes significantly to atherogenesis. EAT plays a significant role in the inflammatory process that contributes to the inflammatory burden within and around atherosclerotic plaque (40). Mazurek *et al.* showed that EAT harvested during cardiac surgery from patients with severe CAD contained a substantial inflammatory infiltrate when compared to subcutaneous fat. They demonstrated a significantly higher expression of the chemokine, MCP-1, and inflammatory cytokines, IL-6, IL-1 β and TNF- α in EAT compared to leg subcutaneous fat in patients with established CAD. These proinflammatory properties of EAT were independent of plasma concentration of circulating biomarkers as well as patient clinical variables such as diabetes, BMI and chronic statin use (27). Adiponectin, which has been shown to have anti-atherosclerotic properties (44), has been shown to be significantly lower in EAT isolated from patients with severe CAD compared to subjects without CAD (58,59). Iwayama *et al.* demonstrated the role EAT may play in the early development of CAD via impairment of adiponectin secretion in non-obese individuals, finding that not only was EAT volume significantly greater in non-obese individuals

with evidence of CAD compared to non-obese patients with no evidence of CAD, but also adiponectin concentration was significantly lower in the pericardial fluid of non-obese patients with evidence of CAD than non-obese patients with no evidence of CAD (18). In addition, lower adiponectin levels correlate with more complex coronary lesions in men with coronary vascular disease (60). Interestingly, it has long been noted that segments of coronary arteries that course through a myocardial bridge (thus are surrounded by myocardium and free of any immediately adjacent epicardial fat) tend to be free from atherosclerotic plaque and immune to atherosclerosis (61,62). Robicsek *et al.* reported a study of 250 patients undergoing coronary bypass surgery for severe CAD. In this cohort, 26 of these patients had a circumflex that gave off a major branch that ran entirely intramyocardially, but required bypass due to severe proximal disease. Of these 26 patients, 24 had no evidence of atherosclerosis in the myocardial segment (63). While this may lend support for a paracrine effect of EAT in the development of atherosclerosis, it must be noted that there is significantly altered flow dynamics within the myocardial segments that may account somewhat for these changes. Additionally, it has been shown that EAT is not required for the development of coronary plaque, as autopsies of patients with congenital generalized lipodystrophy that possess a total absence of EAT, VAT and SCAT, still demonstrated evidence of CAD (64). This does not, however, exclude a secondary role for EAT in the development of CAD, given its association with the development of CAD that will be addressed in the next section.

EAT—association with coronary atherosclerotic plaque

A significant amount of research has investigated the link between increased Epicardial fat volume (EFV) and CAD (Table 2). The presence of coronary artery calcification is intimately associated with vascular injury and atherosclerotic plaque and is considered diagnostic of the presence of coronary atherosclerosis (73). Rosito *et al.* investigated 1,155 patients free of cardiovascular disease from the Framingham Heart Study that underwent MSCT for quantification of paracardial fat volume, EFV and coronary artery calcium (CAC). They found that epicardial fat, but not paracardial fat was associated with coronary artery calcification even after adjustment for cardiovascular risk factors [odds ratio (OR): 1.21; 95% CI, 1.005-1.46; P=0.04] (11). In a study of 159 patients without known CAD, selected from the Multi-Ethnic Study of Atherosclerosis (MESA), Ding *et al.* measured

Table 2 Association between epicardial adipose tissue and coronary artery disease assessed by cardiac computer tomography

Author	CT	N	Cohort	Exposure	Clinical variables/outcome	Measure of association
Ding <i>et al.</i> 2008 (21)	4-slice	398	Participants of MESA study	1 SD increment in EAT	Calcified coronary plaque	OR: 1.92 (95% CI, 1.27-2.90) [†]
Rosito <i>et al.</i> 2008 (11)	8-slice	1,155	Participants of the Framingham offspring study of free CVD	1 SD increment in EAT	CAC score	OR: 1.21 (95% CI, 1.005-1.46) [†]
Sarin <i>et al.</i> 2008 (15)	64-slice	151	Suspected CAD	EAT volume >100 mL	CAC score	CAC score—EAT volume: <100 mLs: 67±155; >100 mLs: 216±39 (P=0.03)
Ding <i>et al.</i> 2009 (65)	4-slice	998	Participants of MESA study	1 SD increment in EAT	Incident CAD	HR: 1.26 (95% CI, 1.01-1.59) [†]
Mahabadi <i>et al.</i> 2009 (12)	8-slice	1,267	Participants of the Framingham Offspring study of free CVD	1 SD increment in EAT	Presence of CVD	OR: 1.32 (95% CI, 1.11-1.57) [†]
Alexopoulos <i>et al.</i> 2010 (66)	64-Slice	214	Suspected CAD	EAT volume <71 cm ³	Presence of coronary plaque	OR: 3.9 (95% CI, 1.1-13.8) [†]
Cheng <i>et al.</i> 2010 (67)	4-slice	232	Suspected CAD	EAT volume >125 cm ³	MACE—4 year follow up	OR: 1.74 (95% CI, 1.03-2.95) [†]
Konishi <i>et al.</i> 2010 (10)	64-slice	171	Suspected CAD	1 SD increment in EAT	Any plaque; non stenotic plaque; non calcified plaque	OR: 2.876 (95% CI, 1.614-5.125) [†] ; OR: 3.423 (95% CI, 1.764-6.642) [†] ; OR: 3.316 (95% CI, 1.435-7.661) [†]
Harada <i>et al.</i> 2011 (68)	64-slice	170	ACS	EAT volume >100 mL	Presence of ACS	OR: 2.84 (95% CI, 1.17-6.87) [†]
Iwasaki <i>et al.</i> 2011 (17)	64-slice	197	Suspected CAD	EAT volume >100 vs. <100 mLs	CAC score; CAD (>50% stenosis)	384.0±782.0 vs. 174.8±395.6, P=0.016; 40.2% vs. 22.7%; P=0.008
Schlett <i>et al.</i> 2012 (9)	64-slice	358	Admitted to ED with chest pain	EAT volume	Presence of high risk lesions vs. without high risk lesions and no CAD	151.9 (109.0-179.0) vs. 110.0 (81.0-137.0) cm ³ (P=0.04); and 74.8 (58.0-112.0) cm ³ (P<0.0001)
Yerramasu <i>et al.</i> 2012 (69)	EBCT	333	Type II diabetic patients	Median EAT volume	CAC progression vs. no CAC progression	93.1 vs. 68.8 cm ³ (P<0.001) [†] ; OR: 1.12 (95% CI, 1.05-1.19) [†]
Ito <i>et al.</i> 2013 (16)	64-slice	1,308	Symptomatic patients with a zero calcium score	EAT volume per 10 cm ³	Obstructive plaque; vulnerable plaque	OR: 1.10 (95% CI, 1.04-1.16) [†] ; OR: 1.19 (95% CI, 1.12-1.27) [†]
Mahabadi <i>et al.</i> 2013 (70)	EBCT	4,093	Participants of the Heinz Nixdorf Recall study	Doubling of EAT volume	Increased risk of coronary events	HR: 1.54 (95% CI, 1.09-2.19) [†]
Rajani <i>et al.</i> 2013 (14)	Dual source CT	402	Suspected CAD	EAT Volume	>70% stenosis; high risk plaque features	OR: 3.0 (95% CI, 1.3-6.6) [†] ; OR: 1.7 (95% CI, 0.9-3.4) [†]
Iwayama <i>et al.</i> 2014 (18)	64-slice	69	Non-obese patients with and without severe CAD	1 SD increment in EAT	Incident CAD in non-obese patients	OR: 8.27 (95% CI, 1.12-61.60) [†]
den Dekker <i>et al.</i> 2014 (71)	Dual source CT	65	Asymptomatic patients with a history of extra-cardiac arterial disease	10 cm ³ increments of EAT	CAD	OR: 1.21 (95% CI, 1.04-1.39) [†]
Kim <i>et al.</i> 2014 (72)	16-slice	209	Suspected CAD	1 SD increment in EAT	Any CAD; significant CAD; CAC score	OR: 1.67 (95% CI, 1.17-2.37) [†] ; OR: 1.55 (95% CI, 1.10-2.17) [†] ; OR: 1.85 (95% CI, 1.15-3.04) [†]

CT, computer tomography; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation; EAT, epicardial adipose tissue; OR, odds ratio; CVD, coronary vascular disease; CAC, coronary artery calcium; EBCT, electron beam computer tomography; CAD, coronary artery disease; HR, hazard ratio; MACE, major cardiac adverse event; ACS, acute coronary syndrome; ED, emergency department. [†], measurements of association are adjusted for age, sex, body mass index and other confounding variables.

CAC and the adipose tissue volume located around the proximal coronary arteries. They found that the volume of adipose tissue was greater in those with a calcified coronary artery plaque than those with no evidence of calcified coronary plaque, as assessed by MSCT (21). They showed that peri-coronary adipose tissue volume (defined as a region of fat surrounding the left main coronary artery) was positively associated with both the presence and amount of calcified coronary artery plaque, even after adjustments for other cardiovascular risk factors. In addition, they demonstrated that BMI and height-adjusted waist circumference in their cohort were not associated with the presence of coronary artery plaque. While it must be noted that this group did not measure total EFV, they demonstrated that their method of measuring peri-coronary fat correlated highly with total EFV quantification on CT (Pearson's correlation coefficient: 0.93; $P < 0.001$). Many other studies have also demonstrated a link between EAT volume and CAD using coronary calcification as a marker for CAD (11,17,74,75). Additionally, in a cohort of 330 asymptomatic diabetic patients with no prior history of CAD, Yerramasu *et al.* investigated the association of EAT with progression of CAC defined as $>2.5 \text{ mm}^3$ increase in square root transformed volumetric CAC scores. They found that EAT showed significant association with CAC progression (OR: 1.12; 95% CI, 1.05-1.19; $P < 0.001$), finding that for each 10 cm^3 increase in the EAT volume, the probability of CAC progression went up by 12% (95% CI, 5-9%; $P < 0.001$) (69). Overall, this demonstrated that local fat depots surrounding coronary arteries were more related to coronary artery calcification than total body fat, and may suggest that EAT plays a role in exerting a toxic effect on the adjacent vasculature.

While the absence of calcified plaque in asymptomatic patients is reassuring and often a good prognosis, there is no doubting that CAD caused by non-calcified plaques do occur and can result in fatal cardiovascular events (76,77). Ito *et al.* showed that EFV was a significant predictor of obstructive coronary disease after multivariate adjustment in patients with a zero calcium score (16), demonstrating the utility of EFV as a useful marker of CAD in symptomatic patients with non-calcified plaques. Additionally, the aforementioned studies indicate that EAT is correlated with CAD independent of traditional risk factors and anthropometric measures of obesity (BMI and waist circumference), and that the accumulation of EAT, rather than abdominal obesity, could be implicated in the early development of CAD.

A study by Konishi *et al.* assessed plaque characteristics in relation to volumetric quantification of EAT in 171 patients. They characterised plaques as calcified, mixed and non-calcified and assessed data for a relationship between plaque characteristics and EAT volume, and found that EAT but not abdominal fat (measured as waist circumference) was independently and significantly associated with the presence of all types of coronary plaques, including both non-stenotic and non-calcified coronary plaques. They found no significant difference among patients with non-calcified, mixed or calcified coronary plaques and EAT volumes (10), concluding that EAT volumes are more associated with early development CAD than other simple anthropometric measures of abdominal obesity such as waist-to-hip ratio.

In contrast, Alexopoulos *et al.* were able to demonstrate that EAT volume differs significantly between different types of plaque. They were the first to demonstrate that EAT volume was not only greater in patients with coronary atherosclerosis, but was also larger in patients with mixed or non-calcified plaques compared to those with calcified plaques (66). This is of particular significance as non-calcified and mixed plaques are associated with a higher rate of cardiovascular events than purely calcified plaques (78). These results extended previous observations that EAT is associated with the presence of coronary atherosclerosis and began to demonstrate a link between EAT and particular plaque compositions.

The association of EAT volume with the presence of non-calcified plaques would suggest that EAT volume may not only be associated with the presence and extent of coronary atherosclerosis, but that EAT accumulation may precede plaque calcification and the development of mature atherosclerotic plaques in general. As such, EAT could provide a future avenue for risk stratification by enabling detection of those at risk of developing significant CAD while plaques are still immature, or potentially before there is detectable evidence of CAD.

Studies have also investigated the association of EAT volume and characteristics of plaque other than composition, such as size and the degree of stenosis. Numerous studies have examined the association between plaque stenosis and volume of EAT (9,14,17,66,79). The degree of coronary stenosis plays a critical role in the outcome of plaque rupture in coronary arteries. The degree of coronary luminal narrowing is decisive for whether plaque rupture causes occlusive thrombus or just internal hemorrhage: the higher the degree of stenosis the more likely the plaque is to cause an occlusive thrombus upon

rupture (80). Several studies have linked increased EAT volume to degree of coronary stenosis, with results showing that greater EAT volumes were an independent risk factor for the development of significant (>50%) coronary artery stenosis (17,79). A more recent study by Rajani *et al.* also showed that EAT is associated with more severe coronary stenosis (>70%) independent of conventional cardiac risk factors (14). Studies that used a Gensini score, or a modified version of it, to assess severity of CAD also found EAT was an independent predictor for CAD severity (72,81).

Degree of coronary artery stenosis is only one of many characteristics describing plaques, and evidence suggests that lesions most at risk of developing complications of CAD are not necessarily those with the greatest degree of stenosis (82,83). High-risk plaque features that are often measured include positive vessel remodeling or low-attenuation plaques, both of which are associated with a significantly higher risk of the occurrence of an acute coronary artery syndrome (84). These pathological characteristics are considered to make plaques more “high-risk” or “vulnerable”, meaning they are more prone to disruption with subsequent superimposed thrombosis, which is the prime mechanism of most acute coronary syndromes (ACS) (85). A number of studies have focused more specifically on the association of EAT and high risk coronary lesions, and found that EFV is in fact positively associated with high risk plaque characteristics such as positive remodeling, spotty calcification and low-attenuation plaque (9,14). A study by Schlett and colleagues suggested that EFV was significantly associated with high-risk coronary artery lesion morphology. They found that EFV was nearly twice as high in patients with high-risk coronary lesions than in those without CAD. Furthermore, they also found that EFV was still significantly higher in patients with high-risk lesions compared to patients with CAD but with no evidence of high-risk plaque morphology. In summary, they concluded that low EAT volume effectively excluded the presence of high-risk coronary morphology (9).

EAT—cardiovascular outcome

EFV has been shown by many to be associated not only with the presence of CAD, but also with characteristics of coronary plaque that deem these lesions to be “high risk” of rupture and the development of ACS such as myocardial infarct, unstable angina or sudden cardiac death. Consequently, one would expect to see this translate into increased incidence of major adverse cardiac events (MACE)

in the population. Increased EFV has been independently linked to adverse cardiovascular outcomes (67). It has been suggested to be an independent risk factor for ACS, with significantly increased EFV shown in patients with ACS when compared to a control group whose coronary CT results were normal (68), as well as being shown to be significantly associated with the presence of myocardial ischemia in patients without known CAD (86,87). Ding *et al.* conducted a case-cohort study in 998 patients who were randomly selected from 6814 MESA participants and found EAT was associated with CAD [relative risk for increase of one standard deviation (SD) in EAT =1.26, 95% CI, 1.01-1.59] even after adjustment for cardiovascular risk factors. A 1-standard deviation increment in EAT presented as significant a risk for CAD as an 18-pack-year increment in cigarette smoking (65). Mahabadi *et al.* quantified EAT volume and incidence of coronary events over a follow-up of 8±1.5 years in 4,093 participants in the Heinz Nixdorf Recall study. They found that incidence of coronary events increased with amount of EAT, with subjects in the highest quartile of EAT having a 5 fold higher risk when compared to subjects in the lowest quartile (0.9% *vs.* 4.7% for 1st and 4th quartiles respectively, P<0.001). In addition, they found that EFV remained independently associated with coronary events, with a doubling of EFV associated with a 1.5 fold risk of coronary events when adjusted for cardiovascular risk factors [hazard ratio (HR), 1.54; 95% CI, 1.09-2.19] (70).

EAT—future research interests

There is growing evidence to suggest that EAT, as a visceral fat depot, may contribute to the development of coronary artery atherosclerosis. Increased EAT correlates not only with increased development of atherosclerotic plaque, but is also associated with the development of high-risk lesions and adverse coronary events. Considering that EAT may precede the development of a mature atherosclerotic plaque, and may contribute to early stages of coronary atherogenesis, it may have a role as a risk stratification tool not only to identify those simply at risk of developing coronary vascular disease, but also to identify those at risk of MACE. Even if EAT is involved in the pathogenesis of coronary atherosclerosis, the question remains whether its quantification would improve risk stratification beyond already existing measures that are used in clinical practice, such as the measurement of coronary calcium score. A study by Forouzandeh *et al.* showed that while overall risk stratification was improved by combining EFV and CACS

severity information, no specific cut off points were found that better defined patients with or without MACE than simply using CACS alone (88). Even though there is a substantial body of evidence from multiple studies linking increased EAT volume to CAD and MACE, the evidence to date would not support performing cardiac CT examination purely for the purpose of quantifying EAT, as the prognostic benefit beyond traditional measurements is not sufficient. However, given that EAT may be the factor triggering atherosclerotic development, its utility may be in screening for subclinical atherosclerosis before the development of coronary calcification. The next step is to investigate the role that EAT volume plays in the development and progression of atherosclerotic plaque, and how its presence and consequent changes to the local environment may alter not only plaque progression but also plaque phenotype. To our knowledge only one study has investigated progression (89), and this was only in regard to coronary artery calcification. It is still unknown, which effects EAT has in the context of coronary atherosclerotic plaque burden, in particular in the development of subclinical atherosclerosis or non-calcified plaque. In addition, there is ongoing research to determine if higher EAT volumes contribute to increased CAD or if progression of EAT alters the microenvironment and leads to inflammatory processes that contribute to atherosclerotic development. Furthermore, before the quantification of EAT may enter the clinician's arsenal as a tool for risk stratification, more work must be completed to develop normal distribution curves of fat volumes in the population, as little data exists to determine cut off values for what should be considered low, moderate, and severe levels of cardiac fat and how they relate to relative risk of plaque development or MACE.

Conclusions

EAT is the true visceral fat deposit of the heart, as it exists directly on the epicardial surface of the myocardium and is contained entirely within the pericardial sac. As the coronary arteries and their major branches are embedded in this fat, this creates a perfect environment for a local interaction between a metabolically active EAT and the coronary vessels it surrounds. Coronary plaque development and phenotype are hypothesized to be influenced by the inflammatory burden created by altered expression and production of adipokines from EAT. As such, EAT is consistently associated not only with increased atherosclerotic plaque, but also high risk lesions and adverse

coronary events. Despite the capacity of different methods to assess EAT there is currently no rationale for its primary use as a risk stratification device, as it is unclear if it provides any greater prognostic benefit than currently employed techniques. Given additional research, the future application of volumetric quantification of EAT may be found to add to the prognostic benefit of pre-existing risk stratification techniques, and screening for sub-clinical atherosclerosis and non-calcified plaque.

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