Original Articles

The role of epicardial and pericoronary adipose tissue in cardiometabolic disease

A Lin, P McElhinney, N Nerlekar & D Dey

Abstract

Epicardial adipose tissue (EAT) is a metabolically active fat depot which modulates coronary arterial function. The measurement of EAT volume and attenuation from non-contrast cardiac computed tomography (CT) provides valuable information on cardiometabolic risk. Pericoronary adipose tissue (PCAT), a subset of EAT which directly surrounds the coronary vessels, may function as a sensor of coronary inflammation. PCAT attenuation on coronary CT angiography associates with coronary plaque morphology, stages of coronary artery disease, and risk of future cardiac events. Quantification of EAT and PCAT has incremental and complementary prognostic value over and above current risk assessment tools. This review covers the biological role of EAT in healthy and dysfunctional states, and CT-based assessment of EAT and PCAT towards the development of clinically meaningful imaging biomarkers.

Keywords

Epicardial adipose tissue, pericoronary adipose tissue, computed tomography, inflammation, coronary artery disease

Key points

1. Epicardial adipose tissue (EAT) is the major visceral fat depot for the heart and modulates coronary arterial function
2. Dysfunctional EAT secrets pro-inflammatory mediators which promote coronary atherosclerosis
3. Pericoronary adipose tissue (PCAT) is a subset of EAT directly surrounding the coronary vasculature
4. PCAT attenuation on coronary computed tomography angiography has emerged as an imaging biomarker of coronary inflammation

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Introduction

Obesity continues to increase in prevalence worldwide and is associated with significant morbidity and mortality.[1] The deposition of adipose tissue in the human body leads to excess visceral adiposity, an independent risk factor for metabolic syndrome and cardiovascular disease.[2] Epicardial adipose tissue (EAT), enclosed within the visceral pericardium of the heart, is a phenotypically unique fat depot which modulates coronary arterial function. It is well-established that dysfunctional EAT secretes inflammatory mediators which can diffuse into the coronary wall and promote atherosclerosis;[3] the so-called "outside-to-inside" theory of vascular inflammation. Recent bench-to-bedside evidence suggests that a subset of EAT directly surrounding the coronary vasculature – pericoronary adipose tissue (PCAT) – may also act as a sensor of coronary inflammation, via "inside-to-outside" signaling pathways.[4] Both EAT and PCAT can be imaged using cardiac computed tomography (CT), and quantification of these adipose tissue components may enable the detection of cardiometabolic disease and coronary inflammation. This review covers the biological role of EAT in the healthy dysfunctional state, and CT-based assessment of EAT and PCAT towards the development of clinically meaningful imaging biomarkers.

Normal structure and function of EAT

Various fat depots exist around the heart, which can be classified according to their anatomic location in relation to the pericardium and coronary arteries:

1. Epicardial adipose tissue (EAT): located between the myocardium and visceral pericardium, EAT is the true visceral fat depot for the heart. EAT is concentrated in the interventricular and atrioventricular grooves, and apart from the lateral wall of the right ventricle and the anterior wall of the left ventricle, the walls of both ventricles are free of EAT.[5]
2. Pericoronary adipose tissue (PCAT): a subset of EAT, which and directly surrounds the coronary arteries and is contiguous with the vessel adventitia.[6] The lack of clear anatomical borders has resulted in various

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definitions of PCAT in the literature. Recently, it was proposed that PCAT be defined as adipose tissue within a radial distance from the outer vessel wall equal to the average diameter of the coronary vessel.[4]

3. Paracardial adipose tissue: found on the external surface of the parietal pericardium, this is also referred to as thoracic or mediastinal fat.
4. Pericardial adipose tissue: refers to the sum of both epicardial and paracardial fat.

EAT is composed of multiple cell types, including adipocytes, macrophages, lymphocytes, and fibroblasts; all of which work together to regulate vascular function. In healthy and lean humans, EAT secretes vasoprotective adipokines such as adiponectin, leptin, and omentin-1 which exert anti-inflammatory, anti-contractile and vasodilatory effects. EAT also releases classical cytokines including interleukin (IL)-6, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1 and plasminogen activator inhibitor (PAI)-1.[7] The macrophages and T lymphocytes residing in EAT or recruited in response to cytokine release by adipocytes can release further inflammatory mediators when activated. The immune cells actively partner with adipocytes to maintain the balance of cytokines and regulate inflammatory responses to disease states.

Dysfunctional EAT in obesity

In response to chronic caloric excess, EAT undergoes morphological changes, including expansion and adverse remodelling. Over time, the secretory status and cellular composition of EAT shifts towards an inflammatory and dysfunctional phenotype. This shift is also seen biochemically through the upregulation of the pro-inflammatory adipokines leptin, resistin, and visfatin. Adipocyte hypertrophy stimulates secretion of MCP-1 which activates macrophage recruitment. The macrophages are lipid-laden foam cells with increased secretion of TNF-α, IL-6, and IL-8. Subsequently, EAT is infiltrated by immune cells and inflammatory signaling pathways are activated, leading to increased production of cytokines and reactive oxygen species. When examining the role of human adipocytes in obesity-related inflammation, it has been shown that an increase in macrophage-secreted factors alters the function of mature adipocytes, inhibits their formation, and also contributes to the systemic chronic low-grade inflammatory state associated with obesity.

Role of EAT in coronary atherosclerosis

The "outside-to-inside" theory of vascular inflammation posits that the inflammatory process begins in EAT and propagates inward to the coronary vasculature. Dysfunctional EAT secretes pro-inflammatory adipokines and cytokines which readily diffuse into the vascular wall. Leptin, resistin, MCP-1, and IL-8 promote monocyte migration and activation into macrophages, which then release additional cytokines such as IL-1 and TNF-α once in the vascular space. Contributing to the inflammatory milieu is a shift in the activation state of macrophages to the pro-inflammatory M1 phenotype, as seen in the EAT of patients with coronary artery disease (CAD), compared to patients without CAD whose macrophages express the anti-inflammatory M2 phenotype.[8] Adventitial vasa vasorum neovascularization also occurs in response to vascular inflammation, providing a direct way to transport inflammatory mediators released by EAT to the inner vasculature. The melange of adipokines and cytokines exert paracrine and vasocrine effects on the vessel wall, inciting atherogenesis and plaque-specific inflammation. Numerous histopathologic studies have confirmed the presence of dense immune infiltrates and increased expression of pro-inflammatory cytokines in the EAT of patients with CAD compared to those without CAD.[9-12]

Imaging EAT with cardiac CT

Due to its high spatial resolution and three-dimensional imaging of the heart, CT has emerged as a robust method for EAT assessment. EAT thickness and volume can be quantified manually or semi-automatically from routine coronary artery calcium (CAC) scoring non-contrast CT scans.[13-15]

EAT thickness on CT can be measured in axial views at various points along the basal right ventricular anterior free wall, linearly from the outside of the myocardium to the visceral pericardium.[16] Fat thickness can also be obtained at the left ventricular lateral free wall and inter- and atrio-ventricular grooves.[17] Yet, the lack of standardized measurement locations prevents determination of reference values,[18] and the measurement of EAT thickness on CT is subject to significant inter-observer variability.[19]

By contrast, three-dimensional volumetric assessment of EAT on CT yields highly reproducible measurements across different scan settings.[20,21] Dey et al.[13] developed bespoke research software (QFAT v2.0, Cedars-Sinai Medical Center) for the semi-automated quantification of EAT from non-contrast CT. In this method, the visceral pericardial contours are automatically detected by the program, followed by manual adjustment by an expert reader. EAT volume is calculated by summing contiguous fat voxels between the Hounsfield Units (HU) limits of -190 HU and -30 HU within the contours, and EAT attenuation is the average HU attenuation of all these voxels.

Recently, Commandeur et al.[22] developed a fully automated deep learning approach for EAT volume quantification using artificial neural networks (Figure 1). The deep learning algorithm was embedded into QFAT software and tested in a large multicenter study, demonstrating strong correlation with expert manual measurements for EAT volume and attenuation ($R = 0.97$ and 0.96, respectively; both $p<0.001$) at a rapid computation speed (~6 seconds per case compared to at least 15-20 minutes by experts).

Association of EAT with cardiometabolic risk factors

It is well established that visceral adiposity confers an adverse metabolic risk profile.[23] EAT thickness and volume correlate strongly with visceral adipose tissue volume on CT[17,24] and represent surrogate measures of general visceral adiposity.

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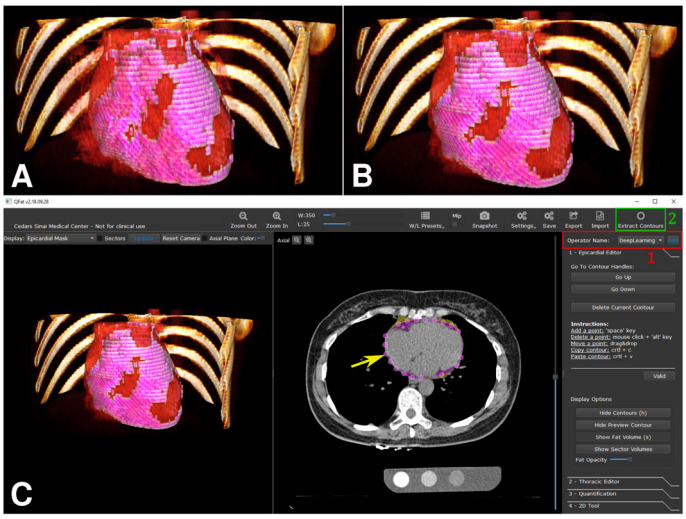


Figure 1. Three-dimensional views of epicardial adipose tissue (EAT) using research software QFAT. (A) Manually identified EAT by the expert and (B) automatically identified EAT by the deep learning algorithm embedded in software (EAT in pink overlay on heart rendered in red). (C) Example of QFAT software with embedded deep learning approach. The pericardium is automatically identified (yellow arrow) after selecting a new operator (1, red) and then the "extract contours" option (2, green). Reproduced with permission from Commandeur et al.[21]

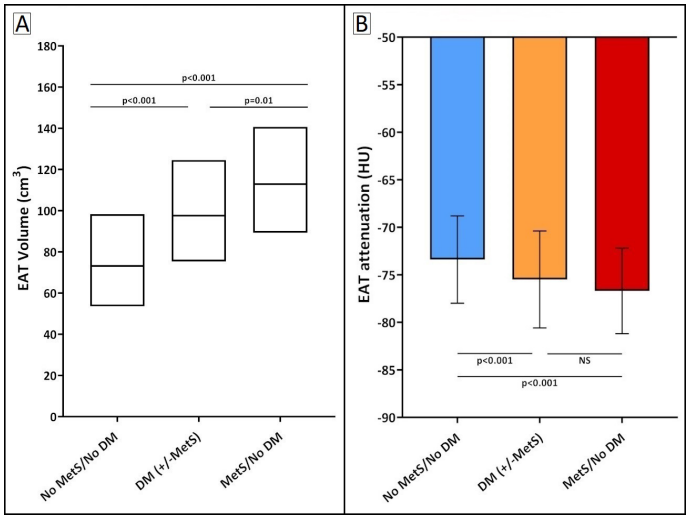


Figure 2. Relationship of epicardial adipose tissue (EAT) volume and attenuation with metabolic syndrome (MetS) and/or diabetes mellitus (DM). (a) EAT volume box plots of participants with: neither MetS nor DM (73.2 [53.6–98.3] cm3), DM with or without MetS (97.6 [75.4–124.6] cm3), and MetS without DM (112.9 [89.3–140.7] cm3), trend p < 0.001). (b) EAT attenuation was −73.4 ± 4.6 Hounsfield Units (HU) vs. −75.5 ± 5.1 HU vs. −76.7 ± 4.5 HU, respectively (trend p < 0.001). Reproduced with permission from Lin et al.[32]

Further, EAT volume and attenuation quantified from non-contrast cardiac CT using manual or semi-automated methods correlate with multiple metabolic risk factors including increased waist circumference, high triglycerides, low high-density lipoprotein-cholesterol, impaired fasting glucose, and elevated blood pressure.[17,25 26-32] (Table I)

In a recent analysis of 2,068 asymptomatic individuals undergoing CAC scoring on non-contrast cardiac CT, Lin et al.[33] showed artificial intelligence-based EAT volume and attenuation to independently associate with metabolic syndrome and its individual components. Subgroup analyses of patients with: 1) neither MetS nor diabetes, 2) diabetes, and 3) MetS without diabetes revealed significant differences in EAT volume (73.2 cm^3 vs. 97.6 cm^3 vs. 112.9 cm^3, trend $p < 0.001$) and attenuation (−73.4±4.6 HU vs. −75.5±5.1 HU vs. −76.7±4.5 HU, trend $p < 0.001$) (Figure 2). EAT measures were also independently associated with non-alcoholic fatty liver disease detected on the same non-contrast CT scans.

Association of EAT with CAD and cardiac events

The role of EAT volume in cardiovascular disease has been explored in large scale cohort studies including the Framingham Heart Study,[27] MESA (Multi-Ethnic Study of Atherosclerosis),[34] Heinz Nixdorf Recall Study[35,36] and Rotterdam Study[37] (Table II). In these asymptomatic low-risk populations, EAT volume quantified semi-automatically from non-contrast cardiac CT was associated with CAC presence, CAC score progression, and incident of major adverse cardiovascular events. In-hospital studies of patients with low-to-intermediate cardiovascular risk including the EISNER (Early Identification of Subclinical Atherosclerosis Using Non-Invasive Imaging Research) registry,[28,29,38-41] ROMICAT II (Rule Out Myocardial Ischemia/Infarction by Computer Assisted Tomography) trial,[42] and various stable chest pain cohorts,[43-46] demonstrated that higher CT-derived EAT volumes were associated with the presence and extent of CAD, stenosis severity, high-risk plaque, and myocardial ischemia. On follow-up, EAT volume was associated with calcium progression and cardiac events in these populations.

There has also been recent clinical interest in the relationship between CT-derived EAT attenuation and atherosclerosis (Table II). Abazid et al.[47] showed a lower EAT attenuation to predict the presence of coronary calcification and a CAC score >100), independently of EAT volume. Lu et al.[42] reported the mean EAT attenuation to be lower in patients with high-risk plaque compared to those without. Further, Goeller et al.[29] demonstrated decreasing EAT attenuation to be an independent predictor of cardiac events, following adjustment for EAT volume and CAC score. Conversely, Mahabadi et al.[48] showed EAT attenuation to be higher in patients with myocardial infarction (MI) compared to those with stable CAD. These conflicting results may be due to the small sample size of the latter studies, the heterogeneity of the study population, or methodological flaws such as selection bias. More importantly, however, evaluating EAT as a homogeneous depot does not account for the biologically important phenotypic variability between the PCAT and non-PCAT components.

Recently, fully automated deep learning-based EAT measurements have shown independent predictive value for future cardiovascular events. In an analysis of 2,068 asymptomatic individuals from the EISNER trial with 14-year follow-up, EAT volume and attenuation were associated with risk of future cardiovascular events (hazard ratio [HR] 1.35,

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Table 1. CT studies examining the association of EAT and PCAT with cardiometabolic risk factors

Authors	n	Measurement	Clinical variables	Measure of association	Other findings
Wang et al[17] 2009	148	EAT thickness	Fasting glucose Triglycerides HDL-C Hypertension hs-CRP Serum resistin	r = 0.29, p<0.001 r = 0.21, p<0.05 r = -0.20, p<0.05 r = 0.19, p<0.05 r = 0.17, p<0.05 r = 0.16, p<0.05	EAT thickness was measured at multiple sites; only the left atrioventricular groove measurement associated with all 3 components of MetS. The EAT thickness cutoff for predicting ≥2 MetS components was 12.4 mm.
Dicker et al[25] 2012	127	EAT thickness	Systolic BP	r = 0.23, p<0.01	Hypertensive subjects had a higher EAT thickness (2.8±1.6 vs 2.1±1.4 mm, p<0.05).
Kim et al[26] 2017	469	EAT thickness	BMI Systolic BP Triglycerides Fasting glucose	r = 0.47 ♀, 0.27 ♂, p<0.001 r = 0.23 ♀, 0.16 ♂, p<0.05 r = 0.26 ♀, 0.10 ♂, p<0.05 r = 0.25 ♀, 0.20 ♂, p<0.05	Multiple linear regression analysis showed age, BMI, systolic BP, and fasting glucose to independently correlate with EAT thickness in men, but not women.
Rosito et al[27] 2008	1,155	EAT volume	Triglycerides HDL-C Systolic BP Fasting glucose	r = 0.31 ♀, 0.22 ♂, p<0.001 r = -0.24 ♀, -0.14 ♂, p<0.001 r = 0.15 ♀, 0.10 ♂, p<0.001 r = 0.27 ♀, 0.10 ♂, p<0.001	A significant sex interaction was found with EAT volume being associated with a more adverse risk factor profile in females than males.
Dey et al[28] 2010	201	EAT volume	VAT area Fasting glucose HDL-C	r = 0.79, p<0.0001 r = 0.31, p<0.0001 r = -0.27, p<0.0001	EAT volume was associated with the MetS (OR 6.1, p<0.001).
Goeller et al[29] 2018	456	EAT volume	Serum PAI-1 Serum MCP-1 Serum adiponectin Triglycerides HDL-C	β = 0.174, p<0.001 β = 0.237, p<0.001 β = -0.123, p<0.028 β = 0.198, p<0.001 β = -0.252, p<0.001	EAT volume and attenuation were independently associated with serum lipid levels and inflammatory markers in multivariable linear regression analysis adjusted for age, BMI, coronary artery calcium score, and number of risk factors.
		EAT attenuation	Serum PAI-1 Serum ICAM-1 Serum adiponectin Triglycerides HDL-C	β = -0.191, p=0.013 β = 0.176, p=0.039 β = 0.192, p=0.011 β = -0.163, p=0.049 β = 0.194, p=0.014	
Franssens et al[30] 2016	140	EAT attenuation	BMI Waist circumference VAT thickness Fasting glucose MetS	β = -0.9, p<0.05 β = -1.2, p<0.05 β = -1.3, p<0.05 β = -0.7, p<0.05 β = -0.7, p<0.05	Multivariable linear regression showed age, BMI, waist circumference, abdominal VAT thickness, fasting glucose and MetS (per number increase) to be associated with EAT attenuation, independently of EAT volume.
De Vos et al[31] 2008	573	PCAT thickness	Systolic BP Triglycerides HDL-C Fasting glucose	β = 0.010, p<0.05 β = 0.502, p<0.01 β = -0.749, p<0.01 β = 0.349, p<0.001	In this study of post-menopausal women, age, weight, waist circumference, and fasting glucose were independently related to PCAT thickness.
Hell et al[32] 2014	63	PCAT attenuation	BMI EAT volume	r = -0.54, p<0.001 r = -0.55, p<0.001	BMI and EAT volume were independently and negatively associated with PCAT attenuation in multivariable regression.

BMI, body mass index; BP, blood pressure; CT, computed tomography; DM, diabetes mellitus; EAT, epicardial adipose tissue; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; MetS, metabolic syndrome; MRI, magnetic resonance imaging; PAI-1, plasminogen activator inhibitor-1; PCAT, pericoronary adipose tissue; VAT, visceral adipose tissue.

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Table 2. Studies examining the association of CT-derived EAT volume and attenuation with CAD

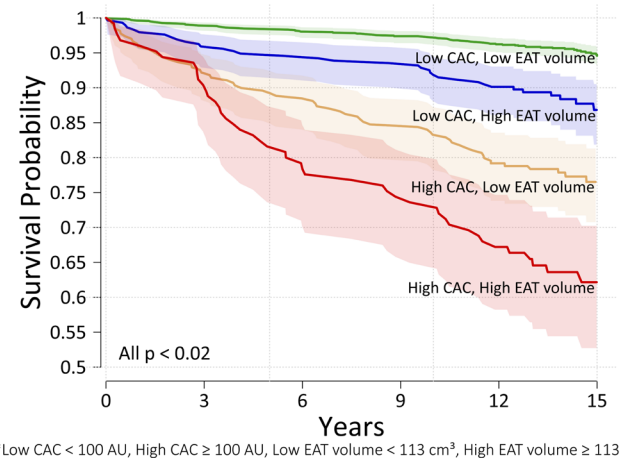
Authors	Study population	n	Male (%)	Age (years)	CAD outcomes	Main findings	Variables in multiple models
A. Cross-sectional studies							
Rosito et al[27] 2008	Framingham Heart Study	1,155	45	63±9	CAC	EAT volume was independently associated with the presence of coronary calcium (OR 1.21, 95% CI 1.01-1.46 per 1 SD increase in EAT, p=0.04).	Age, sex, SBP, hypertension treatment, TC/HDL-C, lipid treatment, DM, smoking, alcohol + VAT, BMI, WC
Dey et al[28] 2010	EISNER study	201	55	61±10	CAC	EAT volume was independently associated with the presence of CAC (OR 2.4, 95% CI 1.2-4.8 per doubling of EAT, p<0.001).	Age, sex, hypertension, LDL-C, HDL-C, triglycerides, DM, smoking, family history of CAD
McClain et al[34] 2013	MESA study	6,814	48	45-84	CAC	EAT volume associated with presence and severity of CAC; the association with CAC severity remained significant adjusted for BMI and risk factors.	Age, sex, race, smoking, physical activity, smoking, alcohol, education + BMI
Bos et al[37] 2015	Rotterdam study	2,298	52	69±7	CAC	Increasing EAT volume was independently associated with coronary calcification volume in men, but not in women.	Age, WC, BP, hypertension treatment, TC, HDL-C, lipid treatment, DM, smoking
Abazid et al[47] 2017	Patients at low to intermediate-risk of CAD	609	65	50±11	CAC	EAT volume was higher and EAT attenuation lower in patients with CAC. EAT volume >100cm^3 (HR 1.69, 95% CI 1.26-3.00, p=0.029) and EAT attenuation (HR 0.88, 95% CI 0.82-0.95, p=0.001) independently predicted the presence of CAC.	Age, male sex, DM
Versteylen et al[43] 2012	Stable chest pain patients	410	49	57±11	CAD presence ≥50% stenosis CAC score	On univariable analysis, EAT volume was associated with the presence and severity of CAD, however these associations did not remain significant after adjusting for CV risk factors.	Age, sex, SBP, TC, DM, IFG, smoking, BMI
Groves et al[63] 2014	Asymptomatic patients with and without T2DM	362	41	57±10	Stenosis severity	EAT volume increased with increasing stenosis severity in DM and non-DM patients. EAT volume >120cm^3 was an independent predictor of >70% stenosis (adj OR 4.47, 95% CI 1.35-14.82, p=0.01).	Age, sex, race, hypertension, dyslipidemia, DM, insulin therapy + BMI + smoking + CAC score
Alexopoulos et al[64] 2009	Patients undergoing clinically indicated CTCA	214	50	54±14	Stenosis severity Plaque composition	EAT volume >71ml was an independent predictor of presence of ≥50% stenosis (OR 3.82, 95% CI 1.24-11.75, p<0.05) and non-calcified or mixed plaques (OR 3.85, 95% CI 1.42-10.45, p<0.01).	Age, sex, race, BMI, hypertension, dyslipidemia, DM, smoking, family history of CAD
Ito et al[44] 2013	Chest pain patients with a CAC score of 0	1,308	46	59±12	>50% stenosis High-risk plaque	EAT volume predicted the presence of obstructive plaque (OR 1.10, 95% CI 1.04-1.16, p<0.01) and CT-derived high-risk plaque (OR 1.19, 95% CI 1.12-1.27, p<0.01).	Age, sex, hypertension, DM, typical symptoms
Lu et al[42] 2016	ROMICAT II trial (Acute chest pain patients requiring risk stratification)	467	53	54±8	High-risk plaque	EAT volume indexed to BSA was greater in patients with HRP vs no HRP. EAT volume >62.3 ml/m^2 was associated with the presence of HRP (adj OR 1.83, 95% CI 1.10-3.05 per ml/m^2 EAT p=0.02). Mean EAT attenuation was lower in patients with CT-derived HRP (-88.1 vs -86.9 HU, p=0.008).	Age, female sex, number of CV risk factors, CAC score, presence of ≥50% stenosis

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Tamarappoo et al[38] 2010	EISNER registry	1,777	90	45-64	Ischemia (SPECT)	EAT volume was an independent predictor of myocardial ischemia on SPECT (OR 2.68, 95% CI 1.33-5.41 per doubling of EAT, p=0.006).	Hypertension, dyslipidemia, DM, smoking, family history of CAD, symptomatic, BMI, CAC score
Romijn et al[45] 2015	Patients with suspected CAD	122	61	61±10	Functionally significant CAD (stenosis >90% or FFR ≤0.80)	EAT volume was an independent predictor of functionally significant CAD (OR 4.95, 95% CI 1.31-18.6, p=0.02). EAT volume had no additive diagnostic value above CAC score and risk factors.	Model 1: age, sex, BMI, CAC score Model 2: Hypertension, dyslipidemia, DM, smoking history, CAC score
B. Longitudinal cohort studies							
Nakanishi et al[39] 2011	EISNER registry	375	68	60±8	CAC score change (%)	At 5-year follow-up, EAT volume and % increase in EAT volume/BSA were greater in 'high progressors' (upper tertile of % CAC score progression) vs 'low progressors'. EAT volume increase >15% was associated with the number of new calcified plaques at follow-up (β=3.0, p=0.02).	Hypertension, dyslipidemia, smoking, BMI, baseline CAC score, scan interval time, baseline EAT volume/BSA
Cheng et al[40] 2010	EISNER registry	2,751	79	61±10	MACE	EAT volume was associated with MACE (adj OR 1.74, 95% CI 1.03-2.95 per doubling of EAT) independently of BMI, CAC score, FRS.	Age, hypertension, dyslipidemia, DM, smoking, family history of CAD + BMI, CAC score, FRS
Mahabadi et al[35] 2014	Heinz Nixdorf Recall Study	3,367	47	59±8	CAC progression	EAT volume was independently associated with CAC progression at 5 years in subjects <55 years with BMI ≤40 kg/m^2 and baseline CAC <100, suggesting EAT may promote early atherosclerosis.	Age, sex, SBP, hypertension treatment, LDL-C, HDL-C, lipid treatment, DM, BMI, smoking
Mahabadi et al[36] 2013	Heinz Nixdorf Recall Study	4,093	47	59±8	Non-fatal MI, cardiac death	At median follow-up of 8 years, doubling of EAT volume was associated with a 1.5-fold increased risk of coronary events (95% CI 1.09-2.19, p=0.01), adjusted for risk factors and CAC score.	Age, sex, BP, hypertension treatment, LDL-C, HDL-C, lipid treatment, DM, smoking, WC, CAC score
Goeller et al[29] 2018	EISNER study	456	64	60±8	MACE CAC score	EAT volume ≥125 cm^3 was predictive of MACE, adjusted for ASCVD risk score and CAC score (HR 4.6, 95% CI 1.6-13.1, p=0.004) at 13.5 years. When added to the model, EAT attenuation was associated with MACE (HR 0.8, 95% CI 0.7-0.98, p=0.029), and the association of EAT volume was no longer significant.	ASCVD risk score (age, sex, race, BP, hypertension treatment, TC, HDL-C, LDL-C, lipid treatment, DM, smoking status, aspirin therapy), CAC score
Eisenberg et al[41] 2020	EISNER study	2,068	59	56±9	MACE	EAT volume and attenuation were associated with MACE at 14 years (HR 1.35, 95% CI 1.07-1.68 per doubling; and HR 0.83, 95% CI 0.72-0.96 per 5 HU increase, respectively, both p<0.01).	ASCVD risk score, CAC score, BMI

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; CRP, C-reactive protein; CT, computed tomography; DM, diabetes mellitus; EAT, epicardial adipose tissue; EISNER, early identification of subclinical atherosclerosis by noninvasive imaging research; FFR, fractional flow reserve; FRS, Framingham risk score; HDL-C, high density lipoprotein cholesterol; HRP, high-risk plaque; HU, Hounsfield units; IFG, impaired fasting glucose; LDL-C, low density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MESA, multi-ethnic study of atherosclerosis; PET, positron emission tomography; ROMICAT, rule out myocardial infarction using computer assisted tomography; SBP, systolic blood pressure; SPECT, single-photon emission computed tomography; TC, total cholesterol; TG, triglycerides; VAT, visceral adipose tissue; WC, waist circumference.

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*Low CAC < 100 AU, High CAC ≥ 100 AU, Low EAT volume < 113 cm³, High EAT volume ≥ 113 cm³

Figure 3. Risk of future major adverse cardiovascular events (MACE) increased with an increase in epicardial adipose tissue (EAT) volume (cm3) and coronary artery calcium (CAC; Agatston units [AU]). Subjects were stratified by CAC and EAT: low CAC <100 AU, high CAC ≥100 AU, low EAT <113 cm3, high EAT ≥113 cm3. MACE risk was highest in subjects with both high EAT and high CAC. Reproduced with permission from Eisenberg et al. [40]

95% CI 1.07-1.68 per doubling; and HR 0.83, 95% CI 0.72-0.96 per 5 HU increase, respectively, both p<0.01), independently of baseline atherosclerotic cardiovascular disease (ASCVD) risk score and CAC score[41] (Figure 3). In a separate EISNER substudy of 1,069 subjects, the integration of deep learning-based EAT measures with other non-contrast CT parameters and serum biomarkers in a machine learning model provided accurate long-term prediction of MI or cardiac death (area under the receiver-operating curve [AUC] 0.81), outperforming the CAC score (AUC 0.75) and the ASCVD risk score (AUC 0.74; both p=0.02).[49]

Detecting PCAT inflammation on CT imaging

A recent seminal study by Antonopoulos et al.[4] linked histopathologic PCAT inflammation to CT attenuation. In patients undergoing coronary artery bypass grafting, PCAT and non-PCAT EAT samples were biopsied from around the proximal right coronary artery (RCA) for histology, gene expression studies, and CT imaging. The investigators showed that exposure of PCAT to pro-inflammatory cytokines inhibited local adipogenesis, resulting in numerous smaller adipocytes with fewer intracellular lipid droplets. On ex vivo CT scans of adipose tissue explants and in vivo coronary CT angiography (CCTA), there was an inverse association of PCAT attenuation with histological adipocyte size and degree of adipocyte differentiation; with higher PCAT attenuation (less negative HU) reflecting smaller adipocytes with a lower lipid content. Further, there was a gradient of increasing adipocyte size and decreasing adipose tissue attenuation (more negative HU) with an increasing radial distance from the coronary artery wall, supporting the notion that PCAT and non-PCAT EAT are phenotypically different.

In this study, PCAT was quantified from CCTA using research software, with the RCA used as the representative vessel due to the abundance of surrounding adipose tissue; a designated proximal 40 mm-long segment was chosen for analysis. Adipose tissue was defined as all voxels with CT attenuation between -190 HU and -30 HU, and PCAT attenuation was defined as the mean attenuation of all adipose tissue-containing voxels within a radial distance from the outer coronary artery wall equal to the average diameter of the vessel. The authors found PCAT CT attenuation around the proximal RCA to be higher in patients with CAD than those without CAD, and to be elevated in the presence of obstructive stenosis anywhere in the coronary tree. PCAT attenuation also correlated with the underlying fibrous plaque volume in the RCA (r=0.32, p<0.05). Hence, this bench-to-bedside study demonstrated the "inside-to-outside" effect of atherosclerosis and vascular inflammation on PCAT, and CCTA-derived PCAT attenuation has since emerged as an imaging biomarker of coronary inflammation.

The same investigators then evaluated the prognostic utility of PCAT attenuation measured around the proximal RCA. In a post hoc-analysis of 3,912 patients who underwent clinically indicated CCTA,[50] patients were stratified as having 'high' and 'low' PCAT attenuation based on an optimum cutoff of -70.1 HU. In the validation cohort of 2,040 patients, a high PCAT attenuation (≥-70.1 HU) was associated with increased risk of cardiac death (HR 5.62, p<0.0001) at a median follow-up of 54 months, following adjustment for age, sex, risk factors, extent of CAD, and high-risk plaque features. When added to a risk prediction model with the same variables, a high PCAT attenuation had incremental value for predicting cardiac death (AUC 0.76 vs. 0.84, p<0.01).

PCAT attenuation in different stages of CAD

At a patient level, PCAT attenuation can distinguish different stages of CAD. In a cross-sectional study, Lin et al.[51] demonstrated PCAT attenuation surrounding the proximal RCA to be significantly higher in prospectively enrolled patients with acute MI (-82.3±5.5 HU) compared to patients with stable CAD (-90.6±5.7 HU, p<0.001) and controls with no CAD (-95.8±6.2 HU, p<0.001) (Figure 4). Moreover, PCAT attenuation was significantly increased in stable CAD patients over controls (P = 0.01). The association of PCAT attenuation with stage of CAD was independent of age, gender, cardiovascular risk factors, epicardial adipose tissue volume, and CCTA-derived quantitative plaque burden. No interaction was observed for clinical presentation (MI vs. stable CAD) and plaque burden on PCAT attenuation.

Association of PCAT attenuation with plaque morphology

Goeller et al.[52] examined the association of PCAT attenuation with high-risk plaque on a per-lesion basis. In a retrospective case-control study, patients with acute coronary syndrome who underwent CCTA prior to invasive angiography were matched to controls with stable CAD. PCAT attenuation was higher around culprit lesions compared to non-culprit lesions (-69.1 HU vs. -74.8 HU, p=0.01) in patients with acute coronary syndrome and the highest-grade stenosis lesions of controls

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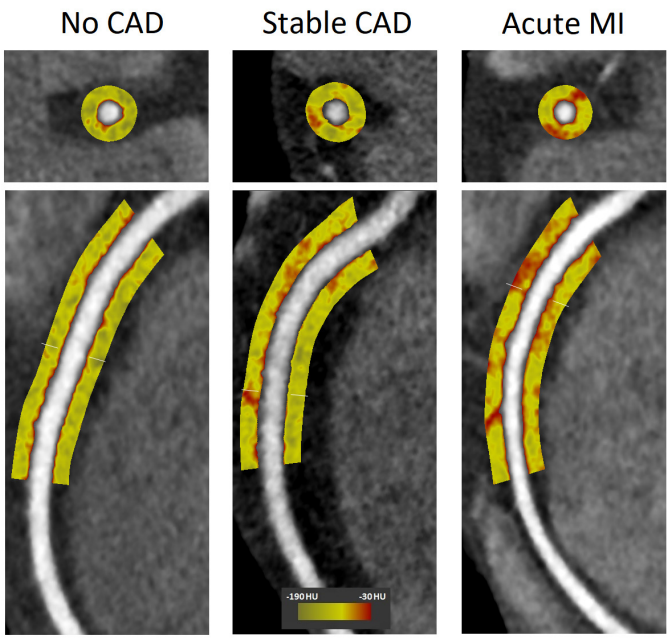


Figure 4. Pericoronary adipose tissue (PCAT) attenuation maps on coronary computed tomography angiography in case examples of patients with no coronary artery disease (CAD) (-105.4 Hounsfield Units [HU]), stable CAD (-88.2 HU), and acute myocardial infarction (MI) (-71.6 HU). Upper panels show cross sections of PCAT around the proximal 10-50 mm of the right coronary artery and lower panels show curved multi-planar views. Reproduced with permission from Lin et al.[51]

(-69.1 HU vs. -76.4 HU, p=0.01) (Figure 5). In patients with acute coronary syndrome, PCAT attenuation correlated only with the burden of intermediate-attenuation (30 to 130 HU) non-calcified plaque (NCP; r = 0.393, p=0.001).

Subsequently, Kwiecinski et al.[53] studied the relationship between CCTA-derived PCAT attenuation and coronary plaque uptake of the radiotracer ^{18}F-sodium fluoride (^{18}F-NaF) on positron emission tomography—a marker of active microcalcification and hence plaque metabolic activity. In 41 patients with high-risk plaque identified on CCTA, 23 had coronary ^{18}F-NaF uptake. Lesions with^{18}F-NaF uptake exhibited a higher surrounding PCAT CT attenuation compared to those without^{18}F-NaF uptake (-73 HU vs -86 HU, p<0.001). There was a moderate correlation between PCAT attenuation and PET tracer uptake as measured by the target-to-background ratio (r = 0.68, p<0.001).

Temporal changes in PCAT attenuation

Goeller et al.[54] evaluated PCAT attenuation around the proximal RCA, the most standardized patient-level measurement, in relation to plaque changes on serial CCTA in a stable CAD cohort over a median of 3.4 years. Progression of quantitative NCP burden was associated with an increase in PCAT attenuation, and regression of NCP burden was associated with a decrease in PCAT attenuation (4.4 vs. -2.78 HU, p<0.0001). Changes in PCAT attenuation correlated with changes in the burden of NCP and low-density NCP—the inflammatory plaque components; however, PCAT attenuation did not correlate with calcified

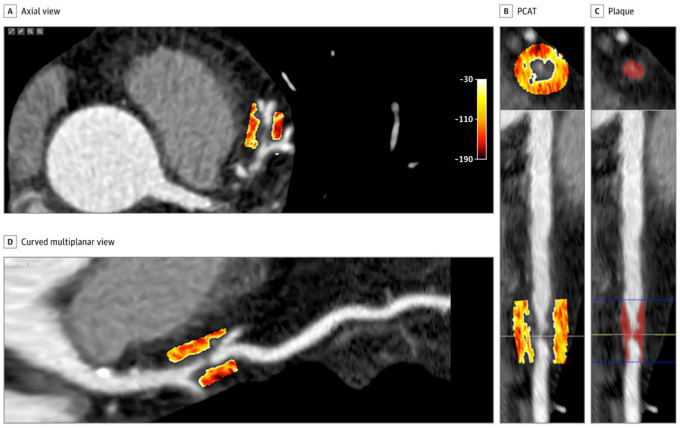


Figure 5. Quantification of coronary plaque and pericoronary adipose tissue (PCAT) attenuation on computed tomography angiography of a culprit lesion in the middle left anterior descending coronary artery. (A) Axial view and range of Hounsfield units to detect PCAT. (B) Cross-section and straightened views of measured PCAT. (C) Cross-section and straightened views of measured plaque (noncalcified plaque in red). (D) Curved multi-planar view of PCAT measure. Reproduced with permission from Goeller et al.[52]

plaque burden. A high baseline PCAT attenuation (≥-75 HU) independently predicted NCP progression.

Elnabawi et al.[55] used PCAT attenuation around the proximal RCA to monitor the response of the local pericoronary microenvironment to systemic anti-inflammatory therapy. In a cohort of patients with psoriasis who underwent serial CCTA, biologic therapy was associated with a significant decrease in PCAT attenuation at 1-year follow-up (-71.2 vs -76.1 HU, p<0.001). Conversely, no change in PCAT attenuation was observed in patients not receiving biologic therapy. These findings were independent of the presence of CAD and consistent across different biologic agents.

Clinical Implications

EAT volume and attenuation provide important information on cardiometabolic risk, and can now be quantified rapidly and automatically from routine CAC scoring CT. Although currently a research tool, deep learning-based EAT measures have the potential for implementation into clinical workflow, without additional radiation exposure to the patient or increased workload for the physician. Studies have shown that EAT is a dynamic fat depot whose relationship with CAD may change over the natural history of the disease in response to signals from the coronary vasculature and systemic circulation, as well as lifestyle and pharmacological interventions.[56] Indeed, a significant reduction in EAT quantity has been demonstrated in response to bariatric-surgery induced weight loss,[57] low-calorie diet[58], aerobic exercise,[59] and intensive statin therapy.[60]

PCAT attenuation is a promising imaging biomarker of coronary inflammation, and its measurement from coronary CT angiography enables the simultaneous evaluation of its association with coronary plaque burden and morphology. The ability to reliably detect inflamed coronary arteries has important treatment implications, especially in patients with

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stable CAD who have a high residual inflammatory risk despite statin therapy. Recent evidence has shown both novel[61] and established[62] anti-inflammatory agents to substantially reduce the rate of recurrent cardiac events in this subgroup. PCAT attenuation could potentially identify individuals with a high coronary inflammatory burden who may benefit from these targeted therapies in addition to aggressive secondary prevention. This biomarker may also be used to track the per-patient response to such treatments or monitor the coronary inflammatory status following acute coronary syndrome, and randomized studies are needed in future.

Conclusion

EAT modulates coronary arterial function in the healthy state; however, in obesity, this adipose tissue depot undergoes adverse remodeling and shifts to a pro-inflammatory and atherogenic phenotype. The quantification of EAT volume and attenuation from non-contrast cardiac CT provides valuable information on cardiometabolic risk. PCAT, the component of EAT which directly encases the coronary vasculature, has recently emerged as a sensor of coronary inflammation. PCAT attenuation on coronary CT angiography associates with plaque morphology, stage of CAD, and risk of future cardiac events. EAT and PCAT measures have incremental and complementary prognostic value over above current risk assessment based on clinical and CT imaging parameters.

Declaration of competing interests

Nothing to declare.

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