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## IMAGING PATIENTS WITH STABLE CHEST PAIN SPECIAL FEATURE: REVIEW ARTICLE

# Novel imaging biomarkers: epicardial adipose tissue evaluation

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**ABSTRACT**

Epicardial adipose tissue (EAT) is a metabolically activated beige adipose tissue, non-homogeneously surrounding the myocardium. Physiologically, EAT regulates toxic fatty acids, protects the coronary arteries against mechanical strain, regulates proinflammatory cytokines, stimulates the production of nitric oxide, reduces oxidative stress, and works as a thermogenic source against hypothermia. Conversely, EAT has pathologic paracrine interactions with the surrounded vessels, and might favour the onset of atrial fibrillation. In addition, initial atherosclerotic lesions can promote inflammation and trigger the EAT production of cytokines increasing vascular inflammation, which, in turn, may help the development of collateral vessels but also of self-stimulating, dysregulated inflammatory process, increasing coronary artery disease severity. Variations in EAT were also linked to metabolic syndrome. Echocardiography first estimated EAT measuring its thickness on the free wall of the right ventricle but does not allow accurate volumetric EAT estimates. Cardiac CT (CCT) and cardiac MR (CMR) allow for three-dimensional EAT estimates, the former showing higher spatial resolution and reproducibility but being limited by radiation exposure and long segmentation times, the latter being radiation-free but limited by lower spatial resolution and reproducibility, higher cost, and difficulties for obese patients. EAT radiodensity at CCT could to be related to underlying metabolic processes. The correlation between EAT and response to certain pharmacological therapies has also been investigated, showing promising results. In the future, semi-automatic or fully automatic techniques, machine/deep-learning methods, if validated, will facilitate research for various EAT measures and may find a place in CCT/CMR reporting.

## INTRODUCTION

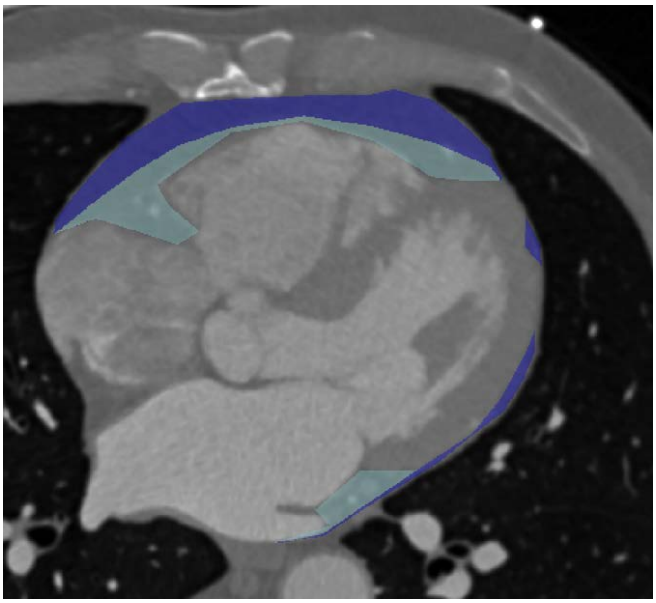
Epicardial adipose tissue (EAT) is the adipose tissue that lies immediately around the myocardium. EAT is in direct contact with both the myocardium itself and the coronary vessels, and it is surrounded by the visceral pericardium.[1]

Since the early 2000s, EAT has become the object of many studies concerning biomarkers of cardiovascular risk, as its volume has been shown to be correlated to the incidence of pathologies such as metabolic syndrome, coronary atherosclerosis, or atrial fibrillation (AF).[2] In recent years, interest has shifted onto a precise EAT quantification, to potentially establish it as a reliable and non-invasive biomarker for cardiovascular risk.[3]

### Epicardial adipose tissue anatomy and physiology

EAT is non-homogeneously distributed around the heart. Most of it lies at the cardiac base and apex, in the cardiac grooves and around the coronary arteries, and it is thicker around the right ventricle than around the left ventricle.[4] Additional adipose tissue surrounding the heart, the so-called paracardial adipose tissue (PAT), can be found outside the parietal pericardium. The whole pericardial fat is defined as the sum of EAT and PAT.[5] Figure 1 shows the respective localizations of these two fat deposits on a contrast-enhanced cardiac CT (CCT) scan.

Figure 1. Segmentation of EAT in light blue, and PAT in dark blue on a contrast-enhanced cardiac CT scan in a 64-year-old female patient. EAT, epicardial adipose tissue; PAT, paracardial adipose tissue.



EAT mass has been found to account for around 15–20% of the total cardiac mass, weighing around 50 g,[6] for an average volume around 55 $cm^3$. The correlation between an increased amount of EAT and visceral fat with obesity is yet under discussion.[7,8] However, recent works have observed a causal link between obesity and accumulation and inflammation of EAT, potentially leading to coronary artery disease (CAD) or AF.[9]

As opposed to PAT, EAT originates from the splanchnopleuric mesoderm, as do mesenteric and omental fat.[10] Physiologically, EAT has been shown to release free fatty acids, which are the main metabolites of cardiomyocytes, to keep toxic fatty acids at a healthy level, and it has a protective role for the coronary arteries against mechanical strain.[4] In physiological conditions, EAT participates in the regulation of inflammation, regulating levels of pro-inflammatory cytokines, stimulates the production of nitric oxide, and reduces oxidative stress.[11]

Moreover, EAT is composed of beige adipose tissue, which represents a conversion of white into brown adipose tissue following hormonal or temperature signals.[12,13] A study by Sacks et al[14] has revealed EAT as a thermogenic source for defending the myocardium and coronary vessels against hypothermia, using uncoupling protein-1 production as a marker. Indeed, uncoupling protein-1 is typically highly expressed in the beige adipose tissue, as it allows the production of heat by uncoupling electron transport from the synthesis of adenosine triphosphate, thus releasing the energy which would have been used for such process in the form of thermic energy.[13] The beiging of white adipose tissue may be regarded as a metabolic activation, and thus as protective against metabolic disease.[15] Moreover, an active thermogenic adipose tissue helps regulate circulating branched-chain amino acids, thus protecting individuals against obesity and diabetes.[16]

On the other hand, EAT, along with perivascular adipose tissue in general, has also been hypothesized to play a key role in the pathological development of cardiovascular disease, as it represents a metabolically active tissue with paracrine interactions with the surrounded vessels.[17] Subjects with related pathologies such as hypertrophic cardiomyopathy or CAD have been found to have higher volumes of EAT than average.[6] Increased EAT volume could be associated with a disruption of its physiological activity of regulating fatty acid levels around the heart.[18] In fact, an excessive uptake of fatty acids by EAT might interfere with myocardial metabolism and with the functionality of the cardiac cycle, leading to arrhythmic complications as, for instance, the insurgence of AF.[19]

Moreover, EAT, as visceral adipose tissue, can be a source of proinflammatory cytokines. Even before cardiovascular pathology is overt and symptomatic, atherosclerotic lesions from CAD at an initial stage can promote inflammation and trigger the production from EAT of cytokines such as interleukin-1β, interleukin-6, interleukin-6 soluble receptor and tumour necrosis factor α.[20] This process promotes an increase in EAT volume and an amplification of vascular inflammation. This, in turn, on one side may help neoangiogenesis and the development of collateral vessels, on the other side, may lead to a self-stimulating, dysregulated inflammatory process and the increase in severity of CAD.[21] By means of the same mechanisms, an increase in EAT and its dysfunction may promote the onset of CAD.[5] Both EAT volume and radiodensity were recently found to be associated with serum inflammatory markers, subclinical atherosclerosis and major cardiac events.[22] EAT inflammation might play a role also in the development of AF.[23] Talman et al[5] provide a comprehensive description and depiction of the pathophysiological role of EAT in their review.

Thus, an alteration in EAT, such as an increase in volume or thickness, or change in density, could be regarded as a marker of cardiovascular risk (a preclinical stage of cardiovascular disease), as also supported by the finding of modifications in EAT transcriptome in presence of severe CAD.[24]

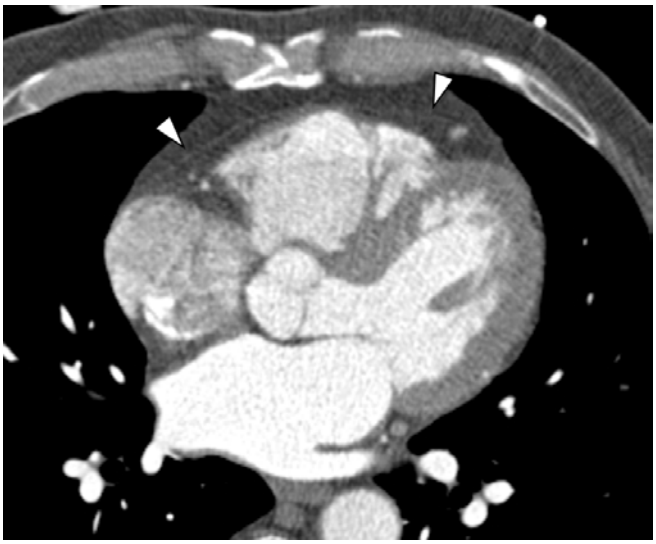
More generally, research has also linked variations in EAT with the presence of metabolic syndrome, a condition characterized by disruption of the physiological pathways regulating inflammation, given the similarities between its metabolic asset and that of visceral adipose tissue.[8]

## IMAGING TECHNIQUES

Given the potential role of EAT in defining cardiovascular risk, different non-invasive techniques have been utilized in the attempts to provide a reliable quantification of its extent. The main methods for assessing EAT have so far been echocardiography, CCT, and cardiac MR (CMR).

At echocardiography, EAT appears as a hyperechoic area situated between the ventricular wall, more prominent around the free wall of the right ventricle, and the parietal pericardium.[25] Echocardiography has provided the first estimates of EAT by allowing to measure its thickness on the free wall of the right

Figure 2. Contrast-enhanced cardiac CT scan of a 64-year-old female patient depicting the thin pericardium (white arrowheads). The epicardial adipose tissue is immediately internal to the pericardium.



ventricle, where it is usually more prominent. EAT echocardiographic thickness measurements are usually performed perpendicularly to the myocardial wall in parasternal view, and long and short axis views.[26] Normal values are around 5 mm: Nelson et al[27] found a mean value of 4.7 ± 1.5 in asymptomatic subjects. In fact, some works suggest a cut-off value of 5 mm for EAT thickness to identify individuals at higher cardiovascular risk.[28,29] Echocardiography is relatively inexpensive, widely available, and it does not bear limiting contraindications or radiation exposure. However, it presents important limitations such as the fact that two-dimensional echocardiography does not allow accurate volumetric EAT estimate, and its high dependence on the experience of the operator.[30,31] Some authors have reported confusing pericardial effusion with EAT is sometimes possible.[31]

Alternatively, CCT is a volumetric technique, which allows for three-dimensional EAT estimates. EAT may be visible on CCT scans as a hypodense layer, with a density usually ranging −190 to −30 Hounsfield units,[3] comprised between the myocardium and the visceral pericardium (Figure 2). EAT may be measured during CCT post-processing, not needing specific acquisitions. It can be quantified from different scans, most often either unenhanced scans for calcium scoring, or CCT angiographic scans, given that the EAT and pericardium are similarly visible in both, especially during the short time interval intercurrent between contrast administration and angiographic acquisition.[32,33] Therefore, adding EAT volume estimate to the output of a CCT report could provide an additional risk estimate for cardiovascular disease, without adding to patient discomfort and radiation exposure.

Studies have reported a high reproducibility of EAT quantification on CCT scans.[34] However, standard electrocardiographically gated CCT, if used only for obtaining EAT estimates, could be questioned due to the ionizing radiation exposure, even though recently, Nagayama et al[35] proposed the use of non-gated CCT to quantify EAT volumes, achieving excellent concordance with gated CCT with reduced radiation dose. Another limitation of EAT quantification by CCT angiography stems from long segmentation times, as a precise measurement is best performed on numerous small slice-thickness images, strongly limiting an integration into routine clinical practice. However, CCT allows the quantification of EAT X-ray radiodensity, which may be a biomarker of metabolic activity of EAT, possibly related to cardiovascular or metabolic disease.[36] EAT volume has also been assessed on positron emission tomography/CCT (PET/CCT), to associate anatomical data to functional information.[37] While to the best of our knowledge no meta-analysis has yet defined normal and pathological values for CCT-derived EAT volume and density, one study by Spearman et al reported values of CCT-derived EAT above 125 ml to be indicators of cardiac pathology.[38]

CMR is, as of now, regarded as the easiest non-invasive approach for estimating the EAT volume mass.[39] Not unlike CCT, CMR is a volumetric technique that can provide highly reproducible, three-dimensional EAT measurements.[40] EAT can be visualized on images obtained with different CMR sequences, however it has been often quantified on cine sequences which are performed in almost all patients undergoing CMR[41] (Figure 3). On cine bright-blood steady-state free-precession sequences, EAT may be visualized as a hyperintense, light grey area comprised between the hypointense myocardium and visceral pericardium (Figure 4). CMR is radiation-free and EAT estimation through CMR does not require the use of gadolinium-based contrast agents, whose safety has become increasingly debated during the last years.[42]

Therefore, CMR can be considered a safe technique, provided that MRI contraindications are absent, such as marked obesity, claustrophobia or MR-unsafe devices.[43] In addition, we should consider drawbacks of CMR such as high cost, relatively long examination times, and limited availability. Obesity is important when EAT quantification for the estimation of cardiovascular risk is under consideration, as obese people are a growing population which could represent an interesting target in this context. Moreover, CMR scans generally have greater slice thicknesses than CCT scans, limiting the accuracy of EAT volume segmentation performed. In fact, to visualize the pericardium on the inferior slices of CMR scans is often challenging, as opposed to CCT scans.

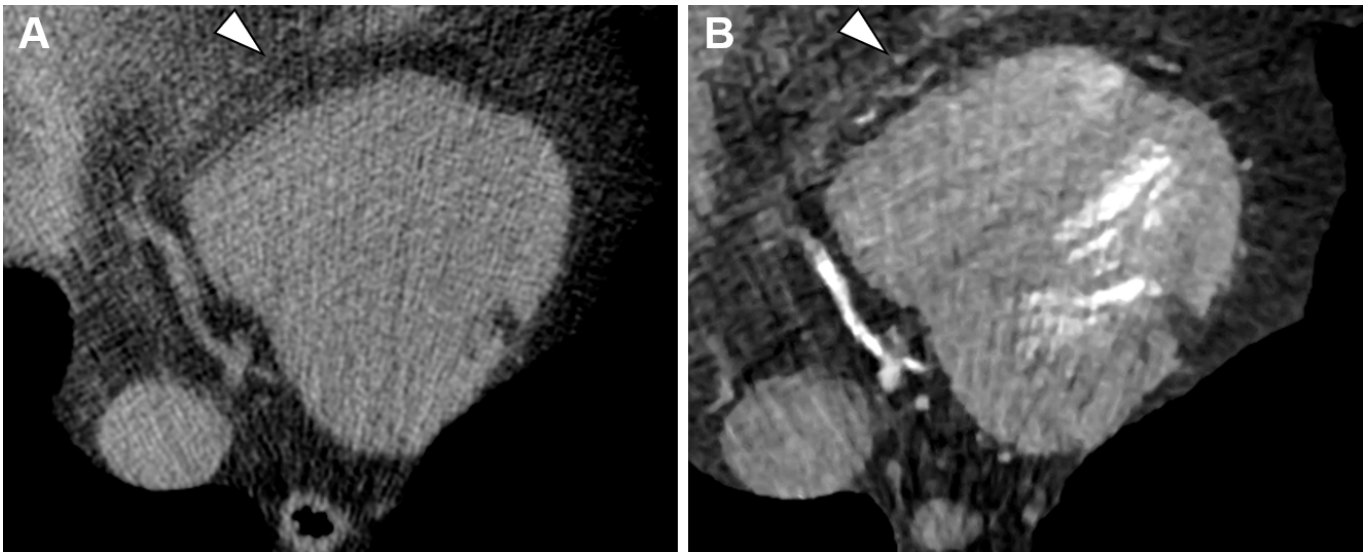
A comparison between the main imaging techniques for the evaluation of EAT is outlined in Table 1.

## Epicardial adipose tissue as an imaging biomarker: actual evidence and open questions

Several studies have investigated the potential role of EAT as an imaging biomarker of various cardiovascular pathologies. EAT has been observed to be an independent risk factor for cardiovascular events in both healthy subjects and in patients with pre-existing diseases. It has been shown to directly correlate to the severity of cardiovascular pathologies, such as CAD, and to respond to metabolic changes originating from some pharmacological therapies.

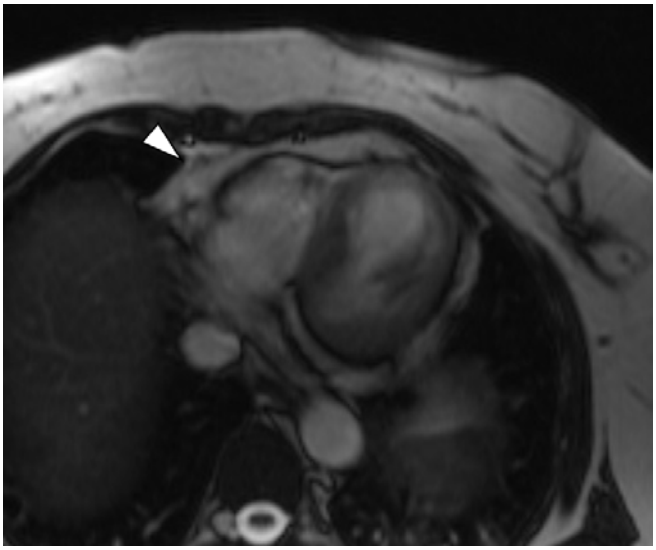
Longitudinal studies, with sample size ranging up to over 4000 subjects, have shown that EAT volume calculated from CCT or

Figure 3. Unenhanced (A) and arterial phase contrast-enhanced (B) cardiac computed tomography scans of a 52-year-old male patient showing the pericardium(white arrowheads), visible in both images as a thin, hyperdense line. This caseis an example of the difficulties in segmenting the epicardial adipose tissue.




CMR may help predict the onset of arrhythmic complications such as AF. In 2010, a study by Thanassoulis et al,[44] part of the Framingham heart study, identified a strong positive independent association between EAT and prevalent AF, promoting a growing interest in EAT as imaging biomarker. In 2014, a study by Mahabadi et al,[45] part of the Heinz Nixdorf Recall study assessing novel cardiovascular risk factors in healthy subjects, also found a strong correlation between increased EAT and the incidence of AF. However, these authors also propose the hypothesis of the real predictor being the atrial size, as atrial size also bore the same correlation with AF incidence, and indexing EAT for atrial size led to a loss of its risk prediction potential. In this regard, in 2016, a meta-analysis by Zhu et al[46] has divided patients for having paroxysmal or persistent AF, revealing that the role of EAT might differ with regards to the type of AF and underlying remodelling. This observation was also confirmed by other studies, investigating the characteristics of EAT in these two different patient groups.[47] Thus, further studies are needed to clarify the role of EAT as an independent predictor of the insurgence of different types of AF.

Figure 4. Cardiac magnetic resonance true fast imaging with steady-state free precession sequence in a 64-year-old female patient, showing the pericardium (white arrowhead) as a thin, just visible, hypointense line surrounded by hyperintense adipose tissue on both sides.



Concerning CAD, one study by Bastarrika et al[48] has observed that EAT, especially when quantified from CCT as opposed to two-dimensional measurements obtained from echocardiography, bears a positive correlation to the extent of CAD, assessed by both calcium scoring and stenosis severity. A study by Alexopoulos et al[49] from 2010 found increased EAT in patients with obstructive CAD or non-calcified plaques, correlating EAT to high-risk CAD. In 2014, a study by Mahabadi et al,[50] also part of the Heinz Nixdorf Recall study, found that the volume of EAT was associated to the progression of calcium scores, especially in younger subjects with low calcium scores, thus presenting it as a potential early predictor of CAD. In 2017, Fuller et al[51] identified EAT as a potential risk predictor for sudden death related to CAD, from the finding that subjects with CAD who died from cardiac-related sudden death had significantly higher EAT volumes than those who died from other causes. One systematic review by Nerlekar et al[52] reported that an increased EAT volume can be associated to the presence of high-risk plaques, though the *primum movens* of this process has yet to be clarified. Another review by Spearman et al[38] suggested that EAT provided incremental value for risk assessment over calcium scoring alone. Overall, the role of EAT as a predictor of CAD-related risk, being also fully supported by studies conducted on the Framingham cohort,[53] is more recognized than that related to AF.

Table 1. Comparison among the main imaging techniques for the evaluation of epicardial adipose tissue.

| | Advantages | Disadvantages |
|---|---|---|
| **Echocardiography** | Readily available, inexpensive, quick | Highly operator-dependent, no volumetric measurements possible, difficult in patients who have motion or breathing issues |
| **CCT** | High definition, volumetric measurements possible, best visibility of the pericardium | Long segmentation times at low slice thickness when analysing contrast-enhanced series, ionizing radiations |
| **CMR** | Absence of ionizing radiations, volumetric measurements possible, allows quantification of attenuation | Expensive, not always available, long scan times, pericardium hard to visualize especially at lower sections of the heart, contraindicated in some patients |

CCT, cardiac CT; CMR, cardiac MR.

Another important topic is the possible use of the radiodensity of EAT at CCT as a potential biomarker. Indeed, EAT radiodensity might differ according to underlying inflammation or due to the different levels of metabolic activity of adipose tissue at different browning degrees.[36] In 2017, one study by Antonopoulos et al[54] quantified fat radiodensity in epicardial, thoracic, and subcutaneous adipose tissue, observing that radiodensity could help in the investigation of the characteristics of different adipose tissues. Browning of EAT is an alternative explanation and is supported by a recent study showing decreased brown fat related genes in patients with acute coronary syndrome compared with stable CAD or non-CAD.[55] Marwan et al[56] found a lower radiodensity of pericoronary adipose tissue in normal segments compared to pathologic ones, however, their finding might also have been affected by the presence of contrast media, which may have a higher distribution in the pericoronary fat that surrounds atherosclerotic segments. Another possible explanation for the variations in EAT radiodensity in presence of cardiac pathology could be found in the higher metabolic activity of segments with CAD, due to underlying inflammation.[57] Conversely, Franssens et al[58] found a lower EAT radiodensity in patients at higher risk of cardiovascular disease, and Hell et al[59] observed decreased EAT density in patients with higher EAT volumes, body mass index, and a family history positive for CAD. Another study by Balcer et al[60] did not find EAT radiodensity differences between segments with or without atherosclerotic lesions in patients with acute myocardial infarction. In a recent study, Goeller et al[22] found a strong association between EAT radiodensity and major adverse cardiac events. An increase in EAT radiodensity has also been linked to the presence of myocardial infarction with nonobstructive coronary arteries, and Tako-Tsubo syndrome.[61]

The correlation between EAT and response to certain pharmacological therapies has also been investigated. One study by Kang et al[62] found an increased EAT thickness in CAD patients as a predictor of the insurgence of statin-associated diabetes mellitus. Moreover, statins have been observed to reduce EAT radiodensity, and this reduction can be associated to a decrease in EAT metabolic activity.[36] This process, which may be found also in other brown adipose tissue deposits, might potentially help explain the pathway between statin therapy and the development of diabetes, as statins inhibit the browning of fat, and have been linked to EAT regression.[63–65] These findings are well in agreement with the fact that treatment with statins lowers risk of CAD, albeit bearing the risk of insurgence of diabetes.[66] One work by Ko et al,[67] conducted in patients undergoing haemodialysis treated with different drugs, found a lack of EAT increase during the treatment with sevelamer, possibly due to its anti-inflammatory effect.

The association of metabolic information to anatomical data stemming from PET/CCT has led to yet debateable findings. A higher metabolic activity has been observed by Mazurek et al[68] in EAT as opposed to other fat deposits, in particular white adipose tissue. While one possible interpretation for this finding is that the increased uptake was secondary to inflammation in adipose tissue,[69] the absence of significant differences in EAT between patients with or without CAD contradicts this explanation. The higher uptake of EAT compared to other deposits could be due to the higher metabolic activity of brown adipose tissue compared to white.[36]

## FUTURE PERSPECTIVES

Methods allowing an automatic and reliable EAT segmentation gained recently a growing attention, as they would permit to integration of EAT estimation in routine practice. In this regard, the target technique for EAT segmentation would be unenhanced, ECG-gated CCT, which is already performed in subjects for the evaluation of calcium scoring, so to theoretically obtain two independent risk biomarkers from only one scan.[70,71] CMR would find its main use on patients who already undergo examinations for clinical indications, that however do not represent the population at higher cardiovascular risk related to CAD. Especially on newer scanners, radiation exposure from scans for calcium scoring have proven to be extremely low, thus overcoming the main limitation of CCT.[72] However, manual quantification of EAT on thin, CCT angiography slices may be highly time-consuming, and would at present not be feasible in routine clinical practice.

Different studies have so far proposed innovative approaches to accelerate EAT segmentation at CCT, ranging from semi-automatic techniques to fully automatic, deep-learning methods. In addition to quickening segmentation times, making EAT quantification fit for clinical practice, the adoption of fully automated segmentation methods would also provide a high reproducibility for EAT volumes.

Nichols et al[32] quantified EAT volume, although calling it "pericardial adipose tissue", with a semi-automatic method on coronary CCT angiographic scans. Their results show a very strong correlation between EAT values obtained by two different readers, albeit with a slight negative bias. A subsequent study by Barbosa et al[73] proposed a semi-automatic method on unenhanced CCT scans,

that bore a maximum interoperator error of around 10%. Goeller et al[22] also used a semi-automatic method, a software named QFAT, to quantify EAT volume and radiodensity when studying such parameters in relation with CAD.

The first fully automatic EAT segmentation method was presented in 2014 by Ding et al[74] who used CCT examinations with 2.5–3 mm of slice thickness, each data set amounting to 50–60 slices. Automatically segmented EAT displayed a very strong correlation ($r$ = 0.96) with EAT volume manually quantified by an expert operator; the segmentation time was under 60 s on a standard computer. However, it also presented difficulties in recognizing the pericardium, especially when segmenting the highest or lowest slices, where the pericardial sac is not always clearly visible. In 2018, Commandeur et al[71] proposed a novel segmentation method employing deep learning techniques. So far, they achieved a high correlation between automatic and manual EAT measurements ($R$ = 0.945), with a non-significant bias (0.12 $cm^3$) at Bland–Altman analysis. However, their method still needs validation on larger cohorts.

## CONCLUSIONS

EAT has emerged as an imaging biomarker especially useful for predicting CAD and its complications. This, along with the recent advances in the development of partially or fully automated methods for EAT segmentation may open road to the possibility of using EAT as a risk predictor in a clinical setting, adding a novel, independent risk biomarker to routine practice and facilitate research which presently is cumbersome to perform.

## CONFLICTS OF INTEREST

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