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Validation of the echocardiographic assessment of epicardial adipose tissue thickness at the Rindfleisch fold for the prediction of coronary artery disease

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Abstract *Background and Aim:* Echocardiography is a promising technique for the assessment of epicardial adipose tissue (EAT). Increased EAT thickness is associated with different cardiac diseases, including; coronary artery disease (CAD). Since several different echocardiographic approaches have been proposed to measure EAT, the identification of a standardized method is needed. We propose the assessment of EAT maximal thickness at the Rindfleisch fold, the reproducibility of this measurement and its correlation with EAT thickness and volume assessed at cardiac magnetic resonance (CMR). Finally, we will test the predictive role of this measurement on the presence of significant CAD.
Methods and Results: In 1061 patients undergoing echocardiography, EAT thickness was measured at the level of the Rindfleisch fold. In 70 patients, we tested the relationship between echo-EAT thickness and EAT thickness and volume assessed at CMR. In 499 patients with suspected CAD, undergoing coronary artery angiography, we tested the predictive value of EAT on the presence of significant CAD.

Echo-EAT thickness measurements had an excellent reliability as indicated by the inter-observer (ICC:0.97; 95% C.I. 0.96 to 0.98) and intra-observer (ICC:0.99; 95% C.I. 0.98 to 0.99) reliability rates. Echo-EAT thickness significantly correlated with CMR-EAT thickness and volume ($p < 0.001$). An EAT thickness value >10 mm discriminated patients with significant CAD at coronary angiography ($p < 0.001$). At multivariable analysis, including demographic data and

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cardiovascular risk factors, EAT thickness was an independent predictor of significant CAD and showed an additive predictive value over common atherosclerotic risk factors.
Conclusions: Echocardiographic assessment of EAT thickness at the level of the Rindfleisch fold represents a simple and trustworthy method. An increased EAT thickness shows an additive predictive value on CAD over common atherosclerotic risk factors, thus suggesting its potential clinical use for CAD risk stratification.

Introduction

Epicardial adipose tissue (EAT) has been proven to be involved to the pathogenesis of several cardiac diseases, including coronary artery disease (CAD) [1–3], aortic stenosis [4], and atrial fibrillation [5–7]. This relationship is independent from obesity and is driven by an excessive EAT accumulation paralleled by a pro-inflammatory EAT phenotype [8]. Nowadays, cardiac magnetic resonance (CMR) represents the gold standard for EAT assessment. However, this technique cannot be routinely used for clinical purposes since the high costs and low availability. Therefore, echocardiographic measurement of EAT should be advised, being echocardiography commonly performed in all patients with or suspected cardiovascular diseases. However, a standardized method for echo-EAT assessment is not available yet. At echocardiography, EAT is described both as an echo-free space and/or a hyperechoic tissue and measured either at end-diastole [1,9] or at end-systole [4,10–12]. Some authors have proposed to measure EAT thickness as the distance between the right ventricular free wall and the parietal pericardium [11]. This approach is in contrast with the true anatomical site of EAT localized between the myocardium and the visceral layer of the pericardium (Fig. 1A). However, it is well known that the echocardiographic identification of visceral pericardium may be difficult, except in the presence of pericardial effusion (Fig. 1B). In this paper, we propose to measure EAT thickness at the level of the fold of Rindfleisch [13], a pericardial recess where the parietal pericardium does not exert a mechanical compression on visceral fat. At this level, it is possible to directly visualize and measure the fat deposit between the visceral layer of the pericardium and the myocardium. In patients with aortic stenosis, we have recently reported [14] that this measure is accurate and reproducible. In the same population, we have also demonstrated that the increase of EAT thickness directly correlates with the levels of EAT-derived inflammatory mediators, thus being expression of an EAT pro-inflammatory phenotype. In the present study, we aim to explore: 1) the reproducibility of our EAT measurement in a large study population of consecutive patients; 2) the correlation between echocardiographic EAT thickness measure with the thickness and volume assessed by CMR; 3) the potential utility of this measurement in the clinical scenario by testing its diagnostic predictive value on the presence of CAD.

Methods

Study population

We consecutively enrolled 1061 patients undergoing transthoracic echocardiography at Federico II University of Naples, Italy. Of these, 588 patients were admitted for the presence of angina and/or signs of inducible myocardial ischemia and referred to coronary angiography to confirm the diagnosis of CAD. We obtained demographic and clinical data before the echo examination. At coronary angiography significant CAD was defined as narrowing of ≥50% in the left main coronary artery and ≥70% in one or several of the major coronary arteries. The EAT echocardiographic measurement proposed in the present study was validated against cardiac magnetic resonance (CMR) in 70 consecutive patients undergoing CMR for clinical purposes. Before CMR study, echocardiographic assessment of EAT was performed and the CMR-EAT thickness and volume were calculated by two independent observers who were unaware of echocardiographic findings, as described below. The local Ethics Committee approved the study protocol. All procedures were performed in accordance with human studies committees. All patients gave written informed consent after receiving an accurate explanation of the study protocol.

Echocardiographic study

A comprehensive echocardiographic examination was performed in all patients using an echocardiographic ultrasound system GE Vivid E9. Standard echocardiographic studies were performed by two independent and experienced cardiologists and intra- and inter-observer reproducibility of EAT measurement were tested offline.

EAT measurement

EAT was visualized in parasternal long-axis view at the level of the fold of Rindfleisch, between the free wall of the right ventricle and the anterior surface of the ascending aorta. To improve image quality, the angle was modified, the depth was reduced, the focus adjusted, and ultrasound beam frequency slightly increased (Fig. 1C). The colorimetric map was then switched into gold (Fig. 1D), thus obtaining a better definition of EAT contours. Once visualized the EAT deposit, the maximum EAT thickness was measured, at end-systole, between the right ventricle wall

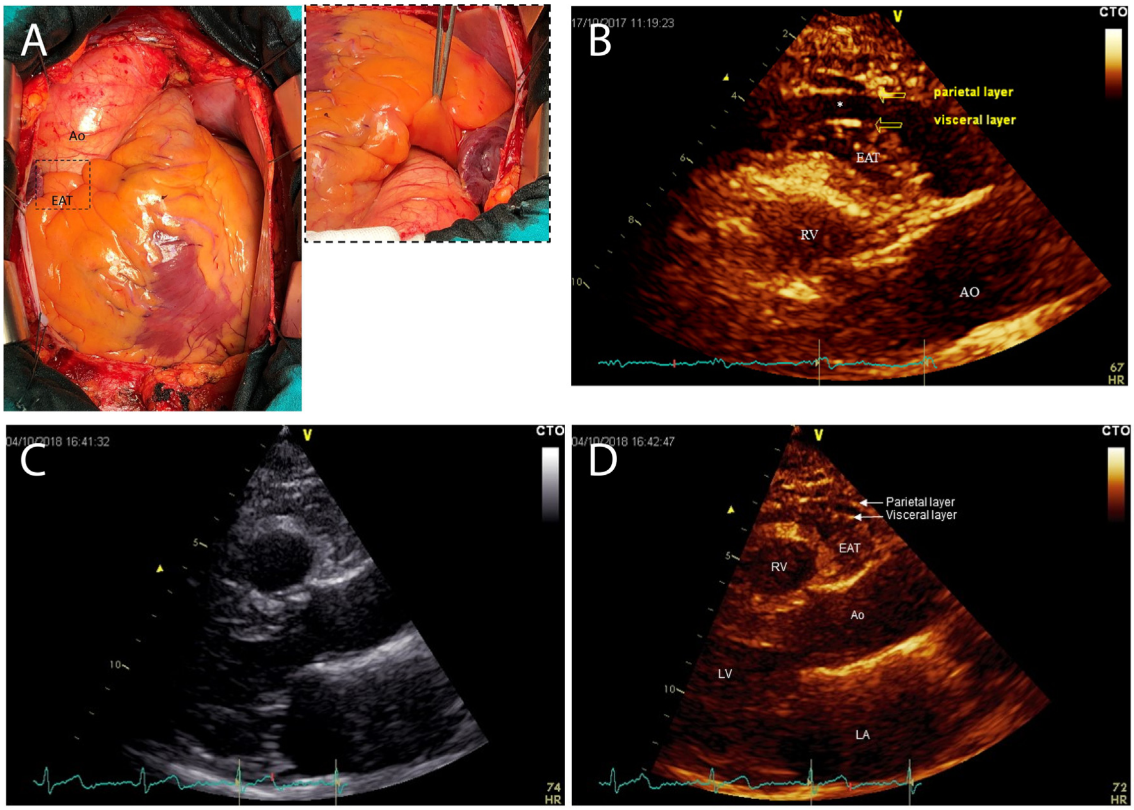

Figure 1 A) Epicardial adipose tissue (EAT) surgical exposure after opening the pericardium. EAT is the fat accumulation between the visceral layer of the pericardium and the myocardium. In the box, the EAT accumulation at the Rindfleisch fold. The right panel clarifies that EAT at this site is adherent to the right ventricle and not to the ascending aorta; B) EAT visualized in parasternal longaxis view at the level of the Rindfleisch fold, between the right ventricle and the ascending aorta. The presence of pericardial effusion allows to clearly distinguish the parietal pericardial layer from the visceral pericardial layer which covers the EAT; C) Standard parasternal long-axis view at end systole. D) Same view of the same patient in figure C. In order to improve EAT visualization, the angle has been modified, the focus adjusted, and the ultrasound beam frequency slightly increased. After these technical adjustments, both parietal and visceral pericardial layers can be clearly visualized, and EAT directly measured. AO, Ascending Aorta; EAT, Epicardial adipose tissue; LA, Left atrium; LV, left ventricle; RV, right ventricle.

and the visceral layer of the pericardium, in three consecutive cardiac cycles.

Cardiovascular magnetic resonance

CMR images were acquired using a 1.5 T whole body scanner (Philips Achieva; Philips Healthcare, The Netherlands) and a 16-channel torso coil. The cardiac imaging protocol included the acquisition of a series of cine steady state free precession (SSFP) images, in short-axis planes as well as in the standard long axis planes for the left ventricle and the right ventricle. FSE T1-weighted or STIR T2 weighted images and post-contrast T1-weighted inversion recovery images were acquired based on the clinical indication. EAT was assessed on the standard short-axis cine SSFP images, normally used for measuring biventricular function. Image analyses were carried on using a commercially available software (CVi42, Circle Cardiovascular Imaging Inc., Calgary, Canada). Areas of EAT were traced on consecutive end-diastolic short-axis images from the mitral valve plane to the last slice containing cardiac adipose tissue, as previously described [15,16]. The border between epicardial and pericardial fat was visually assessed in all slices [17]. For EAT volume determination, the areas traced from all slices were summed and multiplied for the slice thickness plus the slice gap (8 mm + 2 mm respectively) [17,18]. According to the site of EAT echocardiographic assessment, CMR-EAT thickness was measured in long-axis view at the level of Rindfleisch fold.

Statistical analysis

All analyses were performed using the statistical platform R. Numerical variables were described using either mean ± SD or median with interquartile ranges [25th; 75th percentile]. Categorical variables were summarized using absolute frequencies and percentages. Accordingly, comparisons between groups were based on the Student t-test for independent samples, or the Mann–Whitney in case of skewed distribution, and the Chi-square test. Intra- and inter-observer reliability were assessed using the Intra-class Correlation Coefficient (ICC) with the corresponding 95% confidence intervals (95% CI). The correlations between echocardiographic and CMR EAT measurements were computed using the Pearson Correlation Coefficient and the Concordance Correlation Coefficient (CCC). To assess the independent association of EAT measurements with CAD, multivariable logistic regression models were built by adding demographical variables and known risk factors as adjusting factors. Predictive accuracy of EAT measurements was evaluated using the Receiver Operating Characteristic (ROC) analysis and quantified in terms of Area Under the Curve (AUC) with the corresponding 95% CI. All tests were two sided and statistical significance was set at p values less than 0.05.

Results

Of 1061 patients initially enrolled into the study, 11 were excluded due to the low quality of parasternal echocardiographic long axis views. Therefore, the final study population consisted of 1050 patients. Demographic and clinical characteristics are reported in Table 1. In particular, the mean age was 64 years; almost 57% of patients were males and the mean BMI was 27 Kg/m^2. As regard cardiovascular risk factors, 69% of patients were hypertensives, 26% diabetics; 36% had dyslipidemias and 28% of patients were smokers.

EAT thickness measurements had an excellent reliability as indicated by the inter-observer (ICC:0.97; 95% C.I. 0.96 to 0.98) and intra-observer (ICC:0.99; 95% C.I. 0.98 to 0.99) reliability rates. EAT thickness median [25th–75th percentile] value was 11 mm [8; 13]. In the overall population, the distribution of EAT values ranged from 1 to 29 mm (Fig. 2A).

Relationship between echocardiographic and CMR EAT measurements

In 70 patients, we explored the correlation between echocardiographic EAT thickness and EAT volume and thickness assessed by CMR (Fig. 3). Of interest, the correlation between echo-EAT thickness and CMR-EAT volume was statistically significant with a correlation coefficient equal to 0.61 (95% C.I. 0.44 to 0.74; $p < 0.001$). Echo-EAT thickness showed also a significant correlation with the CMR-EAT thickness, both measured at the Rindfleisch fold, with a concordance correlation coefficient of 0.71 (95% C.I. 0.54 to 0.82; $p < 0.001$).

Table 1 Clinical and demographic characteristics of the study population.

	Overall Population (n = 1050)
Age, years (±SD)	63.9 ± 15.5
Male sex, n (%)	597 (56.9)
BMI, kg/m^2 ± SD	27.2 ± 4.6
Hypertension, n (%)	700 (69.1)
Diabetes, n (%)	260 (25.8)
Dyslipidemia, n (%)	360 (35.9)
Smoking habit, n (%)	285 (28.4)
EF, % (±SD)	60.8 ± 10.1
EAT, mm median (25°; 75°percentile)	10 (8; 13)

Predictive value of echocardiographic EAT thickness on the presence of CAD

Among the overall population, 588 patients were referred to elective coronary angiography. Of these, 89 patients had history of previous myocardial infarction and/or elective coronary revascularization. Therefore, in order to test the predictive value of EAT thickness on the presence of CAD, we excluded patients with known history of CAD and analyzed data of the remaining 499 patients. Echocardiographic-EAT measurements were performed before coronary angiography. Three-hundred and forty patients showed significant CAD at coronary angiography. Patients with significant CAD showed higher EAT thickness values than those without significant CAD (EAT: 12 [9–14] vs. 8 [7; 9], $p < 0.001$). At ROC analysis, the cut-off point of EAT that better discriminated the presence of CAD was of 10 mm (Fig. 4A). This value was characterized by a sensitivity of 0.65 and a specificity of 1.0. Furthermore, we tested the independent predictive value of echocardiographic EAT thickness on the presence of CAD by comparing, in terms of AUC, the accuracy of a multivariable logistic regression model (including age, sex, BMI, hypertension, diabetes, smoking, and dyslipidemia) with that of an augmented model including also EAT. The AUC increased significantly ($p < 0.001$) from 0.81 (95% C.I.: 0.77 to 0.85) to 0.88 (95% C.I.: 0.85 to 0.91) (Fig. 4B).

Discussion

In the present study, we propose the echocardiographic measurement of maximal EAT thickness at the level of the Rindfleisch fold. We evaluated the accurateness and reproducibility of such measurement, its correlation with CMR, and its predictive value on the presence of CAD. The main findings of the present study are: 1) the echocardiographic assessment of EAT at the Rindfleisch fold is simple and trustworthy as evidenced by the excellent inter- and intra-observer reliability rates and by the significant correlation with EAT thickness and volume assessed by CMR; 2) increased EAT thickness discriminates patients with significant CAD at coronary angiography; 3) this EAT measurement has an independent predictive value on the presence of CAD that is additional over demographic variables and common atherosclerotic risk factors. Previous anatomic studies [19] have shown that the maximal cardiac visceral fat accumulation occurs on the ventro-lateral edge of the right ventricle with a decrease from the heart base to the apex. This is clearly illustrated in the Fig. 1A showing an intraoperative image of the heart after opening the parietal pericardium. In the present study, we measure echocardiographic EAT thickness at the Rindfleisch fold that is a pericardial recess where the parietal pericardium does not exert a mechanical compression on visceral fat. At this level, the downward curvature of the right ventricle increases the space between the two pericardial layers, thus allowing the EAT expansion (Fig. 1D). This also explains the wide distribution of EAT thickness values found in our study, ranging from a minimum of 1 mm to maximal values of 29 mm (Fig. 2A). This range of values is

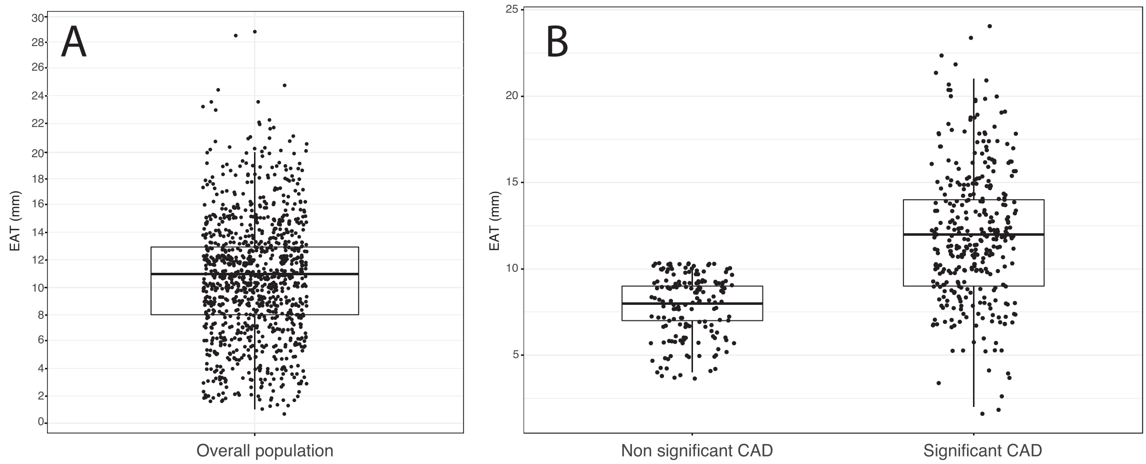

Figure 2 A) Boxplot showing the distribution of EAT thickness values in the overall population; B) Boxplot showing the distribution of EAT thickness values in patients with and without significant CAD at coronary angiography. EAT: Epicardial adipose tissue; CAD: Coronary artery disease.

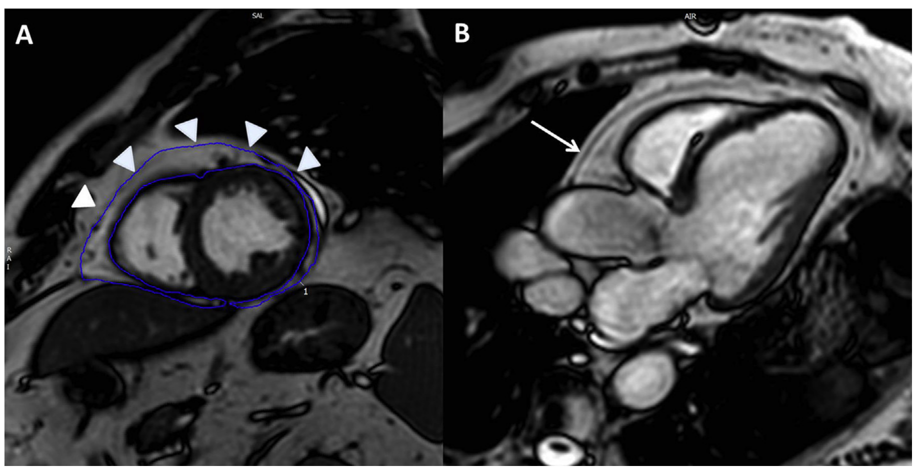

Figure 3 (A) EAT volume quantification by CMR: EAT (blue contour) assessed at end-diastole mid-cavity short-axis view. (B) A 3-chamber CMR view showing the greater EAT accumulation in the Rindfleisch fold (white arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

greater than that described in previous studies evaluating EAT thickness at other sites [3,9], and confirms that, at the level of the Rindfleisch fold, the increase of EAT can be more evident and clearly detected with an excellent reproducibility, as indicated by our results. Importantly, during cardiac surgery, we have also obtained an intra-operative confirmation that the fat found at the level of the Rindfleisch fold is a true visceral fat deposit, adherent to the myocardium and not to the ascending aorta (Fig. 1A). Iacobellis et al. [20], described an occasional abrupt increase in EAT thickness at the downward turn of the free wall of the right ventricle and recommended, in these cases, to measure the largest epicardial fat thickness to the left of the annular plane, as we propose in the present work. However, this measurement has never been validated until now. Although EAT thickness measurement presented in the present paper is the same adopted in our previous investigations conducted in patients affected by aortic stenosis and heart failure, this method was not previously validated since the different aims and the small sample size of our previous studies. EAT volume assessed by CMR is still considered the gold standard to estimate EAT accumulation [21] and CMR-EAT volumetric quantification has been validated ex vivo [16,22]. To our knowledge, this is the first study exploring the accurateness and the reliability of a method for echocardiographic EAT thickness assessment in a large study population of consecutive patients. Furthermore, we validated this method against CMR. Of note, we found a good correlation between echocardiographic EAT thickness and EAT volume assessed by CMR. EAT thickness measured by echocardiography showed also a significant correlation with the CMR-EAT thickness measured at the same anatomical site. The validation of this measurement against the current gold standard for EAT quantification was possible only in 70 patients undergoing CMR for other clinical purposes. This was expected since there are no clear indications for a routine CMR study in such population. However, our data suggest that this echo-EAT measurement reflects the total amount of EAT, whereas recent evidence indicate that other echocardiographic methods for EAT thickness assessment have a poor correlation with EAT volume at cardiac computed

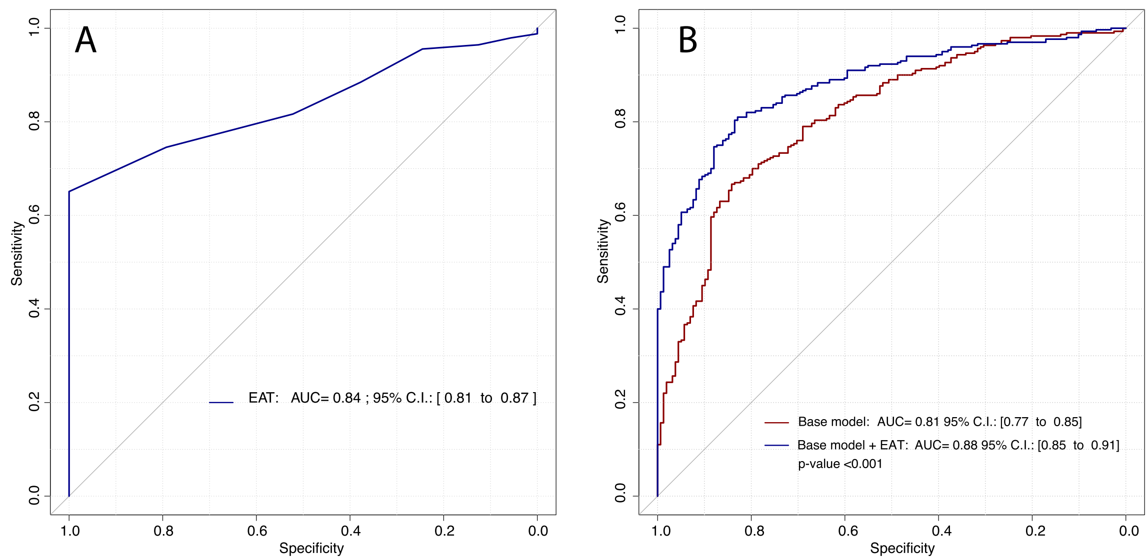

Figure 4 A) ROC curve showing the diagnostic accuracy for CAD of echo-EAT measurements; B) ROC curves showing the additive predictive value for CAD when EAT is added to a base model including age, sex, body mass index, hypertension, diabetes, smoking, and dyslipidaemia. ROC: Receiving operating curve; CAD: Coronary artery disease; EAT: Epicardial adipose tissue.

tomography [23]. Overall, our results could pave the way for a routinely use of echocardiographic EAT assessment in the clinical practice. In fact, expediency of image acquisition, lesser requirement for image analysis, and cost considerations represent all factors favoring the introduction of the EAT assessment during the echocardiographic study.

Since the increasing evidence on the role of cardiac visceral adiposity in the pathophysiology of cardiovascular diseases, the measurement of EAT thickness should be strongly encouraged. In this regard, we have recently observed that EAT measurement proposed in this study is directly correlated with the levels of inflammatory mediators secreted by EAT [14]. Given its proximity to the myocardium and absence of fascial boundaries, EAT directly influences myocardial homeostasis through vasocrine and paracrine mechanisms. This tight anatomical connection with the heart has stimulated, in the last years, many researchers to explore the involvement of EAT in the pathogenesis of cardiac diseases [1–7,24–26]. In this regard, convincing data have been produced on the association between EAT and CAD [1–3]. A recent systematic review by Madonna et al. [27] reports previous studies on this association. However, most of papers cited in this review used CMR or computed tomography for EAT assessment, while almost ten studies quantified EAT by echocardiography, often with different methods (in diastole or in systole), and at different anatomical sites. This generates confusion and strengthens the need of a single standardized method in order to allow the definitive introduction of echo-EAT thickness measurement in the clinical practice, and to share the results between different research groups.

To this aim, once demonstrated the accurateness of this echo-EAT assessment and its validation against CMR, we also aimed to explore, in a large study population, the predictive value of this measurement on the presence of significant CAD in patients referred to coronary angiography. Our results indicate that this measurement of EAT is able to discriminate patients with and without CAD and shows an additive predictive value on CAD when added to a multivariable logistic regression model including age, BMI, sex and cardiovascular risk factors. All these variables are known to be significantly associated with CAD, thus, the evidence of an additive predictive value of EAT thickness is of high interest and strengthens the importance of this echo assessment of cardiac visceral fat.

Conclusions

The present study included 1050 subjects, thus reporting, to date, the largest study population examined for echocardiographic EAT assessment. We proposed and validated an echocardiographic method for EAT thickness assessment at the level of the Rindfleisch fold, measuring, at this site, the maximum EAT thickness. This measurement is simple, reproducible, and clinically useful being independently associated with significant CAD and shows an additive predictive value over common cardiovascular risk factors. Of interest, this measurement well correlates with EAT thickness and volume at CMR. Further studies are requested to investigate whether the introduction of EAT maximal thickness measurement in the routine echocardiographic examination could give additional information for a better cardiovascular risk stratification.

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