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ORIGINAL ARTICLE
Coronary artery disease

Epicardial adipose tissue and obstructive coronary artery disease in acute chest pain: the EPIC-ACS study

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Aims

We tested the hypothesis that epicardial adipose tissue (EAT) quantification improves the prediction of the presence of obstructive coronary artery disease (CAD) in patients presenting with acute chest pain to the emergency department.

Methods and results

Within this prospective observational cohort study, we included 657 consecutive patients (mean age 58.06 ± 18.04 years, 53% male) presenting to the emergency department with acute chest pain suggestive of acute coronary syndrome between December 2018 and August 2020. Patients with ST-elevation myocardial infarction, haemodynamic instability, or known CAD were excluded. As part of the initial workup, we performed bedside echocardiography for quantification of EAT thickness by a dedicated study physician, blinded to all patient characteristics. Treating physicians remained unaware of the results of the EAT assessment. The primary endpoint was defined as the presence of obstructive CAD, as detected in subsequent invasive coronary angiography. Patients reaching the primary endpoint had significantly more EAT than patients without obstructive CAD (7.90 ± 2.56 mm vs. 3.96 ± 1.91 mm, $P < 0.0001$). In a multivariable regression analysis, a 1 mm increase in EAT thickness was associated with a nearby two-fold increased odds of the presence of obstructive CAD [1.87 (1.64–2.12), $P < 0.0001$]. Adding EAT to a multivariable model of the GRACE score, cardiac biomarkers and traditional risk factors significantly improved the area under the receiver operating characteristic curve (0.759–0.901, $P < 0.0001$).

Conclusion

Epicardial adipose tissue strongly and independently predicts the presence of obstructive CAD in patients presenting with acute chest pain to the emergency department. Our results suggest that the assessment of EAT may improve diagnostic algorithms of patients with acute chest pain.

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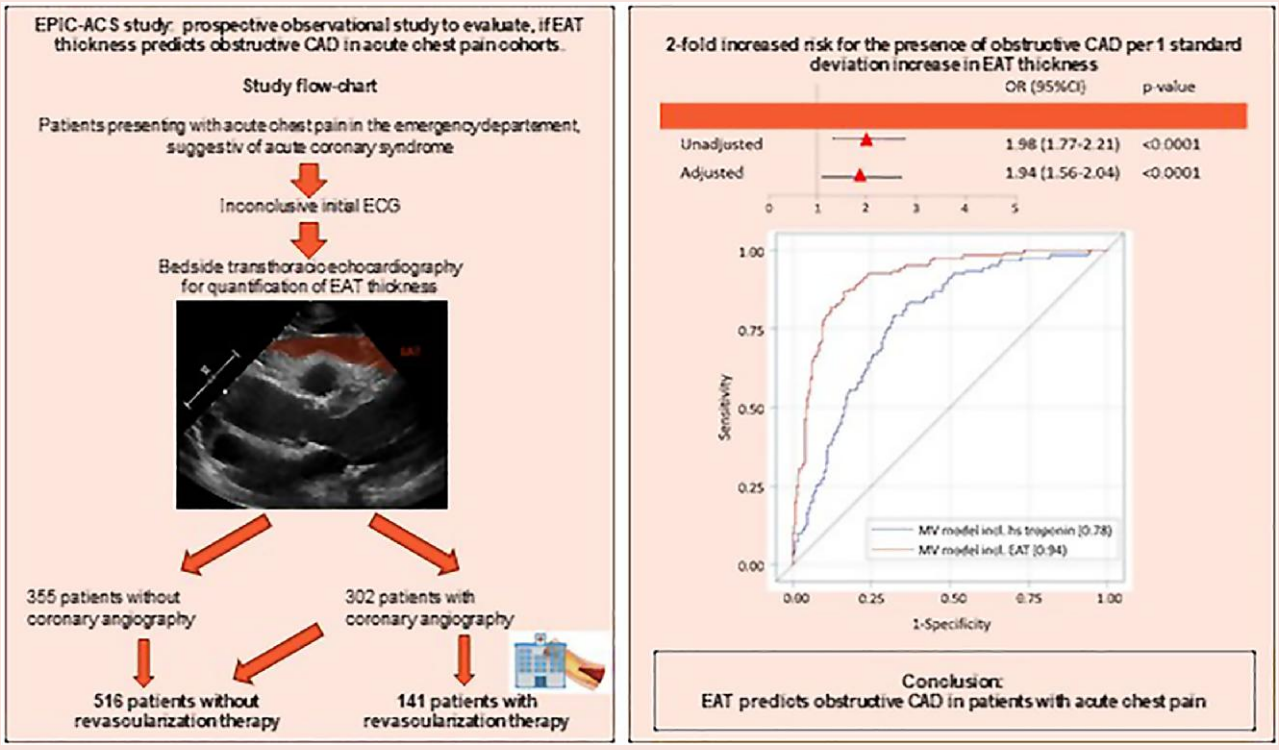
Graphical Abstract



Keywords Epicardial adipose tissue • Acute coronary syndrome • Echocardiography • Myocardial infarction • Coronary artery disease

Introduction

Diagnostic evaluation of patients with acute chest pain in the emergency department is challenging, and initial assessment of electrocardiogram (ECG) and biomarker testing is inconclusive in a majority of patients.[1] This leads to the need for additional testing to facilitate a safe triage of patients.[1–3] For the rule out of coronary artery disease (CAD) and assurance of patients' safety, non-invasive and invasive procedures are frequently performed even among low-risk patients with chest pain.[4,5] Current guidelines suggest the use of computed tomography (CT) coronary angiography (CTA) and non-invasive stress testing for clinical decision-making.[6] This approach takes high demands on resources and expertise and causes increased downstream testing.[5,7] Even in specialized centres, CTA and stress testing, utilizing dedicated accelerated diagnostic protocols, are provided only during weekday daytime hours, limiting their applicability in patients with acute chest pain.[8] While transthoracic echocardiography is routinely available in chest pain units, current guidelines suggest its utilization only with a level C recommendation, acknowledging the need for dedicated clinical trials, evaluating echocardiographic measures to improve established diagnostic algorithms.

Epicardial adipose tissue (EAT) surrounds the heart and the coronary vessels and can reliably be quantified by bedside transthoracic echocardiography.[9] As metabolically active visceral adipose tissue, EAT releases protective and pro-inflammatory/pro-fibrotic cytokines, chemokines, and adipokines to the surrounding tissues.[10,11] Increasing amount of EAT is linked to augmented inflammatory activity,[12,13] leading to coronary atherosclerosis development and progression.[14–18] While cross-sectional and longitudinal studies document the strong association of EAT with myocardial infarction,[19,20] clinical studies, specifically designed to determine how the assessment of EAT can affect patient management, are lacking. We initiated the *Epicardial adipose tissue thickness Predicts obstructive Coronary artery disease in Acute Coronary Syndrome patients* (EPIC-ACS) study to test the hypothesis that echocardiography-derived EAT thickness is associated with the presence of obstructive CAD, requiring coronary revascularization therapy, in patients presenting with acute chest pain and may therefore improve the prediction of underlying CAD in addition to established clinical algorithms.

Methods

The EPIC-ACS trial is a prospective single-centre observational study to investigate whether quantification of EAT thickness via transthoracic echocardiography enables improved prediction of obstructive CAD in patients presenting with acute chest pain to the emergency department (NCT03787797).

Study sample

We included consecutive patients presenting to the emergency department of the University Hospital Essen with acute chest pain suggestive of acute coronary syndrome. Patients presenting during regular office hours between December 2018 and August 2020 were included. Exclusion criteria were defined as ST-elevation myocardial infarction, haemodynamic instability, known obstructive CAD prior to presentation, prior revascularization

therapy, age < 18 years, pregnancy, or inability/unwillingness to provide informed consent. The study was approved by the institutional ethical committee (18-8198-BO). All patients provided written informed consent.

Epicardial adipose tissue quantification

As part of the study protocol, all patients underwent focused bedside echocardiography evaluation by a dedicated study physician, blinded to the patient's anamnesis and clinical presentation, ECG and laboratory results, and prior coronary angiography. Two-dimensional transthoracic echocardiography was performed using standard echocardiography systems without the use of specific applications (Philips CX 50 or Philips Sparq system, Philips Healthcare, Best, the Netherlands). Epicardial adipose tissue was defined as the space between the outer wall of the myocardium and the visceral layer of the pericardium.[21] Three independent measurements of EAT thickness were performed perpendicular to the free wall of the right ventricle at end-systole in parasternal long- and short-axis views, and the mean of these measurements was calculated. Treating physicians remained unaware of the results of the EAT measurement. For evaluation of reproducibility and quality assurance of EAT measurements, a second assessment of EAT thickness was performed offline at the cardiovascular imaging laboratory of the West German Heart and Vascular Center as a core lab in a subset of 264 patients, using a dedicated software programme (Philips QLab, Philips Healthcare, Amsterdam, the Netherlands). The physician at the core lab was blinded to the initial EAT measurement as well as all patient characteristics. Interobserver reliability was evaluated in these 264 patients and demonstrated very good reproducibility [intraclass correlation coefficient: 0.83 (0.79–0.87), $P < 0.0001$].

Endpoint definition

The presence of obstructive CAD, defined as the detection of obstructive CAD requiring coronary revascularization therapy (percutaneous coronary intervention/stent implantation or coronary bypass operation) within 90 days after initial presentation, was considered the primary endpoint. The indication for invasive coronary angiography was at the discretion of the treating physicians. Likewise, revascularization therapy was performed according to the discretion of treating interventional cardiologists. Decisions were based on angiographic findings, intravascular ultrasound (Philips IntraSight, Best, the Netherlands), optical coherence tomography (Infinity OCT system, Medtronic, Dublin, Ireland), and/or functional measurements (instantaneous wave-free ratio, fractional flow reserve, Philips IntraSight, Best, the Netherlands).

Covariate assessment

At study inclusion, age and sex were assessed. The patient's height, body weight, heart rate, and systolic and diastolic blood pressure were measured in a standardized fashion. Body mass index (BMI) was calculated as weight divided by the square of height. Standardized questionnaires assessed smoking status, known hypercholesterinaemia, diabetes, family history of premature CAD, and symptoms (duration of chest discomfort, Killip class). Complementary prior medication of aspirin, P2Y12 antagonist, antihypertensive, lipid-lowering, and antidiabetic treatment was recorded. Serial laboratory results of cardiac markers (troponin, creatinine kinase [CK], myoglobin, and NT-proBNP) as well as baseline creatinine were recorded. At the initiation of the study, a contemporary high-sensitive troponin I assay was available at our site (Siemens Advia Centaur, Erlangen, Germany), which was replaced by a high-sensitive troponin I assay after the inclusion of the first 147 patients (Siemens Atellica, Erlangen, Germany) in clinical routine. After the availability of the high-sensitive troponin assay, both troponin I assays were measured for all baseline and serial assessments in all patients of the present study. For the primary analysis, the contemporary high-sensitive troponin assay was used. Sensitivity analysis was performed in the subgroup of patients with available high-sensitive troponin I, including the more sensitive assay in multivariable models. Total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol as well as triglycerides were assessed using standardized enzymatic methods. Electrocardiogram was evaluated for the presence of ST-segment elevation/depression (≥0.5 mm) or left bundle branch block (LBBB) by a dedicated study physician. Based on the assessed characteristics, the Global Registry of Acute Coronary Events (GRACE) and thrombolysis in myocardial infarction (TIMI) risk scores were calculated.[22,23] Non-ST-segment elevation myocardial infarction (NSTEMI) was diagnosed according to the European Society of Cardiology guidelines based on symptoms and a dynamic elevation of cardiac troponin above the 99th percentile of healthy individuals.[24]

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Discrete variables are given in frequency and percentiles. Baseline characteristics are specified for the overall cohort as well as stratified by patients with and without the need for coronary revascularization. Continuous variables were compared using a two-sided *t*-test or Mann–Whitney *U* test and discrete variables using a χ^2 test. Univariate and multivariable logistic regression analyses were performed for the association of EAT thickness with the primary endpoint. For logistic regression analysis, the following models were used: (i) unadjusted; (ii) age, sex, and BMI adjusted; (iii) multivariable adjusted for traditional cardiovascular risk factors (age, sex, BMI, family history of premature CAD, smoking status, hypercholesterolaemia, diabetes, and systolic blood pressure); (iv) Model 3 and cardiac biomarkers (troponin, CK, and myoglobin); (v) the GRACE score; (vi) Model 5 and sex, BMI, hypercholesterolaemia, family history of premature CAD, diabetes, and smoking; and (vii) Model 6 + CK and myoglobin. In sensitivity analysis, the TIMI risk score instead of the GRACE score was used. Here, Model 6 ancillary contained systolic blood pressure, as this variable is not included in the TIMI risk score. Further sensitivity analyses were performed in the subgroup of patients with available hs-troponin as well as using core lab–based EAT quantification. We performed a subgroup analysis, comparing the association of EAT thickness with obstructive CAD, stratified by target vessel for coronary intervention. Due to the limited number of cases with left circumflex stenosis, only univariate logistic regression analysis was possible. In addition, we performed univariate and multivariate regression analyses (Model 1 for univariate analysis and Model 3 for multivariate analysis) to compare EAT thickness in patients without CAD vs. single-vessel disease vs. multivessel disease. For all regression analyses, effect sizes are expressed as odds ratios and 95% confidence interval (CI) per 1 mm increase in EAT thickness. Subgroup analyses were performed stratifying by age groups (≥ vs. <60 years), sex, BMI groups (<25, 25–<30, and ≥ 30 kg/m^2), and the presence/absence of traditional cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes, smoking, and family history of premature CAD), adjusting for variables of Model 3. Receiver operating characteristic (ROC) analysis was performed, and the area under the curve (AUC) was assessed, evaluating the predictive value of EAT in addition to variables contained in Model 7. Youden's *J* index was assessed to establish a threshold for the prediction of obstructive CAD. The association of this threshold with obstructive CAD was then tested and validated using unadjusted and adjusted logistic regression analyses in Models 1–3. Again, sensitivity analysis was performed, using a model with the TIMI risk score instead of the GRACE score and when using the subgroup of patients with available high-sensitive troponin assays. All analyses were performed using SAS software (Version 9.4, SAS Institute Inc.). A *P*-value of <0.05 indicated statistical significance.

Results

Overall, 657 patients (mean age 58.06 ± 18.04 years, 53% male) were included in our study. From the total cohort, 302 patients (46.0%) underwent coronary angiography, of whom obstructive CAD requiring revascularization therapy was detected in 141 subjects (21.5%, see Supplementary material online, *Figure S1*). Median time to coronary angiography was 1 day (0–40 days; mean time to coronary angiography 5.83 ± 13.72 days). A total of 127 (90.1%) underwent percutaneous coronary intervention/stent, and 14 (9.9%) patients underwent coronary artery bypass grafting. Patients receiving coronary revascularization therapy were older, were more frequently male, had higher levels of cardiac biomarkers, and were more frequently diagnosed as NSTEMI. In addition, a diagnosis of hypercholesterolaemia accompanied by pre-existing lipid-lowering therapy was more frequent in patients with obstructive CAD. Furthermore, prior aspirin, antidiabetic, and

Table 1 Baseline characteristics

	Overall cohort ($n = 657$)	No obstructive CAD ($n = 516$)	Obstructive CAD ($n = 141$)	*P*-value
Demographics				
Age (years)	58.06 ± 18.04	55.62 ± 18.57	67.0 ± 12.38	<0.0001
Male	349 (53.12)	259 (50.19)	90 (63.83)	0.0040
Laboratory parameters				
Troponin initial (ng/L)	6.0 (6.0–19.0)	6.0 (6.0–11.0)	19.0 (6.0–215.0)	<0.0001
Troponin initial (ng/L) positive	129 (19.6)	72 (14.0)	57 (40.4)	<0.0001
CK (U/L)	105.0 (67.0–153.0)	102.5 (67.0–148.0)	117.0 (85.0–173.0)	0.0237
Myoglobin (µg/dL)	54.0 (37.0–82.0)	49.0 (35.0–76.0)	76.0 (46.0–109.0)	<0.0001
Total cholesterol (mg/dL)	180.69 ± 51.32	181.3 ± 48.72	179.8 ± 54.97	0.7995
LDL-C (mg/dL)	121.48 ± 47.69	121.6 ± 46.33	121.3 ± 49.58	0.9602
HDL-C (mg/dL)	48.09 ± 17.02	50.36 ± 16.97	45.1 ± 16.69	0.0095
Triglycerides (mg/dL)	123 (95–186)	119.0 (89.0–182.0)	129.0 (103.0–188.0)	0.0924
Creatinine (mg/dL)	0.96 (0.83–1.1)	0.95 (0.82–1.09)	0.98 (0.85–1.14)	0.1277
Cardiovascular risk factors				
BMI (kg/m^2)	27.3 ± 5.1	27.3 (26.8–27.7)	27.6 (26.9–28.4)	0.3996
Current smoking	175 (26.64)	132 (25.58)	43 (30.5)	0.1869
Diabetes	102 (15.53)	70 (13.57)	32 (22.7)	0.0080
Family history of CAD	136 (20.7)	101 (19.57)	35 (24.82)	0.1728
Hypercholesterolaemia	190 (28.96)	126 (24.47)	64 (45.39)	<0.0001
Clinical presentation				
NSTEMI	144 (21.9)	82 (15.9)	62 (44.0)	<0.001
Systolic blood pressure (mmHg)	135.62 ± 19.27	134.7 ± 19.39	139.1 ± 18.44	0.0140
Diastolic blood pressure (mmHg)	81.26 ± 13.91	81.36 ± 13.98	80.89 ± 13.67	0.7191
Killip class I	628 (95.59)	498 (96.51)	130 (92.2)	0.0271
Killip class II	29 (4.41)	18 (3.49)	11 (7.8)	
Killip class III	0 (0)	0 (0)	0 (0)	
Complementary prior medication				
Aspirin	93 (14.16)	65 (12.6)	28 (19.86)	0.0284
P2Y12 antagonist	13 (1.98)	8 (1.55)	5 (3.55)	0.1316
Antidiabetic	75 (11.42)	50 (9.69)	25 (17.73)	0.0078
Antihypertensive	363 (55.25)	266 (51.55)	97 (68.79)	0.0003
Lipid-lowering	117 (17.81)	73 (14.15)	44 (31.21)	<0.0001
ECG				
LBBB	18 (2.74)	15 (2.91)	3 (2.13)	0.6132
ST-segment derivation	11 (1.67)	6 (1.16)	5 (3.55)	0.051

Values are mean ± SD, median (IQR), or *n* (%).
CAD, coronary artery disease; CK, creatinine kinase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST-elevation myocardial infarction; ECG, electrocardiogram; LBBB, left bundle branch block.

antihypertensive therapy was more frequent in patients meeting the primary endpoint. Average EAT thickness was 4.8 ± 2.62 mm. Comparing patients with and without the presence of obstructive CAD, we observed significantly higher EAT thickness in patients requiring coronary revascularization therapy (7.9 ± 2.56 mm vs. 3.96 ± 1.91 mm, see Supplementary material online, *Figure S2*). Detailed patient characteristics are depicted in *Table 1*.

Table 2 shows the association of EAT with the presence of obstructive CAD, requiring revascularization therapy. In unadjusted regression analysis, we observed a two-fold increased odds of obstructive CAD per 1 mm increase in EAT thickness. Effect sizes remained stable and highly significant when controlling for age, sex, and BMI as well as when ancillary controlling for traditional cardiovascular risk factors and cardiac biomarkers. When ancillary controlling for the GRACE score as a clinically established score for disease prognosis in patients with acute chest pain, we observed stable effect sizes. Further adjusting for traditional risk factors and cardiac biomarkers did not influence the association. In sensitivity analysis, the TIMI risk score was used instead of the GRACE score in multivariable regression analyses, which did not affect the association of EAT with the presence of obstructive CAD (see Supplementary material online, *Table S1*). In the subgroup of patients with available high-sensitive troponin levels ($n = 510$), effect sizes remained unaltered when contemporary values from high-sensitive assays were replaced by values from high-sensitive assays in multivariable models. Likewise, using core lab–based EAT thickness assessment led to a similar association of EAT with the primary endpoint in multivariable analyses (see Supplementary material online, *Table S1*). Comparing the association of EAT thickness with obstructive CAD, stratified by

Table 2 Univariate and multivariable logistic regression analyses for the association of EAT thickness with the presence of obstructive CAD

	OR (95% CI)	*P*-value
Univariate	1.979 (1.771–2.212)	<0.0001
Adjusted for age, sex, and BMI	1.938 (1.723–2.179)	<0.0001
Adjusted for age, sex, BMI, family history of CAD, smoking, hypercholesterolaemia, diabetes, and systolic blood pressure	1.914 (1.700–2.156)	<0.0001
Adjusted for age, sex, BMI, family history of CAD, smoking, hypercholesterolaemia, diabetes, systolic blood pressure, troponin, CK, and myoglobin	1.866 (1.644–2.118)	<0.0001
Adjusted for the GRACE risk score	1.933 (1.723–2.168)	<0.0001
Adjusted for the GRACE risk score, BMI, hypercholesterolaemia, family history of CAD, diabetes, and smoking	1.927 (1.713–2.168)	<0.0001
Adjusted for the GRACE risk score, BMI, hypercholesterolaemia, family history of CAD, diabetes, smoking, CK, and myoglobin	1.938 (1.710–2.197)	<0.0001

BMI, body mass index; GRACE, Global Registry of Acute Coronary Events; CAD, coronary artery disease; CK, creatinine kinase; OR, odds ratio.

target vessel for coronary intervention, we found a significant association for all three vessels with slightly higher effect sizes for the association of EAT thickness with LAD stenoses, however, with overlapping CIs (see Supplementary material online, *Table S2*). When comparing EAT thickness in patients without CAD vs. single-vessel disease vs. multivessel disease, we observed a stepwise increase in EAT thickness (4.44 ± 2.13 CAD, 7.1 ± 2.14 for single vessel, and 8.29 ± 2.65 for multivessel; $P < 0.0001$ for single vs. no, $P < 0.0001$ for multivessel vs. no). Furthermore, we observed significantly higher effect sizes for the association of EAT with obstructive CAD in patients with multivessel disease as compared with single-vessel disease (see Supplementary material online, *Table S3*). *Figure 1* depicts the predefined subgroup analyses for the association of EAT thickness with obstructive CAD. We observed slightly higher effect sizes for younger patients, females, patients with BMI < 25 kg/m^2, and patients without known hypertension or elevated blood pressure. Importantly, no significant interaction of traditional risk factors or elevated troponin levels was observed.

Figure 2 shows the ROC for the improvement of the AUC for EAT in addition to a multivariable model (including the GRACE score, BMI, hypercholesterolaemia, family history of CAD, diabetes, smoking, CK, and myoglobin levels), demonstrating a significant improvement in the prediction of obstructive CAD (AUC 0.759–0.901, $P < 0.0001$). Similar results were observed for a multivariable model containing the TIMI score instead of the GRACE score (AUC 0.777–0.911, $P < 0.0001$, see Supplementary material online, *Figure S3*) as well as when including high-sensitive troponin instead of contemporary high-sensitive troponin to the model (AUC 0.778–0.935, $P < 0.0001$, see Supplementary material online, *Figure S4*). Based on the ROC analysis and Youden's *J* index, we defined an EAT thickness of 5.5 mm as the best threshold to predict obstructive CAD. In univariate regression analysis, patients with an EAT thickness above this threshold had a 44% increased risk of obstructive CAD as compared with patients with EAT below this threshold [odds ratio (OR) 1.44 (95% CI 1.2–1.73, $P < 0.0001$]. Effect sizes remained stable in a multivariate model [1.47 (1.21–1.78) $P < 0.001$].

Discussion

We here demonstrate that EAT is a strong predictor of the presence of obstructive CAD, requiring revascularization therapy, in patients presenting with chest pain to the emergency department independent of traditional cardiovascular risk factors and cardiac biomarkers. Effect sizes were similar in patients with troponin-positive and troponin-negative acute chest pain independent of sex, age groups, and the GRACE or TIMI score. Our results suggest that in haemodynamically stable patients with acute chest pain but with inconclusive initial ECG, routine echocardiography imaging of the heart for quantification of EAT could allow for improved detection of patients with underlying CAD. We determined thresholds of EAT thickness, which served as a predictor of obstructive CAD. EAT thickness above the defined thresholds was associated with a nearly 50% increased risk of obstructive CAD. These data suggest that the utilization of EAT thickness of 5.5 mm for patients presenting with acute chest pain can serve as a novel echocardiography-derived parameter, qualifying for the detection of patients with obstructive CAD in an emergency setting.

Due to the anatomical proximity, EAT and the coronary vasculature are connected by paracrine and vasocrine signalling pathways.[25] Epicardial adipose tissue is referred to a protective role in secreting anti-inflammatory, anti-atherogenic molecules and nutritive fatty acids.[25,26] Intrinsic and extrinsic factors as well as the amount of EAT are inducing a shift of the protective role of EAT to a more pro-inflammatory and pro-atherogenic secretion.[10,11] These pathophysiological properties define the molecular effect of EAT on the myocardium and the coronary arteries, which lead to the development and progression of atherosclerosis.[16,17] Therefore, a link of EAT with coronary plaque burden, high-risk plaque characteristics, and myocardial ischaemia was shown.[27–30]

Different imaging technologies for quantification of EAT are described for scientific and clinical approaches. Computed tomography and magnetic resonance imaging (MRI) are considered the gold standard for the measurement of three-dimensional EAT volume.[31,32] However, quantification of EAT via CT and MRI requires complex and time-consuming processes, which are currently reserved centres with dedicated expertise.[33] In an emergency setting, there is the need for a routinely available, easily accessible, and time-efficient imaging modality. Echocardiography allows for reliable quantification of EAT thickness, is readily available, and can routinely be performed in patients presenting with acute chest pain.[6,34] Our finding supports previous results that echocardiographic assessment of EAT thickness allows for reliable stratification of patients, identifying those with increased probability of CAD.[35]

In the current guidelines for the management of patients with acute coronary syndrome without persistent ST-segment elevations, non-invasive imaging modalities gain importance.[6] Computed tomography enables the exclusion of significant CAD stenosis, non-invasive stress testing provides signs of myocardial ischaemia via detection of wall motion abnormalities, and cardiac MRI displays perfusion as well as wall motion abnormalities.[6,36,37]

Transthoracic echocardiography allows for the evaluation of left ventricular wall motion defects and is able to identify high-risk patients for acute coronary syndrome.[38] Additionally, transthoracic echocardiography differentiates alternative pathologies as the cause of chest pain, such as aortic valve stenosis or signs of pulmonary embolism. Thereby, transthoracic echocardiography provides multiple diagnostic information consolidating the indication for an invasive strategy or

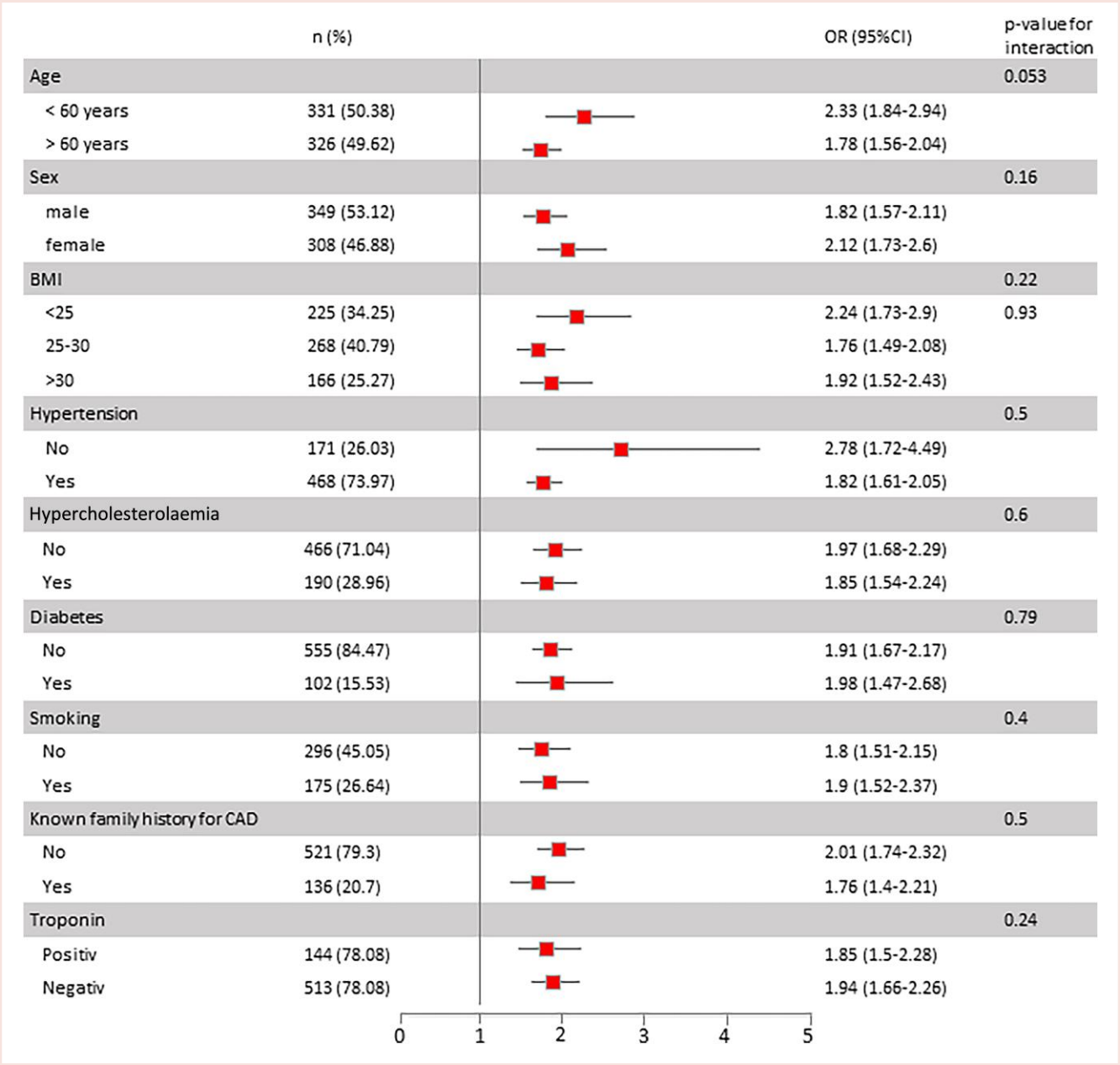


Figure 1 Forrest plot for subgroup analysis for the association of epicardial adipose tissue thickness with the presence of obstructive coronary artery disease. CAD, coronary artery disease; EAT, epicardial adipose tissue.

refuting where not necessary.[34] While transthoracic echocardiography is routinely available in chest pain units, we specifically aimed to test the hypothesis that echocardiography-derived EAT thickness is associated with the presence of obstructive CAD in patients presenting with acute chest pain and may therefore improve the prediction of underlying CAD in addition to established clinical algorithms. The present prospective observational study was designed not only to describe the association of EAT and obstructive CAD but to evaluate whether bedside echocardiographic assessment of EAT can improve the prediction using echocardiography-derived EAT measurements in an emergency setting. While further studies on larger cohorts are needed to confirm our results, the present study indicates that echocardiography-derived assessment of EAT serves as an additional marker for CAD prediction in patients presenting with acute chest pain, supporting the routine utilization of echocardiography in chest pain units.

Timing of invasive strategy is based in particular on conditions, classifying patients as very high risk (i.e. haemodynamic instability, cardiogenic shock, life-threatening arrhythmia, etc.) and high risk (established NSTEMI diagnosis, resuscitated cardiac arrest, etc.).[6] In addition, established risk scores like the GRACE and TIMI risk scores are accounted for in clinical routine and allow therapeutic decision-making based on the patient's mortality risk and risk of ischaemic events.[22,23] As the initial evaluation of ECG and biomarker testing is inconclusive in the majority of patients, many patients undergo additional non-invasive or even invasive testing for further assessment. Adding quantification of EAT thickness measured via transthoracic

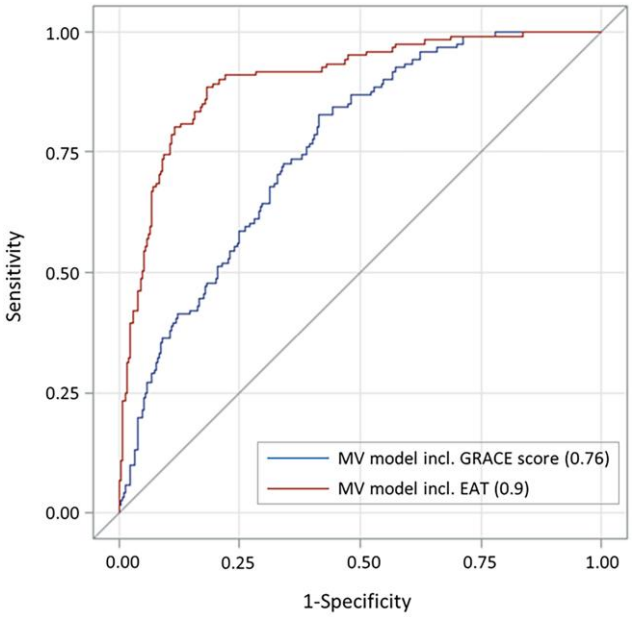


Figure 2 Receiver operating characteristic curve, demonstrating an improved prediction of the presence of obstructive coronary artery disease by epicardial adipose tissue thickness in addition to a multivariable model containing traditional risk factors and the GRACE score. CAD, coronary artery disease; EAT, epicardial adipose tissue.

echocardiography as a reliable predictor of the presence of obstructive CAD may alter patient management with regard to the pre-test probability of CAD as the cause of chest pain. In a subgroup analysis, comparing the association of EAT thickness with obstructive CAD, stratified by target vessel for coronary intervention, we found a relevant link, irrespective of target vessel, with slightly higher effect sizes for the left anterior descending (LAD). In this observational study, we included an all-comers cohort of patients presenting with chest pain. As indicated by our results, this cohort represents a heterogeneous group with an overall relatively low prevalence of obstructive CAD. Further analyses on high-risk cohorts are needed to confirm our results.

Limitations

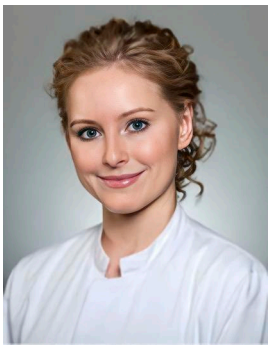
The present study was designed as a single-centre observational study. Additional research is warranted to confirm our results in a multicentre setting and to demonstrate that EAT-based alteration of clinical decision-making leads to improved patient management. The decision for coronary angiography was made at the discretion of treating physicians. Only 302 patients (46%) underwent coronary angiography, which represents an important limitation, as obstructive CAD could not definitely be ruled out in the remaining cohort. However, in a subgroup analysis including only these 302 patients, we observed identical results. As a consequence, definite exclusion of CAD was not possible for all patients discharged without further testing. To address the possibility that potential inadequate discharges with the need for later revascularization therapy may bias the results, we performed a follow-up of 90 days, assessing any late revascularizations. The presence of obstructive CAD was defined at the discretion of treating experienced interventional cardiologists. Additional imaging modalities like intravascular ultrasound or optical coherence tomography as well as assessment of lesion haemodynamics via fractional flow reserve/instantaneous wave-free ratio would have further complemented the diagnostic evaluation of these lesions; however, they were not mandatory according to the study protocol. We performed sensitivity analysis in the subgroup of patients undergoing coronary angiography, providing similar effect sizes as for the overall cohort. Dedicated study personnel, blinded to the patient's clinical presentation and clinical workup results, performed echocardiography in a bedside manner. We cannot rule out that the clinical impression may have influenced the assessment. To address this concern, we performed a core lab–based blinded assessment of echocardiography images for EAT measurement, showing a high correlation with the bedside measures and a similar association with the presence of obstructive CAD. Also, we used transthoracic echocardiography–derived EAT thickness due to its ease of use and broad accessibility over three-dimensional assessment using CT or MRI as the gold standard. However, a recent meta-analysis demonstrated comparable differences in EAT measures in patients with vs. without myocardial infarction independent of the used imaging modality.[35] As part of the study protocol, only a focused echocardiographic evaluation was performed. Therefore, we do not have any information on the relationship of EAT with concomitant valvular disease, which may have been the underlying cause of the symptoms of some patients. Further studies are needed to specifically address the value of transthoracic echocardiography in the emergency department as well as the link between EAT and valvular heart disease in acute chest pain patients. Lastly, our results are based on a predominantly Caucasian cohort; hence, generalization to other ethnic groups remains uncertain.

Conclusions

Epicardial adipose tissue strongly and independently predicts the presence of obstructive CAD, requiring revascularization therapy, in patients presenting with acute chest pain to the emergency department. Our results suggest that routine echocardiographic assessment

with quantification of EAT may improve diagnostic algorithms of patients with acute chest pain.

Lead author biography



Stefanie Jehn studied medicine at the University Duisburg-Essen. After graduating in 2018, she started her training in internal medicine and cardiology at the University Hospital Essen in the Department of Cardiology and Vascular Medicine. For the present study, she was supported by the Junior Clinician Scientist Program by the University Medicine Essen Academy (UMEA), allowing her to combine her clinical training and clinical research.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Consent

All patients provided written informed consent.

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