Original Article

# Association of epicardial adipose tissue volume with increased risk of hemodynamically significant coronary artery disease

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**Background:** Epicardial adipose tissue (EAT) is closely related to coronary artery disease (CAD). Hemodynamically significant CAD has a worse prognosis and is more likely to benefit from revascularization. However, the specific relationship between EAT and hemodynamically significant CAD remains unclear.

**Methods:** A total of 164 inpatients received single-photon emission computerized tomography-myocardial perfusion imaging (SPECT/MPI) and coronary angiography (CAG) between March 2018 and October 2019 at the Third Affiliated Hospital of Soochow University were enrolled in the retrospective cross-sectional study. Data on body mass index (BMI), hypertension, hyperlipidemia, diabetes mellitus (DM), active smoking, and symptoms were gathered. Epicardial fat volume (EFV) and coronary artery calcium (CAC) were quantified by noncontrast computed tomography (CT). Hemodynamically significant CAD was defined by coronary stenosis severity ≥50% with reversible perfusion defects in the corresponding areas of SPECT/MPI.

**Results:** A total of 37.8% of patients had hemodynamically significant CAD. Age and BMI increased with tertiles of EFV (P for trend =0.009 and P<0.001). The ratios of hemodynamically significant CAD in EFV from low to high were 16.4%, 37.0%, and 60.0%, respectively (P for the trend <0.001). In univariate regression analysis, EFV was associated with hemodynamically significant CAD [odds ratio (OR) per 10 $cm^3$ =1.36; 95% confidence interval (CI): 1.20–1.55; P<0.001]. After correcting for traditional risk factors and CAC, EFV was firmly linked to hemodynamically significant CAD (OR per 10 $cm^3$ =1.53; 95% CI: 1.25–1.88; P<0.001). With an increasing trend in EFV for the tripartite groups, the likelihood of hemodynamically significant CAD increased significantly (P for trend <0.001). There was a saturation effect between EFV and hemodynamically significant CAD according to the generalized additive model (GAM). When EFV <134.43 $cm^3$, EFV was linearly correlated with hemodynamically significant CAD (OR per 10 $cm^3$ =2.06; 95% CI: 1.45–2.94; P<0.001). When EFV ≥134.43 $cm^3$, the hemodynamically significant CAD risk was steeper and gradually reached saturation. Hypertension affected the relationship between EFV and hemodynamically significant CAD (P for the interaction =0.02) with an interaction effect.

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**Conclusions:** There was a robust relationship between EFV and hemodynamically significant CAD. After adjustment for confounders, we found that the risk of hemodynamically significant CAD onset increased nonlinearly for EFV above 134.4 $cm^3$. This refined understanding of the relationship is helpful for the accurate clinical prediction of hemodynamically significant CAD.

**Keywords:** Epicardial fat volume (EFV); coronary artery calcium (CAC); coronary artery disease (CAD); myocardial ischemia; noncontrast CT

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## Introduction

Coronary artery disease (CAD) is the major cause of mortality in Chinese residents and has become a serious threat to national health (1). Coronary angiography (CAG) is accepted as a gold standard for diagnosing and treating CAD. However, the anatomically based assessment has significant deficiencies. CAD is the major cause of myocardial ischemia. When myocardial ischemia occurs in CAD patients, the incidence of major adverse cardiovascular events (MACEs) is much higher (2). Patients with CAD should undergo revascularization if myocardial ischemia is present (3). Single-photon emission computerized tomography-myocardial perfusion imaging (SPECT-MPI) is a noninvasive imaging technique to accurately diagnose myocardial ischemia with mature technology and sufficient evidence-based medicine (4). A combination of CAG and MPI can accurately diagnose myocardial ischemia associated with CAD, which is also known as hemodynamically significant CAD. However, CAG is an invasive test, and SPECT-MPI has a certain risk of radiation exposure. Thus, exploring a noninvasive and simple marker to predict hemodynamically significant CAD has important clinical significance for risk stratification, diagnosis and treatment decisions, and providing reliable prognostic information in patients with suspected CAD.

Recently, organ-specific adiposity has attracted increasing attention, especially epicardial adipose tissue (EAT), which can secrete varieties of cytokines and adipokines and damage the myocardium and coronary arteries (5,6). Noncontrast computed tomography (CT) scans can quantitatively assess coronary artery calcium (CAC) and measure epicardial fat volume (EFV). There has been considerable interest in the relationship between EFV and traditional risk factors, CAC, obstructive CAD, myocardial ischemia, and hemodynamically significant CAD; however, research in this area has been controversial (7-9). A large population-based, multicenter study abroad highlighted significant ethnic differences in EFV (10). Our previous study confirmed that EAT was an independent risk factor for obstructive CAD (11), and myocardial ischemia has been significantly predicted by EFV over conventional risk factors and CAC (12). However, the specific relationship between EFV and hemodynamically significant CAD remains unclear. A refined comprehension of the correlation between EAT and hemodynamically CAD may provide insight into predicting hemodynamically CAD and thus contribute to identifying better therapeutic strategies.

In this study, noncontrast CT scans were used to quantify EFV and investigate the association between EFV and hemodynamically significant CAD. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-709/rc).

## Methods

### *Study population*

This retrospective cross-sectional study evaluates the relationship between EFV and hemodynamically significant CAD. The retrospective nature of the study included a predetermined sample size. We consecutively enrolled 164 inpatients who underwent SPECT/MPI and CAG with suspected CAD between March 2018 and October 2019 at the Third Affiliated Hospital of Soochow University. CAG was conducted within 3 months of MPI in all patients. Data on body mass index (BMI), hypertension, hyperlipidemia, diabetes mellitus (DM), active smoking, and symptom (angina, dyspnea, etc.) were gathered as traditional cardiovascular risk factors, which were defined as previously described by our team (11,12). Patients without symptoms were not completely asymptomatic but often had hidden

 

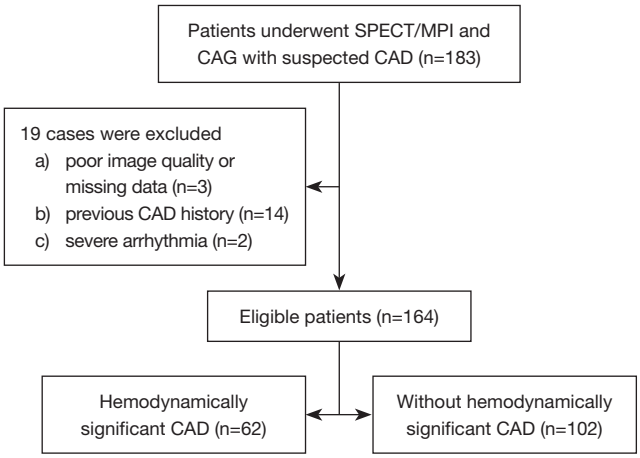


**Figure 1** Patient selection flowchart. SPECT/MPI, single-photon emission computerized tomography-myocardial perfusion imaging; CAG, coronary angiography; CAD, coronary artery disease.

and easily ignored CAD-related symptoms, such as ectopic pain in the throat, teeth, neck, upper abdomen, shoulder and back, left forearm, and even in the lower limbs. They usually had cardiovascular risk factors (i.e., hypertension, DM, hyperlipidemia, smoking, being overweight, being ≥45 years old, and being women ≥55 years old), and hematologic examination or electrocardiographic abnormality identified during medical examinations. *Figure 1* shows the exclusion criteria and the study flowchart. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of the Third Affiliated Hospital of Soochow University approved the study protocol, and the requirement for informed consent was waived due to the retrospective nature of the study.

### *SPECT-MPI image acquisition and analysis*

Twenty-four hours before testing, nitrates and beta-blockers were prohibited. Based on the recommendations of the relevant guidelines and 2-day standard imaging protocol, each patient underwent a gated stress-rest MPI (13). The scanning started 60–90 minutes after intravenous injection of a dose of 740–925 MBq 99mTc-MIBI, which has radiochemical purity >95%. Our previous study provided the specific scan parameters (11). SPECT-MPI images were visually interpreted by 2 nuclear cardiologists (JF Wang and XL Shao, who were attending physicians) who were blinded to patients' clinical data. A third expert (YT Wang, chief physician) was invited when the conclusion was disputed, and then the consensus result was determined. Corresponding to different coronary blood supply areas, the myocardial perfusion images were divided into 17 segments and scored on a 5-point scale, as explained in detail in our previous studies (11,12). The summed stress score (SSS) and summed rest score (SRS) were the sum of the 17-segment stress or resting perfusion scores. The summed difference score (SDS) equaled SSS minus SRS. The definition of myocardial ischemia is a reversible perfusion defect with SDS ≥2 (14).

### *Image acquisition and analysis of CAC and EFV*

A low-dose noncontrast CT chest scan was performed after tomographic image acquisition for stress MPI. Our previous study provides the specific scan parameters (11). Approximately 20 cm were scanned from the tracheal carina diaphragmatic surface of the heart to 1 cm beneath the plane underneath the tracheal carina.

CAC was defined as the presence of at least 3 contiguous pixels with a density surpassing 130 Hounsfield unit (HU) and was determined with Agatston automatic analysis software (Syngo Casoring, Siemens Healthineers, Erlangen, Germany) (15).

EAT was defined as the adipose tissue between the myocardium and the pericardium with a window width of −190 to −30 HU. EAT was manually delineated from the bifurcation of the pulmonary trunk to the level of the diaphragm by layer at 5-mm intervals with the reconstructed axial slices. Using Syngo Volume (Siemens Healthineers), we calculated the EFV as the sum of the cross-sectional areas of fat multiplied by the slice thickness with the noncontrast CT scan (16). The intraclass correlation coefficient for EFV was 0.96 [95% confidence interval (CI): 0.89–0.98; P<0.001].

### *CAG*

CAG was performed through the radial approach and interpreted by 2 experienced cardiologists independently (XY Yang and YJ Chen, who were attending physicians). Obstructive CAD was defined as ≥50% stenosis in at least 1 of the major epicardial coronary arteries (17).

### *Diagnosis of hemodynamically significant CAD*

Hemodynamically significant CAD was defined as (I) coronary stenosis severity ≥50% and (II) reversible perfusion defects in the corresponding areas of SPECT-MPI. If none or 1 of the above criteria was satisfied, this was

 

**Table 1** Baseline characteristics stratified by tertiles of EFV

| Characteristics | Bottom tertile | Middle tertile | Top tertile | P value for trend |
|---|---|---|---|---|
| EFV ($cm^3$), range | 37.30–107.36 | 107.36–128.49 | 128.49–246.49 | |
| EFV ($cm^3$), mean ± SD | 83.34±18.69 | 117.06±6.60 | 157.97±28.31 | |
| EFV ($cm^3$), median (IQR) | 84.80 (31.32) | 114.49 (12.01) | 144.63 (34.68) | |
| Age (years), mean ± SD | 58.18±10.62 | 62.28±8.81 | 63.73±9.62 | 0.009* |
| Male, n (%) | 40 (72.7) | 34 (63.0) | 37 (67.3) | 0.550 |
| BMI ($kg/m^2$), mean ± SD | 22.98±2.86 | 24.93±2.35 | 26.38±2.96 | <0.001* |
| Symptom, n (%) | 33 (60.0) | 35 (64.8) | 40 (72.7) | 0.36 |
| Active smoking, n (%) | 19 (34.5) | 14 (25.9) | 21 (38.2) | 0.38 |
| Hypertension, n (%) | 32 (58.2) | 40 (74.1) | 41 (74.5) | 0.11 |
| Diabetes mellitus, n (%) | 13 (23.6) | 17 (31.5) | 22 (40.0) | 0.18 |
| Hyperlipidemia, n (%) | 15 (27.3) | 14 (25.9) | 24 (43.6) | 0.09 |
| CAC prevalence, n (%) | 25 (45.5) | 28 (51.9) | 27 (49.1) | 0.80 |
| Hemodynamically significant CAD, n (%) | 9 (16.4) | 20 (37.0) | 33 (60.0) | <0.001* |

*, P for trend <0.05. EFV, epicardial fat volume; SD, standard deviation; IQR, interquartile range; BMI, body mass index; Symptom, angina, dyspnea, atypical chest pain, and dyspnea with angina or atypical chest pain; CAC, coronary artery calcium; CAD, coronary artery disease.

defined as without hemodynamically significant CAD.

### *Radiation exposure*

The effective radiation dose received by patients during the whole scanning process was 10–14 mSv (9–12 mSv for SPECT/MPI, and 1–2 mSv for noncontrast CT).

### *Statistical analysis*

Continuous variables with a normal distribution are expressed as mean ± standard deviation (SD); otherwise, they are expressed as a median (25–75th percentile). The Mann-Whitney test, independent samples *t*-test, and $\chi^2$ test were conducted according to the appropriate paradigm. Using trend tests, we illustrated the influencing factors associated with the tertiles of EFV. The relationships between the characteristics and hemodynamically significant CAD were evaluated using univariate logistic regression analysis. Three models were created to determine the relationship between EFV and hemodynamically significant CAD, including unadjusted, preliminarily adjusted, and fully adjusted models based on our team's interpretation of a broad literature review. Covariates were included as potential confounders in the model if they changed the estimates of EFV on hemodynamically significant CAD by more than 10% or were significantly related to hemodynamically significant CAD (P<0.10) (18). EFV was converted into categorical variables using 3 equal division ratios, and P values for trends were calculated to test the robustness of the results as a sensitivity analysis. A generalized additive model (GAM) and smooth curve fitting were used to test whether there was a nonlinear relationship, and a piecewise binary logistic regression model was used to explain nonlinearity (19). A hierarchical binary logistic regression model was used to assess whether there was an interaction effect on the relationship between EFV and hemodynamically significant CAD in different subgroups. All tests were performed 2-sided with the following R 3.4.3 (http://www.R-project.org) software packages: "glmnet", "pROC", "rms", and "dca". A P value less than 0.05 was considered significant.

## Results

### *A general overview of EFV tertiles*

*Table 1* demonstrates the influence factors of tripartite EFV. There were 55 cases in tertile 1 (EFV: 37.30–107.36 $cm^3$), 54 cases in tertile 2 (EFV: 107.36–128.49 $cm^3$), and 55 cases

 

**Table 2** Crude association between risk factors and hemodynamically significant CAD

| Characteristics | Statistic, n (%) or mean ± SD | OR (95% CI) | P value |
|---|---|---|---|
| Male | 111 (67.7) | 1.44 (0.72–2.88) | 0.30 |
| Age (years) | 61.39±9.94 | 1.02 (0.99–1.06) | 0.18 |
| BMI (kg/m$^2$) | 24.76±3.06 | 1.14 (1.02–1.27) | 0.02* |
| Active smoking | 54 (32.9) | 1.07 (0.55–2.09) | 0.84 |
| Hypertension | 113 (68.9) | 3.49 (1.60–7.66) | 0.002* |
| Hyperlipidemia | 53 (32.3) | 1.42 (0.73–2.76) | 0.31 |
| Diabetes mellitus | 52 (31.7) | 1.87 (0.96–3.67) | 0.06 |
| Symptom | 108 (65.9) | 2.75 (1.33–5.68) | 0.006* |
| CAC | 80 (48.8) | 7.50 (3.62–15.53) | <0.001* |
| EFV (per 10 cm$^3$) | 116.69±35.15 | 1.36 (1.20–1.55) | <0.001* |

*, P<0.05. CAD, coronary artery disease; OR, odd ratio; CI, confidence interval; SD, standard deviation; BMI, body mass index; Symptom, angina, dyspnea, atypical chest pain, and dyspnea with angina or atypical chest pain; CAC, coronary artery calcium; EFV, epicardial fat volume; SD, standard deviation.

in tertile 3 (EFV: 128.49–246.49 cm$^3$). Age, BMI, and incidences of hemodynamically significant CAD were increased with tertiles of EFV (trend P=0.009, P<0.001, and P<0.001, respectively). The proportions of hemodynamically significant CAD in the EFV of low, middle, and high were 16.4%, 37.0%, and 60.0%, respectively.

### *Crude association between risk factors and hemodynamically significant CAD*

Among the 164 patients enrolled, there were 111 males, the mean age was 61.39±9.94 years, the mean BMI was 24.76±3.06 kg/m$^2$, and the mean EFV was 116.7 cm$^3$. A total of 80 (80/164, 48.8%) patients had CAC, and 62 (62/164, 37.8%) had hemodynamically significant CAD. We used hemodynamically significant CAD as the dependent variable (Y=1) and traditional risk factors, CAC, and EFV as the independent variables to conduct the univariate logistic regression analysis. BMI, hypertension, symptom, CAC, and EFV were related to hemodynamically significant CAD (P=0.02, P=0.002, P=0.006, P<0.001, and P<0.001, respectively; *Table 2*).

### *Multivariable logistic regression analysis on the effect of the EFV on hemodynamically significant CAD*

An analysis of logistic regressions for continuous and categorical EFV is shown in *Table 3*. Adjust I covariates included BMI, symptoms, DM, hypertension, and CAC. Fully adjusted (adjust II) covariates included age, gender, BMI, hypertension, DM, active smoking, hyperlipidemia, symptom, and CAC prevalence. For continuous EFV, a 10 cm$^3$ increase in EFV was related to an elevated risk of hemodynamically significant CAD in the unadjusted, adjust I, and adjust II regression models, and the odds ratios (ORs) were 1.36, 1.46, and 1.53, respectively (all P values <0.001). For categorical EFV, there was also a significant correlation between increasing EFV and hemodynamically significant CAD in the unadjusted, adjust I, and adjust II regression models (P values for all trends <0.001), particularly when the comparing the high and low tertile (ORs =7.67, 10.00, and 17.32, respectively; all P values <0.001).

### *Curve fitting and threshold saturation effect*

GAM was used to test the relationship between EFV and hemodynamically significant CAD. The results showed that, with the increase of EFV, the risk of hemodynamically significant CAD showed a significant increase at first and then tended to be flat, exhibiting a piecewise linear relationship after adjustment for traditional risk factors and CAC prevalence (*Figure 2A*). When EFV was processed as tertiles, the adjusted mean probability of hemodynamically significant CAD increased with tertiles of EFV, which was 16.4% (95% CI: 4.6–44.3%), 39.6% (95% CI: 16.7–68.3%), and 77.2% (95% CI: 48.8–92.3%) from tertile 1 to tertile 3,

 

**Table 3** Multivariate regression analysis for the effect of EFV on hemodynamically significant CAD

| Variables | Nonadjusted | | Adjusted I | | Adjusted II | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| EFV (per 10 $cm^3$) | 1.36 (1.20–1.55) | <0.001 | 1.46 (1.20–1.77) | <0.001 | 1.53 (1.25–1.88) | <0.001 |
| Tertiles | | | | | | |
| Bottom tertile (events/n=9/55) | 1 | | 1 | | 1 | |
| Middle tertile (events/n=20/54) | 3.01 (1.22–7.42) | 0.02 | 2.57 (0.83–7.95) | 0.10 | 3.35 (1.00–11.20) | 0.049 |
| Top tertile* (events/n=33/55) | 7.67 (3.13–18.77) | <0.001 | 10.00 (2.76–36.24) | <0.001 | 17.32 (3.95–75.89) | <0.001 |

Adjusted I, model adjusted for BMI, hypertension, DM, symptom, and coronary artery calcium prevalence; Adjusted II, model adjusted for age, gender, BMI, hypertension, DM, active smoking, hyperlipidemia, symptom, and coronary artery calcium prevalence; *, P for trend <0.001. EFV, epicardial fat volume; CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

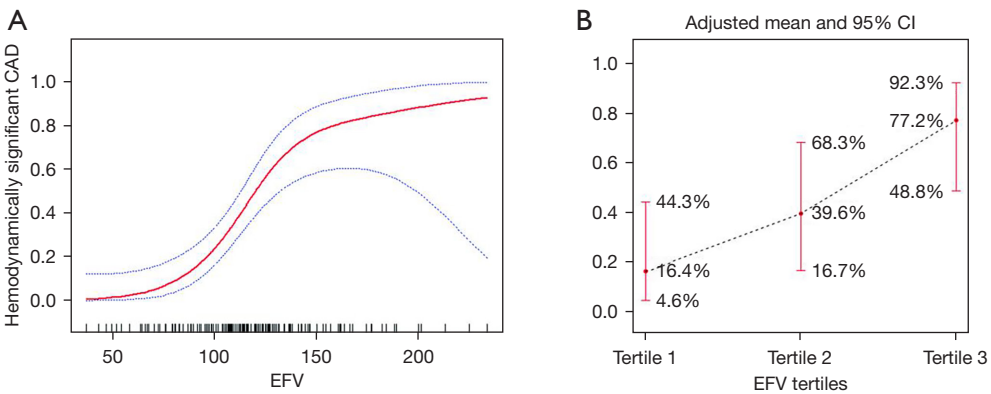


**Figure 2** The general additive model demonstrates the relationship between EFV and the risk of hemodynamically significant CAD. (A) The relationship between EFV and hemodynamically significant CAD (the solid red line indicates the fitted line; the blue dotted lines are the 95% confidence interval), adjusted for age, gender, BMI, hypertension, DM, active smoking, hyperlipidemia, symptom, and CAC prevalence. (B) The relationship between EFV tertiles and hemodynamically significant CAD (the black dotted line indicates the fitted line; the red line is the 95% CI), adjusted for age, gender, BMI, hypertension, DM, active smoking, hyperlipidemia, typical symptom, and CAC prevalence. CAD, coronary artery disease; EFV, epicardial fat volume; CI, confidence interval; CAC, coronary artery calcium; BMI, body mass index; DM, diabetes mellitus.

**Table 4** Threshold effect analysis of EFV on hemodynamically significant CAD using piecewise linear regression

| Inflection point of EFV | Effect size (OR, per 10 $cm^3$) | 95% CI | P value |
|---|---|---|---|
| <134.43 $cm^3$ | 2.06 | 1.45–2.94 | <0.001 |
| ≥134.43 $cm^3$ | 1.06 | 0.76–1.47 | 0.73 |

EFV, epicardial fat volume; CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

respectively (*Figure 2B*).

The fitting curve was further evaluated by a piecewise logistic regression model to determine if there was a saturation effect after adjustment for traditional risk factors and CAC. The results showed that when the EFV was 134.43 $cm^3$, the log-likelihood ratio test results were statistically significant (P=0.014) and that the piecewise regression model should be applied (*Table 4*). When the

 

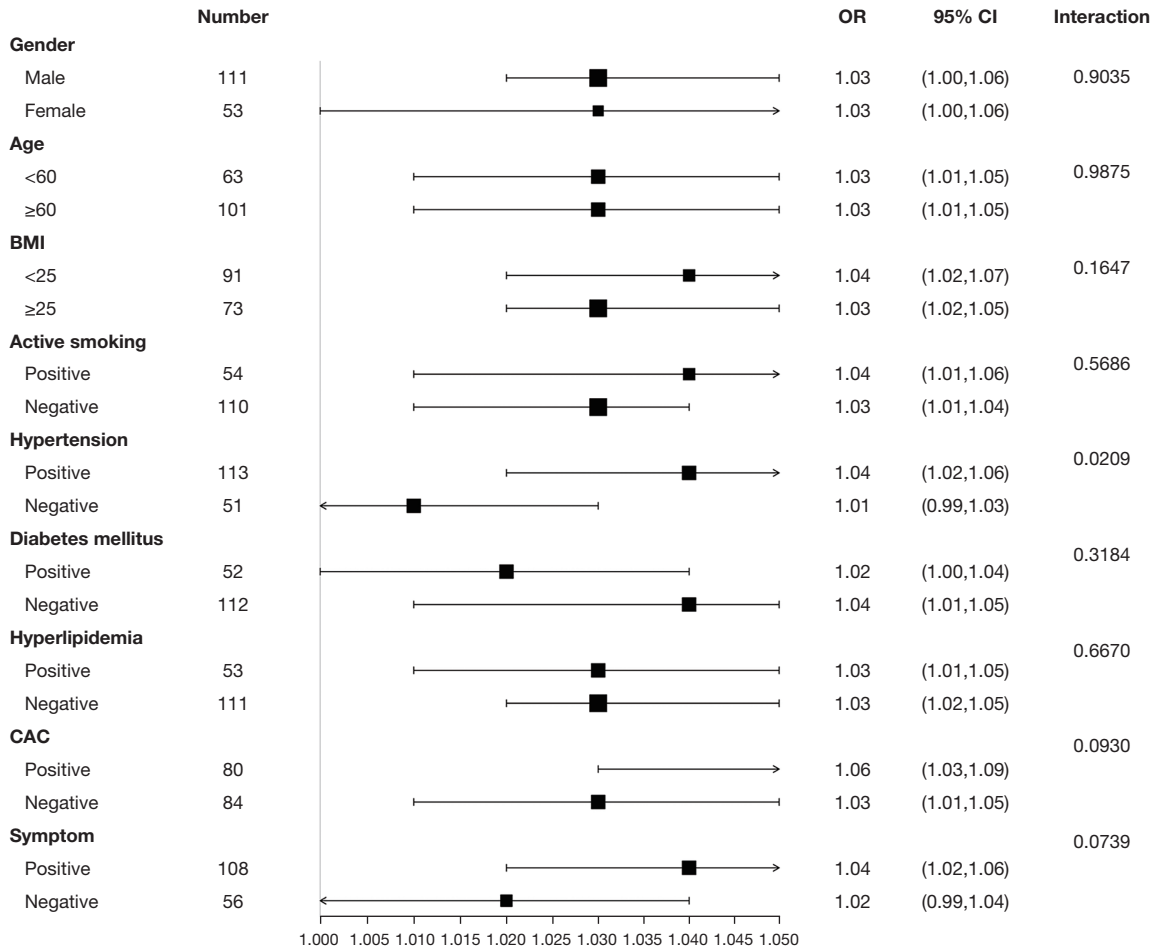


**Figure 3** Stratification analysis of EFV and hemodynamically significant CAD. BMI, body mass index; CAC, coronary artery calcium; OR, odds ratio; CI, confidence interval; EFV, epicardial fat volume; CAD, coronary artery disease.

EFV was <134.43 $cm^3$, the EFV was linearly associated with the risk of hemodynamically significant CAD. With each additional 10 $cm^3$ of EFV, there was a 1.06-fold increase in the risk of hemodynamically significant CAD (OR per 10 $cm^3$ =2.06; 95% CI: 1.45–2.94; P<0.001). In contrast, EFV ≥134.43 $cm^3$ showed a steeper risk of hemodynamically significant CAD and a saturation effect (OR per 10 $cm^3$ =1.06; 95% CI: 0.76–1.47; P=0.73).

### *Stratified analysis*

The relationship between EFV and hemodynamically significant CAD in each subgroup was further evaluated by stratified analysis, including age, gender, BMI, hypertension, DM, active smoking, hyperlipidemia, symptom, and CAC prevalence (*Figure 3*). The interaction analysis revealed that hypertension played an interactive role in the relationship between EFV and hemodynamically significant CAD. The P value for interaction was 0.02. Further analysis found that the OR value of EFV and hemodynamically significant CAD in the hypertension subgroup was 1.04 (95% CI: 1.02–1.06; P<0.001). The characteristics of the hypertension groups are compared in Supplementary Material Table S1. No other variables significantly changed the association between EFV and hemodynamically significant CAD (interaction: P=0.90, P=0.99, P=0.16, P=0.57, P=0.32, P=0.67, P=0.09, and P=0.07, respectively).

## Discussion

The main findings of the study were as follows. First, age, BMI, and incidences of hemodynamically significant CAD

increased with tertiles of EFV. Second, each 10 $cm^3$ increase in EFV raised the risk of hemodynamically significant CAD by 53% after adjustment for traditional risk factors and CAC. Third, after the adjustment for confounders, the risk of hemodynamically significant CAD onset increased nonlinearly for EFV above 134.4 $cm^3$. Fourth, the interaction analysis revealed that hypertension played an interactive role in the association between EFV and hemodynamically significant CAD.

We found that EFV was independently related to hemodynamically significant CAD. The mechanisms underlying the association between EFV and hemodynamically significant CAD are complicated and not thoroughly elucidated. Potential mechanisms include inflammatory response, oxidative stress, impairment of the endothelium, influence of coronary blood flow, and damage to the microcirculation, among others (20-22). Previous investigations evaluated the relationship between EFV and hemodynamically significant CAD, but the results were controversial. Brandt *et al.* (23) demonstrated that EFV was significantly higher in patients with hemodynamically significant CAD compared to patients without hemodynamically significant CAD as detected by fractional flow reserve (FFR). Although FFR was found to quantitatively reflect flow limitation caused by coronary artery stenosis, it was not considered suitable for clinical screening. Romijn *et al.* (24) also found that EFV was independently associated with hemodynamically significant CAD in a multivariable-adjusted model (OR: 4.95; 95% CI: 1.31–18.6; P=0.02). However, FFR was only performed in 32% of patients, which might have overestimated the effect of EFV. Furthermore, Nakazato *et al.* (25) found that indexed EFV (EFVi) predicted the concurrent presence of both myocardial ischemia and obstructive stenosis. We used SPECT-MPI to detect myocardial ischemia instead of positron emission tomography-computed tomography (PET-CT), which is more clinically practiced. In contrast, Muthalaly *et al.* (26) demonstrated there to be no observable relationship between EFV and functionally significant stenosis as detected with myocardial CT perfusion imaging, as well as invasive FFR. Since EAT is influenced by a large number of factors, without adjusted analyses, the study was unable to confirm the independent relationship between EAT and hemodynamically significant CAD. Tanami *et al.* (10) also did not find there to be association between EFV, the severity of CAD, or the presence of myocardial perfusion abnormalities. The study also highlighted significant ethnic differences in EFV.

We extended information gained from those investigations in Chinese patients with suspected CAD by evaluating the specific relationship. We found that that there was nonlinear relationship between EFV and hemodynamically significant CAD after fully correcting the confounding and interaction factors; more specifically, a significant positive linear correlation existed between the 2 within a certain threshold range, then the trend flattened, and a saturation effect occurred when the threshold was exceeded. The cutoff value was 134.43 $cm^3$, and this result provided a preliminary basis for the subsequent development of clinical prediction models. This nonlinear relationship suggests that subsequent studies may better use a nonlinear model, such as multivariate fractional polynomials (MFP), for predicting hemodynamically significant CAD (27). We also divided the EFV into 3 equal parts. With the increase of the EFV levels, the probability of hemodynamically significant CAD still had a similar trend, indicating that the relationship was robust.

Through stratified analysis, we found hypertension had an interactive role in the relationship between EFV and hemodynamically significant CAD. The different characteristics of the hypertension subgroups may account for the interaction effect. The hypertension subgroup had a large sample size (n=113), which may account for the more significant relationship between EFV and hemodynamically significant CAD. Hypertension is an important risk factor associated with obesity (28). It has been reported that patients with hypertension have lower levels of EAT messenger RNA expression of adiponectin (29). It is also well known that hypoadiponectinemia is a risk factor for CAD (30). A stronger association between EFV and hemodynamically significant CAD in hypertensive populations could be associated with the decline of the protective endocrine and the local paracrine effects of adiponectin.

Hemodynamically significant CAD is clinically significant in patients, as they will have a worse prognosis and are more likely to benefit from revascularization (31). Therefore, it is necessary to find simplified, innovative, reproducible, and noninvasive cardiovascular risk markers of hemodynamically significant CAD to improve risk stratification and guide clinical treatment decision-making. Besides EAT, several investigations focused on pericoronary adipose tissue (PCAT) and evaluated the relationship with hemodynamically significant CAD. Ma *et al.* (32) found that a lesion-specific fat attenuation index was independently associated with abnormal FFR. However, Wen *et al.* (33) indicated that PCAT had no merit in identifying hemodynamically

 

significant coronary stenosis. Moreover, it has been reported that volumetric quantification of EAT was highly reproducible compared to more simple measurements, such as pericoronary fat thickness and area (34). The repeatability of EFV measurements was notably high in the present study. Thus, measuring EFV, the global information of EAT, with noncontrast CT and without extra protocols or radiation exposure is still helpful for the initial screening of high-risk, hemodynamically significant CAD because it can facilitate clinical decision-making and risk stratification more safely. Moreover, Alam *et al.* (35) concluded that EAT is related to vessel inflammation and microcirculation dysfunction. Another study also found that EFV could effectively predict a patient's long-term MACE risk (36). The clinical significance of EFV is worth evaluating in further prospective studies.

### *Limitations*

In the present study, we had several limitations. First, as our study was retrospectively designed, we were unable to infer causal relationships. Only enrolling inpatients undergoing CAD testing might have resulted in selection bias, and low-risk individuals may not be represented. Prospective, multicenter studies are still needed to support the effect of EAT on hemodynamically significant CAD. Second, automatic software is still necessary to make EFV clinically practicable. This study did not measure the pericoronary fat, and we will quantitatively measure the pericoronary fat in the future to evaluate its application in CAD. Third, there are no standardized quantitative categories for EFV. There are significant racial differences in EAT; therefore, it is necessary to improve the relevant database of EAT in the Chinese population and find the appropriate threshold to assist further risk stratification, diagnosis, and treatment decisions of cardiovascular diseases. Finally, follow-up is required to expand the sample size to evaluate the effect of EFV on the prognosis of hemodynamically significant CAD. In a follow-up study, the sample size will be expanded to further explore the practicality and feasibility of using EFV as a gatekeeper prior to CAG or SPECT-MPI.

## Conclusions

There was a robust relationship between EFV and hemodynamically significant CAD independent of traditional risk factors and CAC. After adjustment for confounders, there was a nonlinear relationship, saturation, and segmentation effects between EFV and hemodynamically significant CAD, with a steeper risk in incidence rates noted for values over 134.4 $cm^3$. Understanding and recognizing the relationship between EFV and hemodynamically significant CAD may help improve the accuracy of diagnosis and develop more specific predictive models.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-709/rc

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-709/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of the Third Affiliated Hospital of Soochow University approved the study protocol, and the requirement for informed consent was waived due to the retrospective nature of the study.



 

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## Supplementary

**Table S1** Characteristics of the different hypertension subgroups

| | Hypertension (n=113) | Without hypertension (n=51) | P value |
|---|---|---|---|
| Male, n (%) | 73 (64.6) | 38 (74.5) | 0.21 |
| Age (years, mean ± SD) | 62.55±9.57 | 58.82±10.37 | 0.05 |
| BMI (kg/m$^2$, mean ± SD) | 24.35±3.34 | 24.99±2.92 | 0.13 |
| Active smoking, n (%) | 34 (30.1) | 20 (39.2) | 0.25 |
| Hyperlipidemia, n (%) | 34 (30.1) | 19 (27.3) | 0.36 |
| Diabetes mellitus, n (%) | 36 (31.9) | 16 (31.4) | 0.95 |
| Symptom, n (%) | 73 (64.6) | 35 (68.6) | 0.62 |
| EFV (cm$^3$, mean ± SD) | 121.07±35.55 | 106.98±32.52 | 0.04* |
| CAC, n (%) | 61 (54.0) | 19 (37.2) | 0.04* |
| Hemodynamically significant CAD, n (%) | 52 (46.0) | 10 (19.6) | 0.001* |

*, P for trend <0.05. EFV, epicardial fat volume; BMI, body mass index; CAC, coronary artery calcium; symptom, angina, dyspnea, atypical chest pain, and dyspnea with angina or atypical chest pain; SD, standard deviation.


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