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Relation of coronary collateral circulation with epicardial fat volume in patients with stable coronary artery disease

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Abstract

Objective To investigated the relationship between epicardial fat volume (EFV) and coronary collateral circulation (CCC) in patients with stable coronary artery disease (CAD). **Methods** The study population consisted of 152 consecutive patients with CAD who underwent coronary angiography and were found to have at least 95% significiant lesion in at least one major coronary artery. EFV was assessed utilizing 64-multislice computed tomography. The patients were classifield into impaired CCC group (Group 1, Rentrop grades 0–1, n = 58), or adequate CCC (Group 2, Rentrop grades 2–3, n = 94). **Results** The EFV values were significantly higher in paitients with adequate CCC than in those with impaired CCC. In multivariate logistic regression analysis, EFV (OR = 1.059; 95% CI: 1.035–1.085; P = 0.001); and presence of angina were independent predictors of adequate CCC. In receiver-operating characteristic curve analysis, the EFV value > 106.5 mL yielded an area under the curve value of 0.84, with the test sensitivity of 49.3%, and with 98.3% specifity. **Conclusions** High EFV, and the presence of angina independently predict adequate CCC in patients with stable coronary artery disease. This association offers new diagnostic opportinities to assess collateral flow by conventional ultrasound techniques.

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1 Introduction

Coronary collateral circulation (CCC) is an adaptive compensatory response to myocardial ischemia.[1] In addition, CCC is an alternative source of blood supply to the myocardium which can be jeopardized by the failure of the original stenotic, or occluded vessel, to provide adequate blood flow to the targeted ischemic region.[2] There are multiple collateral coronary arteries connecting to the normal coronary arteries in individuals without documented coronary artery disease (CAD); however, most of these additional vessels are not angiographically visible.[3,4] In contrast, patients with coronary stenosis, or occlusion, develop various visible CCC. A well-developed CCC has a favourable impact on the prognosis of patients with CAD by minimizing infarct size, reducing evolution of left ventricular aneurysm formation, improving ventricular function, and may lead to improved survival.[5–7]

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Epicardial fat volume (EFV) is a biomarker of visceral adipose tissue that has been shown to be correlated with adverse cardiovascular events, both short, and long-term.[8–10] Endothelial dysfunction, and structural changes of the microcirculation are well established features of patients with increased EFV.[11–13] On the other hand, the relationship between EFV and CCC is still unclear. Therefore, we sought to investigate the relationship between EFV level and CCC in patients with CAD.

2 Methods

2.1 Study population

The study was approved by the institutional ethics committee. The study population consisted of 400 consecutive patients with stable CAD who underwent coronary angiography. The patients with a history of coronary angiogram showing a lesion of < 80% stenosis, history of percutaneous coronary intervention, or coronary artery bypass grafting were excluded from the analyses. Finally, 152 patients with stable CAD were included in our study. The clinical risk factors for the patients, such as age, gender, hypertension, diabetes mellitus (DM), history of hyperlipidemia, smoking status, and family history, were recorded.

Hypertension was defined as systolic blood pressure >140 mmHg and/or a diastolic pressure > 90 mmHg at least two times, or if the individual was taking antihypertensive medications. The diagnosis of DM was based on the previous history of diabetes treated with, or without, drug therapies. Current smokers were defined as those who had smoked for some period during the past year. Furthermore, on admission, each patient was evaluated for blood pressure, heart rate, previously used drugs, presence of angina, high sensitivity C-reactive protein (hs-CRP), serum creatinine, glucose, lipid profile and hematological indices. Also each patient underwent transthoracic echocardiography using the biplane Simpson method measuring left ventricular ejection fraction (LVEF). Hematological indices were measured as part of the automated complete blood count (CBC) using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc, Mervue, Galway, Ireland).

2.2 Coronary angiography

Quantitative coronary angiography was performed using standard Judkins method *via* transfemoral route. The inclusion criteria were the presence of 80%, or greater, degree of diameter stenosis in at least one coronary artery. Therefore, since development of CCC is known to be inadequate in patients not comlpying with this criteria, they were excluded from the index study.[14] The CCC was graded according to the Reentrop classification. Accordingly, Grade 0 was classified as no filling; Grade 1 classified as filling of side branches *via* collateral channels without visualization of the epicardial segment; Grade 2 classified as a partial filling of epicardial major coronary artery *via* collateral channels; and Grade 3 classified as complete filling of epicardial major coronary artery. In patients with more than one coronary lesion, and when there was more than one CCC, the CCC with the highest Reentrop was used. The patients were classified into impaired CCC (Group 1, Reentrop grades 0–1) or adequate CCC (Group 2, Reentrop grades 2–3). Multivessel disease was defined as the presence of a lesion in two, or more major epicardial arteries.

2.3 Statistical analysis

Continuous variables are expressed as mean ±SD, whereas categorical variables are expressed as percentage. Comparisons between two CCC groups were made using the Student *t* test or Mann-Whitney *U* test or Chi square tests, as appropriate. Comparison between Rentrop grades were made using the analysis of variance, and Turkey honestly significant difference test was chosen as a *post hoc* test. Multiple logistic regression analysis was performed to identify the independent predictors of CCC using variables showing marginal association with it on univariate testing ($P > 0.01$). Receiver-operating characteristics (ROC) analyses were used to detect the cutoff value of EFV in the prediction of CCC. Correlation analysis between variables were performed using Pearson or Spearman correlation. $P < 0.05$ was considered significant. All statistical analyses were carried our using SPSS 16.0 for Windows (SPSS Inc, Chicago, Illinois).

Table 1. Baseline characteristics according to coronary collateral circulation.

Variable	Impaired CCC (*n* = 58)	Adequate CCC (*n* = 94)	*P*
Age (yrs)	65.65 ± 10.65	65.14 ± 10.34	0.765
Sex, male	48 (64.0)	59 (76,6)	0.088
Diabetes	43 (53.8)	37 (46.2)	0.252
Hypertension	55 (73.3)	54 (70.1)	0.661
Smoking	36 (48.0)	52 (67.5)	0.008
Family history of CAD	31 (41.3)	30 (39.0)	0.368
BMI, kg/m^2	27 ± 3.0	22 ± 6.9	0.08
Presence of angina	52 (69.3)	38 (49.4)	0.006
Heart rate	79.2 ± 8.54	74.3 ± 6.87	0.246
Systolic blood pressure, mm Hg	138 ± 12	131 ± 11	0.368
Diastolic blood pressure, mm Hg	86 ± 7	87 ± 8	0.589
LVEF	49.6 ± 7.5	48 ± 8	0.4
White blood cell count, × 10^3	9.1 ± 2.95	8.6 ± 3.08	0.285
Platelet count, × 10^3	188.2 ± 12.6	184.6 ± 11.5	0.489
Red cell distribution width, %	15.4 ± 1.5	12.9 ± 1.8	0.085
Mean platelet volume, mL × 10^{-9}	9.82 ± 0.97	8.33 ± 1.07	0.004
Estimated GFR, mL/min per 1.73 m^2	82.04 ± 14.57	76.33 ± 12.52	0.160
Oxygen Saturation	96.4 ± 0.8	96.2 ± 0.9	0.624
Previous medications, %			
Aspirin	85.3	87	0.339
Beta-blocker	83.3	85	0.339
Statin	63.6	66.5	0.4
ACE-inhibitors/ARB	46.6	44.5	0.6
CCB	35	36	0.339
OAD	83.3	85	0.339
Insulin	24	22	0.256
Diuretic	6.6	6,5	0.448
LDL-cholosterol, md/dL	124 ± 37.2	120 ± 31	0.6
HDL-Cholosterol, md/dL	34 ± 8	36 ± 9	0.8
Triglyceride, mg/dL	207 ± 68	168 ± 66	0.09
hs-CRP, mg/dL	6.0 ± 6.1	4.5 ± 3.3	0.03
Multivessel disease, %	58	56	0.8
EFV, mL	88 ± 33	114 ± 47	0.001

Data are presented as mean ± SD, or *n* (%). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index. CAD: coronary artery disease; CCB: calcium channel blocker; CCC: coronary collateral circulation; hs-CRP: high sensitivity C-reactive protein; EFV: epicardial fat volume; GFR: glomerular filtration rate; HDL: high-density lipoprotein; hs- OAD: oral antidiabetic drug; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction.

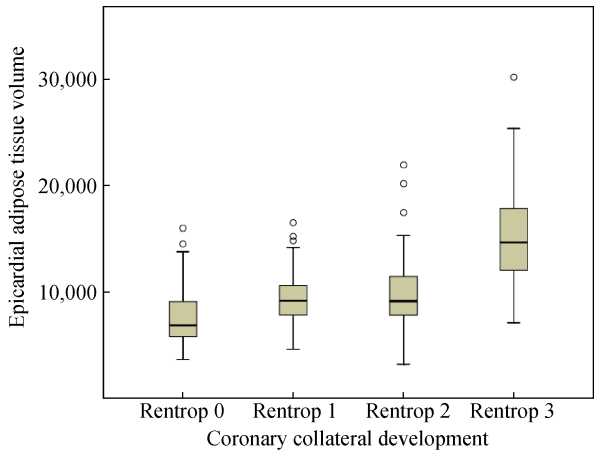

Figure 1. Epicardial fat volume (EFV) value according to Rentrop grades.

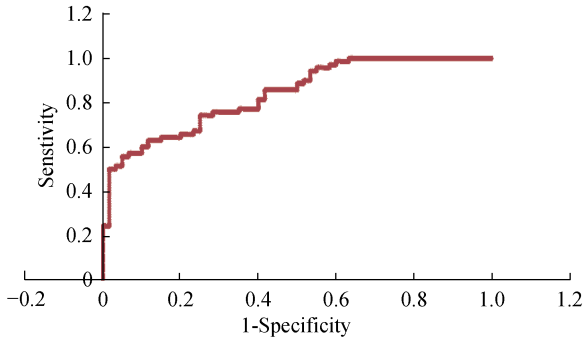

Figure 2. Receiver-operating characteristics (ROC) curves for epicardial fat volume (EFV) value in prediction of impaired coronary collateral circulation (CCC).

Table 2. Multivariate logistic regression analysis to detect the independent predictors of impaired coronary collateral circulation.

Variables	Univariate OR (95% CI)	Univariate *P* value	Multivariate OR, 95% CI	Multivariate *P* value
RDW	1.176 (0.948–1.458)	0.140		
MPV	0.542 (0.369–0.797)	0.002	0.738 (0.470–1.160)	0.188
TG	0.997 (0.992–1.001)	0.166		
BMI	1.051 (0.998–1.106)	0.062		
Presence of angina	0.35 (0.15–0.68)	0.006	0.23 (0.10–0.54)	0.001
EFV	1.062 (1.038–1.088)	0.001	1.059 (1.035–1.085)	0,0001

BMI: body mass index; EFV: epicardial fat volume; MPV: mean platelet volume; RDW: red cell distrubution width; TG: triglyceride.

3 Results

A total of 152 patients with stable CAD (Age: 65 ± 10 years, male ratio: 70%) were included in the study. Table 1 shows the comparison of Groups 1 and 2 relative to baseline characteristics. Compared to the patients with adequate CCC, patients with impaired CCC exhibited higher red cell distrubution width (RDW), mean platelet volume (MPV), triglyceride (TG), hs-CRP values and frequency of BMI and preinfarction rates. Compared to the patients with impaired CCC, patients with adequate CCC manifested significantly higher EFV levels. Furthermore, Reentrop grade 2 and 3 patients had significantly higher EFV levels when compared to the Reentrop grade 0 and 1 patients. Multivariate logistic regression test was employed for determining the independent predictors of impaired CCC (Figure 1, Table 2). The variables that were found to have significance in the univariate analysis (preinfarction angina, RDW, MPV, TG, body mass ındex (BMI), hs-CRP) were included in the multivariate model. Among those, EFV (OR: 1.059; 95% CI (1.035– 1.085); $P = 0.00$), presence of angina were found to be the independent predictors of adequate CCC. In receiver-operating characteristic curve analysis, the EFV value > 106.5 mL yielded an area under the curve value of 0.84, with 49.3% sensitivity and 98.3% specificity (Figure 2).

4 Discussion

Our study demonstrated that the presence of angina and high EFV levels may serve to be independent predictors of adequate CCC. The clinical significance of our findings is unclear, but may help in developing prediction models in the near future.

Coronary collateral vessels are structures that are normally present in the human heart, though being invisible by angiography.[3,4] These are interconecting branches between the main arteries which serve as an alternative conduits for blood flow in obstructive coronary heart disease.[15] The CCC development occurs as a result of new vessel formation and growth of pre-existing arterioles (arteriogenesis).[16] There are many factors influencing the development of the CCC, such as percent diameter of coronary artery stenosis, duration of angina, DM, hypertension smoking status, hypoxia, endothelial dysfunction, exercise, oxidative stress genetic factors, and drugs used.[1] A well-developed CCC has a favourable impact on the prognosis of patients with coronary artery disease by minimizing infarct size, reducing evolution of left ventricular aneurysm formation, improving ventricular function, and leading to improved survival.

Epicardial adipose tissue is a type of visceral adipose

tissue functioning as a metabolically active endocrine organ. The relationship between EFV presence and components of cardiovascular diseases have been described in several studies.[17–19] Moreover, it has been shown that epicardial adipose tissue is in direct contact with the myocardium, and it is very metabolically active and can secrete a large number of cytokines and vasoactive peptides, including free fatty acids, interleukin-6, tumor necrosis factor (TNF)-α, angiotensin II, and plasminogen activator inhibitor-1.[20] All of these molecules can independently play a role in terms of CCC development. Although the causes of CCC are completely unknown, one of the responsible mechanisms is thought to be the activation of immune sytems with predominant involvement of cytokines and chemokines.[21] Cytokines, which are one of the important sources of inflamatory mediators, have emerged as key cellular determinants of progression of the CCC.[22] Previous articles alerted the scientific community that hyper activation of cytokines and adhesion molecules which were in concordance with the severity of diseaese may give prognostic data about the severity of the CCC.[23,24] Recent studies have shown that cytokines, which mediate the immune response to inflamatory disorders, were also secreted from epicardial adipocyte tissues.[25–28] On the basis of these facts, EFV may be associated with the patholophysiological processes causing CCC. There are also several other pathogenic mechanisms thought to be the causative role for the association between increased EFV and the severity of the disease. Endothelial dysfunction plays a key role in terms of CCC development. Epicardial fat tissue seems to affect the endothelial function and increase sympathetic activity by its paracrine effect. Aydin *et al*.[29] showed that EFV correlated with endothelial dysfunction assessed by flow-mediated dilatation in patients with metabolic syndrome. Based on these data, associated endothelial dysfunction can be considered as one of the mechanisms for predicting severity of CAD by assessing EFV levels.

There are a few limitations of the study worth mentioning. The present study findings do not prove a direct link between increased epicardial fat volume and the development of CCC. Although increased EFV could be a marker of CAD severity, and also be a predictive factor for adequate CCC, the possible causative effect of epicardial fat accumulation has not been clarified. Qualitative analysis of epicardial fat using biochemical techniques will be required to confirm the effect of accumulated epicardial fat on the progression of coronary atherosclerosis. The relatively small sample size is one of the major limitations of our study and certainly should be confirmed in a larger, better designed, randomized trial. Morover, the cross-sectional design of our study makes it difficult to comment on the causal relationship of EFV and impaired CCC, and the observational design preclude us to adequately assess these important links. We conducted the index study in the experimental setting, and applied the observational design, therefore, not drawing any definite pathophysiologic mechanisms for the association between increased EFV and the severity of CCC. It is possible that similar mechanisms may be attributable for increase in EFV level in patients with CCC. Finally, one of the most important limitations was the failure to measure some parameters, such as FGF (fibroblast growth factor), vascular endothelial growth factor, NO, TNF-α that could be helpful in evaluating the relationship between EFV and impaired CCC in detail.

In conclusion, higher EFV level was associated with adequate CCC in patients with stable CAD. Further studies to investigate the cause and effect relationship between EFV and CCC are required.

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