Original Article

Association between the Epicardial Adipose Tissue Thickness and the Presence of Multivessel Disease in Patients with Acute Myocardial Infarction

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Aim: Epicardial adipose tissue (EAT) is implicated in the development of coronary atherosclerosis. We sought to investigate the association between the EAT thickness and presence of multivessel disease (MV) in patients with acute myocardial infarction (AMI).

Methods: We enrolled 45 consecutive patients with AMI who underwent primary percutaneous coronary intervention (PCI). The EAT thickness was measured on echocardiography. A follow-up study was performed using coronary angiography with coronary angioscopy two weeks after primary PCI.

Results: Based on the angiographic findings, 21 patients had single-vessel disease (SV) and 24 patients had MV. The EAT thickness in the patients with SV was significantly smaller than that in the patients with MV (1.9 ± 0.9 mm vs 2.8 ± 1.3 mm, $p=0.005$, respectively). A multivariate logistic analysis demonstrated that the EAT thickness was the only independent predictor of MV (odds ratio = 1.987, 95% confidence interval: 1.089-3.626, $p=0.025$). An EAT thickness of 2.3 mm was determined to be the optimal cut-off value for predicting MV, with a sensitivity of 70.8% and specificity of 71.4%. Between the thin EAT (<2.3 mm) and the thick EAT (≥ 2.3 mm) groups, there were no difference in the number of intense yellow plaques in the non-infarct-related artery evaluated on angioscopy (2.0 ± 2.2 vs 1.8 ± 2.0 , $p=0.365$, respectively).

Conclusions: The EAT thickness is closely associated with the presence of MV, but not vessel vulnerability in the non-infarct-related artery, in patients with AMI. Measuring the EAT provides important information for treating patients with AMI.

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Key words: Acute myocardial infarction, Epicardial adipose tissue, Coronary atherosclerosis, Multivessel disease

Introduction

The development of the pathophysiological process of atherosclerosis is not limited to the infarct-related artery (IRA) in patients with acute myocardial infarction (AMI)¹⁾. It is estimated that nearly half of patients presenting with AMI have multivessel disease

(MV), which is associated with worse clinical outcomes than single-vessel disease (SV)²⁾. The extent of coronary plaques in the non-IRAs, as an indicator of the development of pan-coronary vulnerability, has also been observed using imaging devices, such as coronary angioscopy and optical coherence tomography^{3, 4)}. Physicians are expected to recognize the presence or absence of MV in AMI patients as soon as possible before treating the patients in the catheterization laboratory. However, it remains difficult to estimate the extent and severity of atherosclerotic changes in the non-IRAs based on the findings of clinical examinations, such as chest X-rays, electrocardiograms and laboratory tests.

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Epicardial adipose tissue (EAT) is now recognized to be a component of visceral adiposity⁵⁾. EAT generates various bioactive molecules, including inflammatory cytokines, that can activate the atherosclerotic process related to the development of coronary artery plaque⁵⁾. The quantitative estimation of EAT on echocardiography or cardiac multi-slice computed tomography is related to the presence and severity of coronary plaque⁶⁻⁸⁾, and the EAT volume is increased in patients with acute coronary syndrome⁹⁾.

We hypothesized that EAT is associated with the development of atherosclerosis in both the IRA and non-IRAs in patients with AMI. In the present AMI study, we sought to examine the relationship between the EAT thickness measured on echocardiography and presence of MV determined on coronary angiograms (CAG). Since yellow plaques can be found in sites with completely normal findings on angiography, the degree of vessel vulnerability evaluated using angiography is not necessarily associated with the extent of vessel stenosis determined on CAG³⁾. We therefore also sought to examine the relationship between the EAT thickness and degree of vessel vulnerability in all three coronary arteries evaluated on angiography.

Methods

Study Population and Protocol

Forty-five patients with AMI who underwent single-vessel primary PCI at admission between May 2012 and November 2013 were consecutively enrolled in this study. The exclusion criteria were as follows: 1. cardiogenic shock or congestive heart failure, 2. significant stenosis in the left main segment, 3. a history of previous PCI or coronary bypass surgery, and 4. insufficient images on echocardiography. AMI was diagnosed based on an increase in cardiac troponin T/I with sustained symptoms of ischemia. The study population included 37 ST-segment elevation myocardial infarction (STEMI) and eight non-STEMI patients. ST-segment elevation was defined as elevation of more than 0.1 mV in two contiguous ECG leads or new left bundle-branch block on a 12-lead ECG. MV complicating AMI was defined as the concomitant presence of one or more sites of significant stenosis in major epicardial coronary arteries that were not related to the region of myocardial infarction. Significant stenosis was defined as a visually estimated degree of stenosis of $>70\%$ ²⁾. Echocardiograms were recorded in order to measure the EAT thickness after the primary PCI in the coronary care unit by a physician who was blinded to the angiographic results. Two weeks after the primary PCI procedure, follow-up CAG was per-

formed. The present study complied with the Declaration of Helsinki with regard to investigations of human subjects, and our hospital's ethics committee approved the study protocol. All patients provided their written informed consent to participate in this study.

Measurement of Epicardial Adipose Tissue

The echocardiographic examinations were performed using a ACUSON SC2000 ultrasound machine with a 2.5-Mhz transducer (Siemens Healthcare, Malvern, PA, USA) after primary PCI. All patients were examined in the left lateral supine position, and routine studies were performed. EAT appears as an echo-lucent space between the linear echo-dense parietal pericardium and right ventricular epicardium, as previously described⁵⁾. EAT was measured on the free wall of the right ventricle on the still images of the 2D echocardiogram obtained at end diastole in both the parasternal long-axis and short-axis views. The anterior echo-lucent area between the parietal pericardium and the right ventricle epicardium was considered to be EAT. EAT was distinguished from pericardial effusion by its inhomogeneous, whitish-speckled appearance. The average value of two images obtained in the parasternal long-axis and short-axis views was calculated. All images were reviewed two weeks later to assess the interobserver and intraobserver correlations for the measurement of EAT. In order to determine the interobserver correlation, the analysis was repeated by a second observer who was blinded to the values obtained by the first observer.

Angioscopic Image Acquisition

Angioscopic observations of the IRA and non-IRAs were performed at the follow-up study. Twenty-five of the 45 patients completed the angioscopic study of all three major vessels. The other 20 patients underwent angioscopic observation in the IRA and a single non-IRA. The reasons for the incomplete angioscopic studies in the other non-IRA were as follows: 1) a small vessel diameter in 13 patients and 2) tortuous vessels in seven patients. Angioscopic images were obtained using the Fiber Imaging System FT-201 (FiberTech Co Ltd, Tokyo, Japan), and the color of each plaque was classified as previously described¹⁰⁾: 0. no yellow color; 1. pale yellow; 2. yellow; 3. deep yellow; 4. bright yellow. A plaque with a color grade of ≥ 2 was defined as an intense yellow plaque. We also examined the presence or absence of thrombi and rupture and/or erosion in the IRA and non-IRAs. In addition, we counted the number of intense yellow plaques in order to evaluate the degree of vessel vulnerability in the IRA and non-IRAs. Among the 25 patients who

Table 1. Baseline Characteristics

	SV (<i>n</i> =21)	MV (<i>n</i> =24)	<i>p</i> value
Age, years	60 ± 15 (33-84)	67 ± 15 (37-88)	0.050
Male gender, <i>n</i>	17	16	0.280
STEMI, <i>n</i>	20	17	0.033
BMI	24.7 ± 4.2	23.8 ± 3.1	0.381
Current smoking, <i>n</i>	11	10	0.472
Hypertension*, <i>n</i>	12	16	0.511
Total cholesterol (mg/dL)	188 ± 43	172 ± 23	0.071
LDL cholesterol (mg/dL)	119 ± 33	104 ± 22	0.045
HDL cholesterol (mg/dL)	39 ± 9	44 ± 10	0.073
Triglyceride (mg/dL)	110 ± 126	63 ± 35	0.042
HbA1c (NGSP) (%)	6.6 ± 1.2	6.5 ± 1.6	0.450
CRP (mg/dL)	0.86 ± 1.3	0.35 ± 0.55	0.066
BUN (mg/dL)	13.6 ± 5.0	15.0 ± 7.2	0.447
Cr (mg/dL)	0.82 ± 0.2	0.76 ± 0.2	0.315
Uric acid (mg/dL)	6.1 ± 1.6	5.6 ± 1.9	0.426
NT-pro BNP (pg/mL)	1108 ± 1469	1763 ± 3387	0.198
Drugs			
Beta blocker, <i>n</i> (%)	1 (5)	2 (8)	0.632
Ca ²⁺ channel blocker, <i>n</i> (%)	4 (19)	10 (42)	0.102
ACEI/ARB, <i>n</i> (%)	3 (14)	4 (17)	0.826
Aspirin, <i>n</i> (%)	1 (5)	1 (4)	0.923
Statin, <i>n</i> (%)	1 (5)	4 (17)	0.205
Nitrate, <i>n</i> (%)	0 (0)	1 (4)	0.344
Diuretic, <i>n</i> (%)	0 (0)	0 (0)	not detectable

The data are presented as the mean ± SD or number of patients.

STEMI=ST-elevation myocardial infarction; BMI=body mass index; LDL=low-density lipoprotein; HDL=high-density lipoprotein; hs CRP=high-sensitivity C-reactive protein; BUN=blood urea nitrogen; NT-pro BNP=n-terminal pro brain natriuretic peptide; NGSP=national glycohemoglobin standardization program; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker

*Defined as a systolic blood pressure of > 140 mmHg and/or the use of any prescribed hypertension therapy.

underwent angioscopic observations in two non-IRAs, we selected the larger number of intense yellow plaques (of the two vessels) for the further analysis. The number of patients with thrombi and rupture and/or erosion in the IRA and non-IRAs was also counted.

Statistical Analysis

Continuous variables are described as the mean ± SD. The statistical analyses were performed using the JMP 9 software program (SAS Institute Inc., Cary, NC, USA). Student's *t*-test was used to compare continuous variables, and Pearson's chi-square analysis was used to compare categorical variables. A multivariate logistic regression analysis was performed to identify the independent predictors of MV. Univariate logistic regression analyses were first conducted to identify the candidate variables from among the clinical and laboratory parameters, including the EAT thickness, age,

BMI, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, HbA1c, CRP, BUN, Cr, uric acid and NT-pro BNP. The multivariate model included the variables with a significance level of $p < 0.1$ in the univariate analysis. We then performed a step-down logistic regression analysis, and the least significant variable was dropped at each step until only covariates with a value of $p < 0.05$ remained. A receiver-operator characteristic curve for the variable predicting the presence of MV was generated from multiple sensitivity/specificity pairs. A value of $p < 0.05$ was considered to be significant.

Results

Baseline Characteristics and Procedural Results

The study population consisted of 33 men and 12 women (64 ± 14 years old, median 65). The base-

Table 2. Quantitative Angiographic Lesion Characteristics and Procedural Results

	SV	MV	<i>p</i> value
IRA, LAD/LCx/RCA	13/2/6	15/5/4	0.441
Reference diameter, mm	2.4 ± 0.7	2.2 ± 0.9	0.146
% stenosis	89 ± 19	83 ± 21	0.165
Minimum lumen diameter, mm	0.3 ± 0.5	0.5 ± 0.8	0.221
Stent diameter, mm	3.2 ± 0.45	3.2 ± 0.34	0.500
Stent length, mm	25 ± 7.9	26 ± 7.4	0.426
Minimum stent diameter, mm	2.4 ± 0.8	2.5 ± 0.6	0.221
% stenosis post PCI	13 ± 12	12 ± 8	0.322

The data are presented as the mean ± SD or number of patients.

IRA=infarct-related artery; LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; RCA=right coronary artery

Fig. 1. Representative case of an AMI patient with multi-vessel disease. An 80-year-old man with AMI underwent successful primary PCI to RCA. A. Parasternal long- (left) and short-axis (right) 2D echocardiographic images of the epicardial adipose tissue. The mean EAT thickness on the two images is 3.2 mm. B. A coronary angiogram shows a severe stenotic lesion with a filling defect in the RCA and another stenotic lesion in the obtuse marginal branch. White arrows 1 and 2 indicate the plaques observed on coronary angioscopy. C. Intense yellow plaques detected on coronary angioscopy.

line characteristics of the study population are summarized in **Table 1**. According to the CAG findings, 21 patients had SV and 24 patients had MV. Patients with STEMI were dominant in the SV group. The LDL cholesterol and triglyceride levels were significantly higher in the SV group than in the MV group. The number of patients given statin therapy for dys-

lipidemia was four (17%) in the MV group and one (5%) in the SV group. The lesion characteristics measured on quantitative coronary angiography and the procedural results are shown in **Table 2**. Primary PCI was successfully performed without technical complications. A representative case presenting AMI with MV is shown in **Fig. 1**.

Fig. 2. Comparison of the EAT thickness between single- and multivessel disease. The empty bar represents the SV group, and the solid bar represents the MV group. The mean EAT thickness of all enrolled patients was 2.4 ± 1.2 mm. The EAT thickness was significantly greater in the MV group than in the SV group (2.8 ± 1.3 mm vs. 1.9 ± 0.9 mm, $p=0.005$, respectively).

Table 3. Logistic Regression Analysis: Relationship with Multivessel Disease

Variables	odds ratio	95% CI	<i>p</i> value
Univariate analysis			
EAT thickness (mm)	2.029	1.130-3.643	0.018
Age	1.039	0.993-1.087	0.098
BMI	0.925	0.783-1.094	0.363
Total cholesterol (mg/dL)	0.986	0.968-1.004	0.130
LDL cholesterol (mg/dL)	0.980	0.957-1.003	0.088
HDL cholesterol (mg/dL)	1.049	0.983-1.120	0.149
Triglyceride (mg/dL)	0.992	0.982-1.003	0.141
HbA1c (%)	0.973	0.639-1.481	0.898
CRP (mg/dL)	0.556	0.256-1.209	0.139
BUN (mg/dL)	1.04	0.938-1.153	0.455
Cr (mg/dL)	0.200	0.009-4.440	0.309
NT-pro BNP (pg/mL)	1.000	0.999-1.000	0.428
Multivariate analysis			
EAT thickness (mm)	1.987	1.089-3.626	0.025
Age	1.035	0.987-1.085	0.155
LDL cholesterol (mg/dL)	0.988	0.963-1.013	0.338

CI=confidence interval

Epicardial Adipose Tissue Thickness and Presence of Multivessel Disease

The mean EAT thickness in the pooled data was

2.4 ± 1.2 mm. For interobserver correlations, the mean difference of EAT was 0.29 and the 95% limit of agreement was ± 0.24 . For intraobserver correlations,

the mean difference of EAT was 0.17 and the 95% limit of agreement was ± 0.11 . There were no differences in the mean EAT thickness between men and women (2.4 ± 1.2 mm vs. 2.3 ± 1.4 mm, respectively, $p=0.42$). The EAT thickness was significantly greater in the MV group than in the SV group (Fig. 2). A logistic regression analysis was used to assess independent associations between the clinical and laboratory parameters and MV (Table 3). Consequently, the univariate logistic analysis showed that the EAT thickness, age and LDL cholesterol level exhibited a significant association with MV ($p<0.1$), while the multivariate logistic analysis demonstrated that the EAT thickness was the only independent predictor of MV (odds ratio=1.987, 95% confidence interval: 1.089-3.626, $p=0.025$). The receiver-operator characteristic curve for the EAT thickness in predicting the MV is shown in Fig. 3. An EAT thickness of 2.3 mm was determined to be the optimal cut-off point for predicting MV, with a sensitivity of 70.8% and specificity of 71.4%. The area under the curve was 0.705 (95% confidence interval: 0.552-0.859, $p=0.019$).

Follow-up Study and Evaluation of Vessel Vulnerability in the Non-IRAs

A follow-up study was performed using coronary angiography with coronary angioscopy. The study population was divided into the thin (<2.3 mm; $n=22$) and thick (≥ 2.3 mm; $n=23$) EAT groups. The thin EAT group included 15 patients with SV, and the thick EAT group included 17 patients with MV. The angioscopic data, including the number of intense yellow plaques, presence or absence of thrombi and presence or absence of rupture and/or erosion are indicated in Table 4. The number of intense yellow plaques in the IRA was smaller than that observed in the non-IRAs, although the difference was not significant ($p=0.17$ in the thin EAT group and $p=0.47$ in the thick EAT group). In addition, there were no differences in the number of intense yellow plaques in the IRA or non-IRAs between the two groups. Moreover, there were no differences in the number of patients with the presence of thrombi or rupture and/or erosion between the two groups.

These findings indicate that the non-IRAs in patients with AMI are as vulnerable as the IRA and that the degree of vessel vulnerability is not dependent on the EAT thickness.

Discussion

The present study demonstrated that the EAT thickness in patients with AMI is closely associated

Sensitivity

Fig. 3. Receiver-operator characteristic curve for the EAT thickness in predicting multivessel disease. The optimal cut-off value for the EAT thickness was 2.3 mm, with a sensitivity of 70.8% and specificity of 71.4%. The area under the curve was 0.705 (95% confidence interval: 0.552-0.859, $p=0.019$).

with the presence of MV. In the present study, measurement of the EAT on echocardiograms was performed after primary PCI. Considering that echocardiograms can be performed quickly in the emergency room, we propose that measuring the EAT thickness using echocardiography prior to cardiac catheterization is useful for determining the proper treatment strategy, as measurements of the EAT thickness provide physicians with important information regarding the progression of whole-vessel atherosclerosis before treating the patient.

To the best of our knowledge, this is the first study to describe the association between the EAT and the development of coronary atherosclerosis in non-IRAs in AMI patients. Recently, several investigations regarding the association between EAT and the development of coronary atherosclerosis have been published^{6-9, 11-16}. For example, measurements of the EAT can be used to predict coronary artery disease (CAD) in both symptomatic and asymptomatic patients^{6-9, 11, 13, 16}, and, in stable CAD patients, a large EAT is closely associated with plaque vulnerability^{12, 14}. In addition, Bachar *et al.* demonstrated that an EAT thickness of

Table 4. Angioscopic Observations in the IRA and Non-IRAs

	Thin EAT (<i>n</i> =22)	Thick EAT (<i>n</i> =23)	<i>p</i> value
Number of intense yellow plaques per vessel			
IRA	1.5 ± 1.5	1.5 ± 1.5	0.479
Non-IRA	2.0 ± 2.2	1.8 ± 2.0	0.365
Number of patients with the presence of thrombus			
IRA	14	19	0.344
Non-IRA	6	10	0.360
Number of patients with the presence of rupture/erosion			
IRA	3	4	0.826
Non-IRA	4	4	0.835

The data are presented as the mean ± SD or number of patients.

≥2.4 mm can be used to predict CAD in asymptomatic patients⁷⁾, and Harada *et al.* reported that an EAT volume of ≥100 mL is a risk factor for acute coronary syndrome⁹⁾. These findings are consistent with our results, and an EAT thickness of 2.3 mm is considered to be a reasonable and proper cut-off value for predicting MV in AMI patients. Furthermore, we found that the degree of whole-vessel vulnerability in the heart in patients with AMI is not dependent on the EAT thickness. This finding appears to be reasonable because patients with AMI are expected to be “vulnerable” patients with multiple vulnerable vessels^{1, 3, 4, 17)}. However, it has been reported that the extent of vessel vulnerability is not related to the severity of vessel stenosis³⁾, and Park *et al.* demonstrated that a thick EAT is associated with a high level of plaque vulnerability based on a larger plaque volume, higher plaque burden and higher necrotic core burden assessed using virtual histology intravascular ultrasound. The differences in results between our study and Park’s study may be attributed to the differences in the study populations. Based on the findings of our study, we suggest that the administration of optimal medical therapy to stabilize vulnerable plaques in the IRA and non-IRAs is required in patients with AMI, regardless of the EAT thickness.

Study Limitations

The present study is associated with some limitations. First, this study was a single-center study with a relatively small study population composed exclusively of Japanese patients. Second, we used echocardiography to assess the quantitative value of EAT, as reported in previous studies^{6, 8, 14, 18)}. In contrast, other studies have employed multi-slice computed tomography to

assess the volume of the EAT^{7, 9, 11-13, 15, 16)}. Measurements of the EAT thickness obtained on echocardiography may not exactly represent the total EAT volume. On the other hand, echocardiographic assessments of epicardial fat are simple and practical to perform in the clinical setting and are frequently conducted in the emergency room. Therefore, we used the EAT thickness, as evaluated on echocardiography, in the present study. Third, observations of all three coronary arteries on angiography were not completed in 20 patients for lesion-related reasons. Therefore, the evaluations of atherosclerotic progression in the non-IRAs may be insufficient.

Conclusion

In conclusion, the EAT thickness in AMI patients is closely associated with the presence of multivessel disease. Measuring the EAT thickness may provide useful information for evaluating the severity of the clinical condition of AMI patients.

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The authors have no financial relationships with any industry groups to declare.

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