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The Relationship between Epicardial Adipose Tissue Thickness with Severity of Coronary Artery Disease in Indonesia

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Abstract

Epicardial adipose tissue (EAT), which is thought to be a component of visceral adiposity, is associated with the metabolic syndrome and considered as an indicator of cardiovascular risk. Correlation of EAT with coronary artery disease (CAD) in Indonesia is unknown. To address this issue, we examined the relationship between EAT thickness with severity of coronary lesion in Indonesian patients with CAD. Results revealed that one hundred and thirty one consecutive patients who underwent transthoracic echocardiography (TTE) and diagnostic coronary angiography were studied. The EAT thickness on the free wall of the right ventricle was measured at end-diastole from the parasternal long-axis views. Coronary angiograms were analyzed for severity of coronary artery disease using modified Gensini score. Accordingly, we classified the study population into two angiographic groups: patients with non-severe CAD (Gensini score ≤13) and patients with severe CAD (Genisini score >13). There were no significant differences between the groups with respect to anthropometric measurements, including body mass index and waist circumference (p=0.473 and 0.947, respectively).

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The patients in severe CAD group had greater EAT thickness compared with non-severe CAD group (mean EAT thickness was 8.5±2.4 mm and 6.1±2.5 mm, respectively with p<0.001).EAT thickness of >7.0 mm had an 78.2 % sensitivity and an 71.7% specificity (ROC area of 0.800, p<0.001, 95% CI [0.72-0.88] for predicting severe CAD. In conclusions EAT thickness was significantly correlated with the severity of CADin Indonesian patients with stable CAD.

***Keywords*:** epicardial adipose tissue; coronary artery disease; echocardiography; Indonesia.

1. Introduction

Cardiovascular disease (CVDs) is the number one cause of death globally; more people die annually from CVDs than from any other cause. An estimated 17.3 million people died from CVDs in 2008, representing 30% of all global death [1]. Of these deaths, an estimated 7.3 million were due to coronary artery disease (CAD) [2].

Inflammation plays an integral role in the pathogenesis of atherosclerotic CAD [3-5]. Therefore the interest in the EAT that is located between the myocardium and the pericardium surrounding both ventricles with variable extent and distribution patterns arouse [6-8]. Because of its endocrine and paracrine activity, secreting pro-inflammatory and anti-inflammatory cytokines and chemokines, it has been suggested to influence coronary atherosclerosis development [9-13].

TTE enables non-invasive assessment of EAT [14,15]. To date, the correlation of EAT with severity of CAD in Indonesia remains unknown. To address this issue, we examined the relationship between EAT thickness measured by transthoracic echocardiography with severity of CAD in Indonesian patients with stable CAD.

2. Materials and Methods

2.1 Study Design

The study was designed as an observational cross-sectional study. The study was approved by Hasanuddin University ethic committee and written informed consent was obtained from all participants.

2.2 Patients

We studied 131 consecutive patients who had undergone coronary angiography from July 2015 through March 2016 because of clinical diagnoses of stable CAD. The prospective study was performed in a single tertiary center. Patient with acute coronary syndrome, severe heart failure (New York Heart Association Class III-IV), poor echocardiographic images, severe valvular pathologic condition, and chronic kidney disease were excluded.

Patients were defined as hypertensive (JNC VII Guidelines), if they had a systolic pressure greater than 140 mmHg or a diastolic pressure greater than 90 mmHg, or if they were being treated with an antihypertensive medication. Patients were considered to have type II diabetes mellitus if they were previously diagnosed or

following the 2010 American Diabetes Association (ADA) diabetes diagnostic criteria, or if the patients were being treated with antidiabetic medication. Whereas dyslipidemia was defined from the NHLBI ATP III prevention guidelines, or the subjects were being treated with a lowering lipid medication.

2.3 Echocardiography

Transthoracic echocardiographic (TTE) examinations were performed using a Vivid 7®cardiac ultrasound system (GE Medical Systems; Horten, Norway) with a 2.5- to 3.5-MHz transducer with patients in the left lateral decubitus position. We measured EAT thickness on the free wall of right ventricle from the parasternal long-axis views. EAT was identified as an echo-free space in the pericardial layers on the 2-dimensional echocardiography, and its thickness was measured perpendicularly on the free wall of the right ventricle at end-diastole [15,16]. As illustrated in Figure 1. EAT thickness was measured at end-diastole from parasternal long- and short-axis B mode still-frame images by two echocardiographers who were blinded to coronary angiography data. Parasternal long- and short-axis measurements were averaged to obtain the mean thickness.

2.4 Coronary Angiography

Selective coronary angiography was applied to all patients with Judkins technique. Angiograms were recorded in multiple projections with a biplanar digital cardiac imaging system (Philips Integris DCI, Eindhoven, the Netherlands). Cine angiograms were evaluated by two experienced cardiologists. By examining all of the coronary angiograms, the localization and luminal stenosis rate of all coronary artery lesions were identified.

The severity of coronary artery lesions was scored using a modified Gensini score [17,18]. In brief, the coronary circulation was divided into eight proximal segments; the percentage by which each lesion in the proximal coronary circulation narrowed the artery was assessed according to the maximal narrowing of the diameter of the artery in all projections. The extent and severity of proximal coronary disease was assessed by assigning points to each lesion as follows: less than 50% of the luminal diameter, 1 point; 50% to 74% stenosis, 2 points; 75% to 99% stenosis, 3 points, and total obstruction, 4 points. The points of each lesion in the proximal coronary circulation were summed and a score for severity of coronary atherosclerosis was obtained. According to the modified Gensini score for classification of the degree of coronary stenosis [19]; the results of total scores can be separated into mild lesions (1-6 points), moderate lesions (7-13 points), and severe lesions (>13 points). Accordingly, we classified the study population into two angiographic groups: patients with non-severe CAD (Gensini score ≤13) and patients with severe CAD (Genisini score >13).

2.5 Statistical analyses

Continuous variables are expressed as means±standard deviation. Categorical variables were compared with the chi-square test. The Pearson correlation analysis was used to determine the relationship between mean values. The cut-off value of EAT thickness for predicting severe CAD with corresponding specificity and sensitivity was estimated by receiver operating characteristic (ROC) curve analysis. A *p*value of less than 0.05 was considered statistically significant. SPSS software (Statistical Package for the Social Sciences, version 21.0, SSPS Inc., Chicago, IL, USA) was used for all statistical calculations.

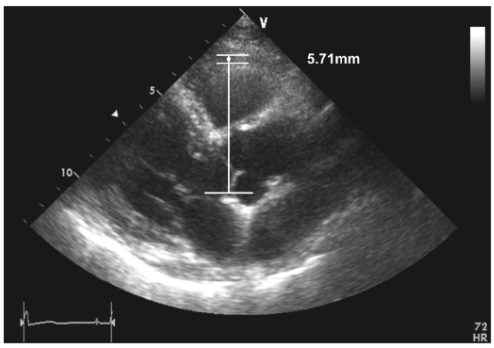

Figure 1: Example of measurenment of epicardial adipose tissue thickness. Epicardial adipose tissue was identified as an echo-free space in the pericardial layers on the 2-dimensioanl echocardiography and its thickness was measured perpendicularly on the free wall of the right ventricle at end-diastole.

3. Results

3.1 Demographic and Echocardiographic Characteristics of Study Population

There were 100 male and 31 female in the study population. The mean age was 57.0±8.0 years. The demographic and echocardiographic data of study groups are presented in Table 1. Patients with severe CAD were significantly more male smoker and had lower ejection fraction than were patients with non-severe CAD. Mean EAT thickness was 6.1±2.5 mm in the non-severe CAD group and 8.5±2.4 mm in the severe CAD group (p<0.001). There were no significant differences between the groups with respect to anthropometric measurements, including body mass index and waist circumference.

3.2 Relationship between EAT Thickness with CAD Severity

Analysis of the relationship between EAT thickness with severity of CAD measured by Gensini score showed that a positive linear relationship for the entire subjects (R^2=19.6%; Figure 2). The thickness of EAT was increased in those with severe CAD in comparison to those with non-severe CAD (Figure 3).

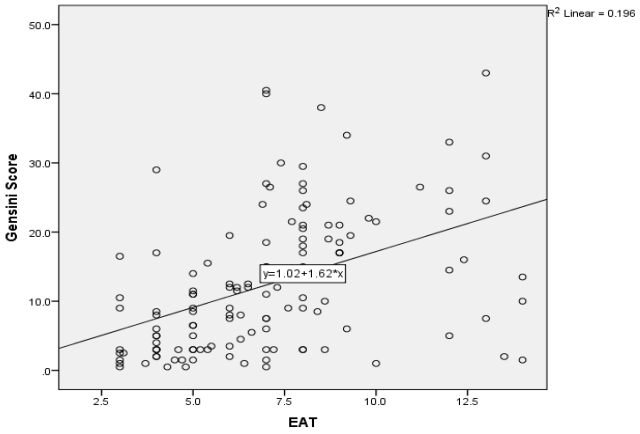

Figure 2: Scatter plot illustrating the relationship between epicardial adipose tissue thickness and Gensini score.

Table 1: Demographic and echocardiographic characteristics of subjects by study groups

Variable (*n*=131)	Non-severe CAD (*n*=78)	Severe CAD (*n*=53)	*p* value
Demographic characteristics			
Age (years)	55.9±7.9	57.9±7.3	0.137
Gender (male/female)	51/27	49/4	<0.001
BMI (kg/m^2)	25.2±4.4	24.7±2.8	0.473
Waist circumference (cm)	91.3±13.2	91.5±11.9	0.947
Hypertension, *n*(%)	30 (53.6)	26 (46.4)	0.306
Smoker, *n*(%)	33 (49.3)	34 (50.7)	0.023
Diabetes mellitus, *n*(%)	13 (46.4)	15 (53.6)	0.168
Dyslipidemia, *n*(%)	73 (60.3)	48 (39.7)	0.375
Family history, *n*(%)	6 (54.5)	5 (45.5)	0.480
Echocardiographic characteristics			
Ejection fraction (%)	60.7±8.7	57.2±7.4	0.019
EAT thickness (mm)	6.1±2.5	8.5±2.4	<0.001

Values are presented as mean±standard deviation or number (%).

EAT,epicardial adipose tissue.

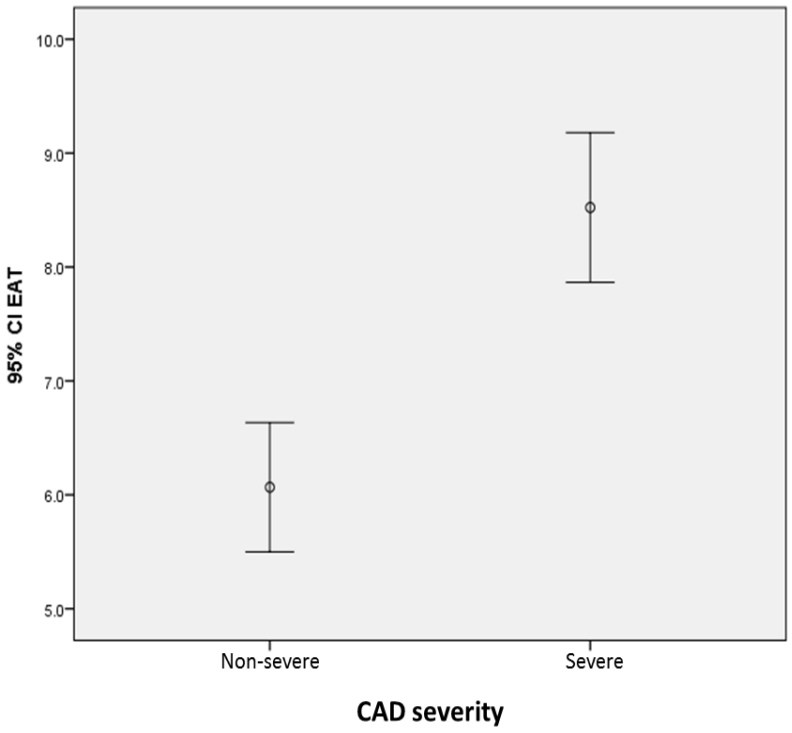

Figure 3: Box and whisker diagram illustrating the relationship between Epicardial adipose tissue thickness and severity of coronary artery disease.

3.3 EAT Thickness as Predictor of CAD Severity

EAT thickness of >7.0 mm had an 78.2 % sensitivity and an 71.7% specificity (ROC area of 0.800, $p<0.001$, 95% CI [0.72-0.88] for predicting severe CAD); Figure 4, Table 2.

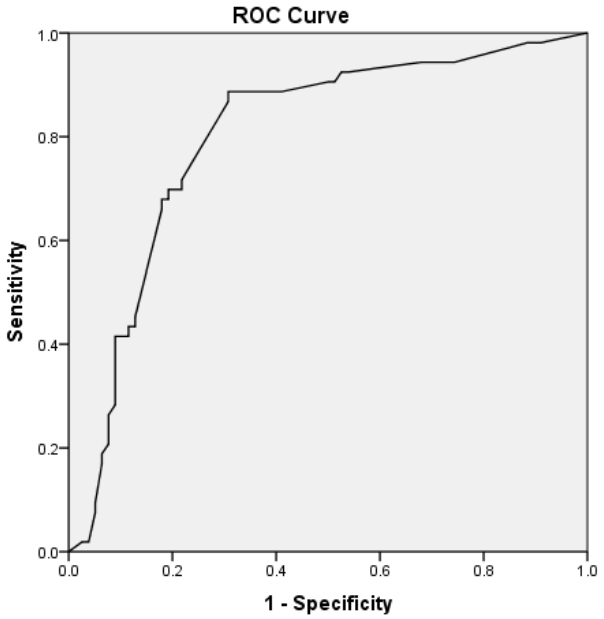

Figure 4: Receiver operating characteristic curve of the epicardial adipose tissue thickness in predicting severe coronary artery disease.

Table 2: Predictor of coronary artery disease severity by epicardial adipose tissue thickness

Predictor	Accuracy	Cutoff	Sensitivity	Specificity	PPV	NPV	*p*
EAT	**80.0%**	**>7.0 mm**	**78.2%**	**71.7%**	**80.3%**	**69.1%**	**<0.001**

PPV, positive predictive value; NPV, negative predictive value

4. Discussion

To the best of our knowledge, this is the first study to analyze the relationship between EAT thickness and CAD severity in Indonesia. This study shows an association between EAT thickness measured by TTE and the severity of CAD.

Until now, magnetic resonance imaging (MRI) has been accepted as a gold standard for measuring EAT thickness. In 2003, Iacobellis and his colleagues first reported the development of the echocardiographic measurement of EAT. They showed that echocardiographic EAT thickness has good correlation with MRI abdominal, epicardial fat measurements, anthropometric and metabolic parameters [15,16].

Our result showed that patients with severe CAD measured by Gensini score had thicker EAT compared with

patient with non-severe CAD. Two potential mechanisms for this association have been proposed. First, EAT is a component of visceral adiposity and is related to metabolic syndrome and cardiovascular risk factors. Secondly, it has paracrine and endocrine functions. Sacks and his colleagues pointed out the paracrine and vasocrine signaling effects of epicardial adipokines for the development of atherogenesis [14,16,20,21].

Furthermore, we found that there were no significant differences between the groups with respect to body mass index and waist circumference. This finding highlights the importance of visceral adiposity but not total adiposity with respect to cardiovascular risk. Thickness in EAT is also associated with metabolic syndrome [22], insulin resistance [23], endothelial dysfunction [24], and overt atherosclerotic CAD [25].Clinical observations suggest that proximal portions of the coronary arteries are more deeply embedded in epicardial fat than are distal portions and are thus more susceptible to atherosclerosis. This has been attributed to the relative paucity of periadventitial adipose tissue, which is in continuity with the epicardial adipose tissue.

Epicardial adipose tissue produces miscellaneous proinflammatory and proatherogenic mediators, including interleukin-6, interleukin-1, tumor necrosis factor-α, monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, angiotensinogen, leptin, resistin, and visfatin. On the other hand, adiponectin, which exerts an antiatherogenic effect via the improvement of endothelial function and the mitigation of inflammation, has been shown to be under expressed in the EAT of patients who have CAD [26-28].

Gökdeniz and associates analyzed relationship of EAT thickness to the CAD complexity in non-diabetic subjects. They found EAT thickness to be significantly correlated to SYNTAX score (r =0.629; p<0.001). They also determined a cutoff value of 5 mm EAT thickness for the prediction of an intermediate to high SYNTAX score (ROC area of 0.851, 95% CI [0.77–0.91] at a specificity of 92.2% and a sensitivity of 77.4%.However, those investigators studied non-diabetic patients only, whereas we analyzed the relationship of EAT thickness with CAD severity in a diabetic and non-diabetic population [29]. They analyzed the severity of CAD by SYNTAX score, whereas we used Gensini score.

5. Limitation

Our analysis was limited by the studied population because it included only those patients pre-selected to undergo coronary angiography. As non-invasive tools for the diagnosis of coronary artery disease have been developed, a population-based prospective study with a large number of patients can be performed. Therefore, an epidemiologic study is required to confirm these results. Serum levels of interleukins, cytokines, and adipokines, which could hint at the underlying mechanisms of atherosclerosis in CAD, were not evaluated

6. Conclusion

Our results could help identify severe CAD by transthoracal echocardiography-relatively inexpensive and readily available- before coronary angiography, thereby indicating whether early invasive coronary angiography and timely interventions should be performed especially in the setting where catheter lab resources are scant and waiting time for the examination is long.

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