EPICARDIAL ADIPOSE TISSUE THICKNESS AS A PREDICTOR OF CORONARY LESION SEVERITY IN STABLE CORONARY ARTERY DISEASE PATIENTS

MirnawatiMappiare, Abdul Hakim Alkatiri, Peter Kabo
Department of Cardiology, Faculty of Medicine, University of Hasanuddin, Makassar, Indonesia

ABSTRACT

Background: Epicardial adipose tissue (EAT) is a visceral adipose tissue surrounding the heart. Correlation of EAT with coronary artery disease (CAD) in Indonesia is unknown. To address this issue, we evaluate the capacity of EAT thickness measured by transthoracic echocardiogram (TTE) to predict the severity of coronary lesion.
Methods: In this cross sectional study conducted in Wahidin Sudirohusodo Hospital, Makassar, Indonesia, 127 stable CAD patients were enrolled. EAT was identified as an echo-lucent area on the free wall of the right ventricle of the two-dimensional TTE at end diastole in the parasternal long-axis view. Coronary angiograms were analyzed for severity of CAD using modified Gensini score. Accordingly, we classified the study population into two angiographic groups: patients with non-severe CAD (score ≤13; n=73) and severe CAD (score >13; n=54).
Results: There were no significant differences between the groups with respect to body mass index and waist circumference (p=0,562 and 0,659, respectively). There was a positive linear relationship between EAT thickness and modified Gensini score for the entire subjects (R2=21.4%). EAT thickness was significantly greater in patients with severe CAD than in those with non-severe CAD (8,4±2,1 mm vs6,1±2.5 mm, p<0,001). EAT thickness of >7,0 mm had 79,6% sensitivity and 71,2% specificity (ROC area of 0,812, p<0,001)for predicting severe CAD.
Conclusion: Our results could help identify severe CAD by readily available and relatively inexpensive TTE, thereby indicating whether early invasive coronary angiography and timely interventions should be performed.
Keywords: epicardial adipose tissue, echocardiography, coronary artery disease, Indonesia.

ABSTRAK

Latar Belakang: Lemak epikardial (epicardial adipose tissue, EAT) merupakan jaringan lemak viseral yang mengelilingi jantung. Hubungan antara EAT dan penyakit jantung koroner (PJK) di Indonesia belum diketahui. Studi ini dilakukan untuk mengidentifikasi nilai prediktor ketebalan EAT yang diukur melalui ekokardiografi terhadap severitas lesi koroner.
Metode: Studi yang bersifatcross sectional ini dilakukan di Rumah Sakit Wahidin Sudirohusodo, Makassar, Indonesia pada 127 pasien PJK stabil. Ketebalan EAT diukur pada freewall ventrikel kanan dari potongan parasternal long axis di akhir fase diastolik. Lemak epikardial tampak sebagai daerah yang echo-free. Severitas lesi koroner dinilai pada angiografi koroner dengan menggunakan modifikasi skor Gensini. Berdasarkan skor tersebut subyek dibagi menjadi dua grup yaitu pasien dengan PJK tidak berat (skor ≤13; n=73) dan PJK berat (skor>13; n=54).
Hasil: Tidak ada perbedaan signifikan indeks massa tubuh dan lingkar pinggang pada kedua grup (nilai p masing-masing 0,562 dan 0,659). Terdapat korelasi positif antara ketebalan EAT dan modifikasi skor Gens ini dengan kontribusi sebesar 21.4%. Subyek dengan lesi koroner berat memiliki rerata EAT yang lebih tebal dibandingkan dengan lesi koroner tidak berat (8,4+2,1 mm banding 6,1+2,5 mm, p<0,001). Ketebalan EAT > 7,0 mm dapat memprediksi lesi koroner berat dengan sensitivitas 79,6% dan spesifitas 71,2% (area ROC 0,812, p<0,001).
Simpulan: hasil studi ini dapat membantu identifikasi PJK berat dengan menggunakan ekokardiografi yang banyak tersedia dan relatif tidak mahal, sehingga berperan dalam perencaaan angiografi koroner serta waktu intervensi yang tepat.
Kata kunci: lemak epikardial, ekokardiografi, penyakit jantung koroner, Indonesia.

INTRODUCTION

Cardiovascular disease is the leading global cause of death, accounting for 17,3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030.1Of these deaths, an estimated 7,3 million were due to CAD.2Inflammation 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.14,15To 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 TTE with coronary lesion severity in Indonesian patients with stable CAD.

METHODS

Study Design

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

Address for Correspondance : dr. MirnawatiMappiare
Email: mirnamappiare@gmail.com

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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 TTE with coronary lesion severity in Indonesian patients with stable CAD.

Methods

Study Design

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

Patients

In this study, 127 consecutive patients who had undergone coronary angiography from July 2015 through March 2016 because of clinical diagnoses of stable CAD were enrolled. Patient with acute coronary syndrome, severe heart failure (New York Heart Association Class III-IV), poor echocardiographic images 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.

Echocardiography

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 two echocardiographers who were blinded to coronary angiography data.

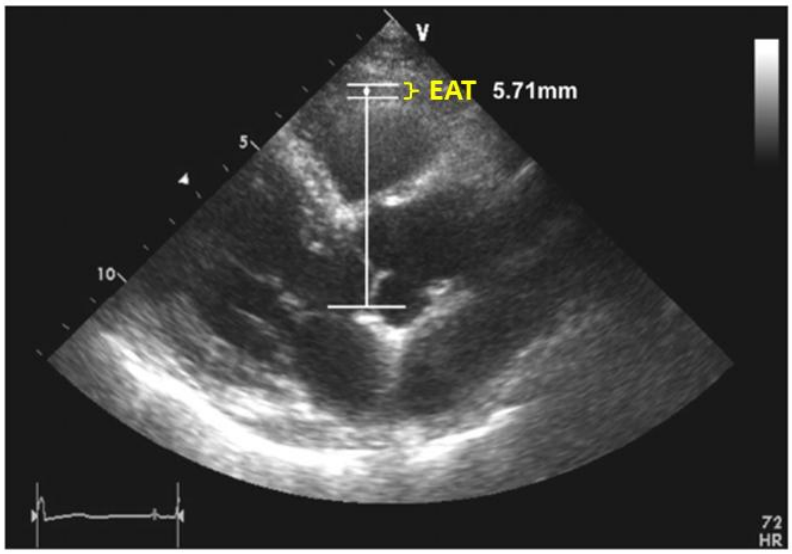

Figure 1. Example of measurement of EAT thickness. EAT was identified as an echo-free space in the pericardial layers on the 2-dimensional echocardiography and its thickness was measured perpendicularly on the free wall of the right ventricle at end-diastole.

Coronary Angiography

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 (score ≤13) and patients with severe CAD (score >13).

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.

Results

Characteristics of Study Population

There were 96 male and 31 female in this study. The mean age was 57,6±7,4 years. The demographic and EAT thickness data of study groups are presented in table below. Mean EAT thickness was 6,1±2,5 mm in the non-severe CAD group and 8,4±2,1 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.

Characteristics of subjects by study groups

Variable (*n*=131)	Non-severe CAD (*n*=73)	Severe CAD (*n*=54)	*p* value
Age (years)	56,5±7,4	59,1±7,2	0,053
Gender (male/female)	58/15	38/16	0,166
BMI (kg/m^2)	24,9±4,3	25,3±3,1	0,562
Waist circumference (cm)	91,0±13,2	92,1±12,3	0,659
Hypertension, *n* (%)	27 (50,9)	26 (49,1)	0,140
Smoker, *n* (%)	35 (52,2)	32 (47,8)	0,139
Diabetes mellitus, *n* (%)	12 (42,9)	16 (57,1)	0,060
Dyslipidemia, *n* (%)	68 (58,1)	49 (41,9)	0,429
Family history, *n* (%)	5 (45,5)	6 (54,5)	0,297
EAT thickness (mm)	**6,1±2,5**	**8,4±2,1**	**<0,001**

Values are presented as mean ± standard deviation or number (%).
EAT, epicardial adipose tissue.

Relationship between EAT Thickness with CAD Severity

Analysis of the relationship between EAT thickness with coronary lesion severity measured by modified Gensini score showed that a positive linear relationship for the entire subjects (R^2=21,4%; Figure 2). The thickness of EAT was increased in those with severe CAD in comparison to those with non-severe CAD (Figure 3).

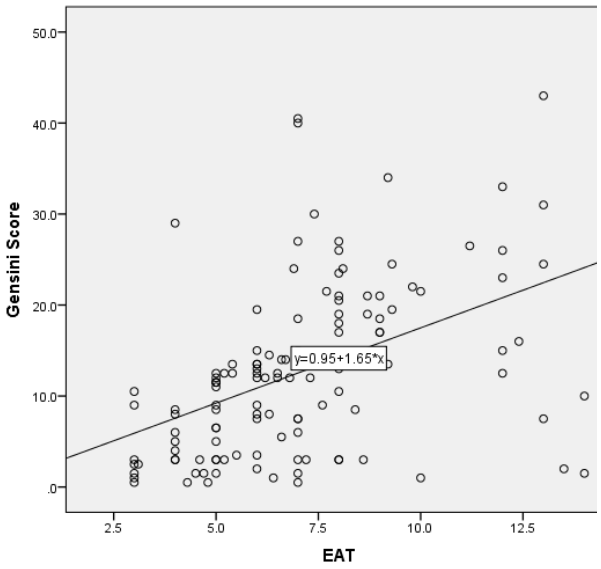

Figure 2. Scatter plot illustrating the relationship between EAT thickness and modified Gensini score.

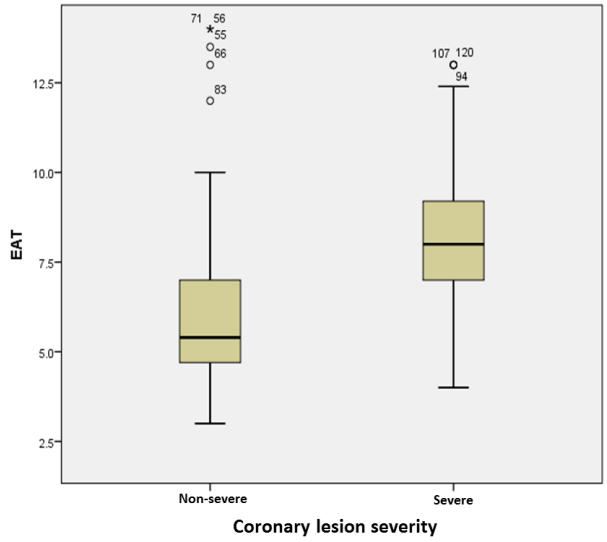

Figure 3. Box and whisker diagram illustrating the relationship between EAT thickness and coronary lesion severity.

EAT Thickness as Predictor of Coronary Lesion Severity

EAT thickness of >7,0 mm had79,6 % sensitivity and 71,2% specificity (ROC area of 0,812, p<0,001) for predicting severe CAD); Figure 4.

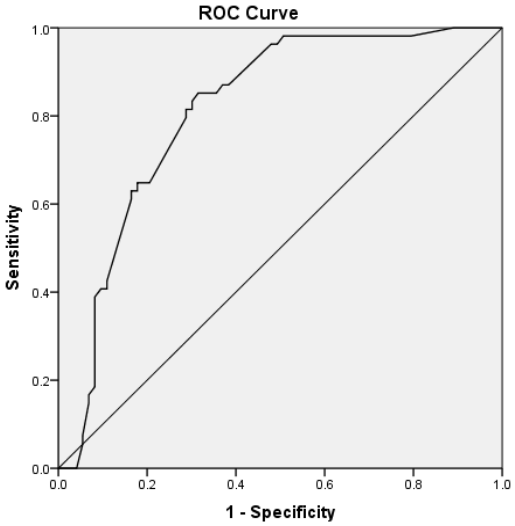

Figure 4. The area under curve on ROC curve analysis of EAT thickness as the predictor of severe CAD.

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 coronary lesion severity in stable CAD patients.

Until now, magnetic resonance imaging (MRI) has been accepted as a gold standard for measuring EAT thickness. In 2003, Iacobellis et al. 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 modified 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 et al. pointed out the paracrine and vasocrine signaling effects of epicardialadipokines 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 EAT.

EAT 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 underexpressed 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.[29]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. They analyzed the severity of CAD by SYNTAX score, whereas we used Gensini score.

Limitation

We could not confirm EAT thickness using the standard MRI. In addition, as EAT has a three-dimensional distribution, two-dimensional echocardiography may not completely assess the total amount of epicardial adiposity.

Conclusion

EAT thickness measured by TTE (relatively inexpensive and readily available) might be beneficial in the early identification of patients who have severe coronary lesion, thereby indicating whether early invasive coronary angiography and timely interventions should be performed.

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