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Epikardiyal yağ dokusu kalınlığı ve safen ven greft hastalığının patofizyolojisi ile ilişkisi

Epicardial adipose tissue thickness and its relationship with the pathophysiology of saphenous vein graft disease

Mustafa Doğduş[1], Fethi Yavuz[2], Mehmet Küçükosmanoğlu[2], Arafat Yıldırım[2], Salih Kılıç[2]

1Uşak Üniversitesi, Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Uşak, Türkiye

2Sağlık Bilimleri Üniversitesi, Adana Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Adana, Türkiye

ÖZ

GİRİŞ ve AMAÇ: *Teknik ve tıbbi ilerlemelere rağmen SVGH, yüksek morbidite ve mortalite oranları ile önemli bir sorun olmaya devam etmektedir. EYD, parakrin veya vazokrin yolaklar ile lokal olarak koroner damarlar ve miyokard ile iletişim kurar. EYD ve KAH arasındaki ilişki iyi bilinmesine rağmen, EYD'nin SVGH üzerindeki etkisi hakkında yeterli bilgi yoktur. Bu nedenle EYD ve SVGH arasındaki ilişkiyi araştırmayı amaçladık.*

YÖNTEM ve GEREÇLER: *Çalışma popülasyonu, KABG cerrahisinden bir yıldan fazla bir süre sonra elektif KAG uygulanan 124 ardışık hastadan oluşmaktaydı. Hastalar SVG açıklığının derecesine göre iki gruba ayrıldı. EYD kalınlığı ölçümleri, parasternal uzun ve kısa eksenlerden sağ ventrikülün serbest duvarına çizilen çizgilere dik olan düşük ekojenik yoğunluk alanından belirlendi.*

BULGULAR: *EYD kalınlığı SVGH (+) grubunda SVGH (-) grubuna göre anlamlı olarak daha yüksekti (p <0.001). Çok değişkenli lojistik regresyon modelleri, EYD kalınlığının (p <0.001, Risk oranı (OR) = 3.65,% 95 Güven aralığı (C.I.) = 2.52–8.12) SVG darlığını öngörmede bağımsız bir faktör olduğunu ortaya koymuştur. 7,4 mm'den büyük bir EYD kalınlığı değeri, SVG darlığının öngörülmesi için% 86,4 duyarlılığa,% 69,1 özgüllüğe sahiptir.*

TARTIŞMA ve SONUÇ: *EYD kalınlığı SVG darlığının varlığı ile ilişkilidir. Bu nedenle EYD kalınlığı, SVG darlığının öngörülmesi için klasik risk faktörlerine ilave olarak kolayca ölçülebilen girişimsel olmayan bir yardımcı belirteç görevi görebilir.*

Anahtar Kelimeler: *epikardiyal yağ dokusu, koroner arter hastalığı, safen ven grefti*

ABSTRACT

INTRODUCTION: *Despite technical and medical advances, SVGD remains a significant problem that is associated with high morbidity and mortality rates. EAT communicates locally with coronary vessels and myocardium through paracrine or vasocrine pathways. Although the relationship between EAT and CAD is well known, there is not sufficient information about effect of EAT on SVGD. Therefore, we aimed to investigate the relationship between EAT and SVGD.*

METHODS: *The study population consisted of 124 consecutive patients who underwent elective CAG more than one year after CABG surgery. The patients were divided into two groups depending on the extent of SVG patency. EAT thickness measurements were determined from the low echogenic density area perpendicular to lines drawn from the parasternal long and short axes to the free wall of the right ventricle.*

RESULTS: *EAT thickness was significantly higher in the SVGD (+) group than in the SVGD (-) group (p < 0.001). The multivariate logistic regression models revealed that EAT thickness (p < 0.001, Odds ratio (OR) = 3.65, 95% Confidence interval (C.I.) = 2.52–8.12) was found to be independent factor for predicting SVG stenosis. An EAT thickness value of > 7.4 mm has 86.4 % sensitivity, 69.1 % specificity for the prediction of SVG stenosis.*

DISCUSSION AND CONCLUSION: *EAT thickness is related to the presence of SVG stenosis. EAT thickness therefore could serve as an easily measurable non-invasive adjunctive marker to classical risk factors for the prediction of SVG stenosis.*

Keywords: *epicardial adipose tissue, coronary artery disease, saphenous vein graft*

İletişim / Correspondence:

Dr. Mustafa Doğduş

Uşak Üniversitesi, Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Uşak, Türkiye

E-mail: mdogdus@hotmail.com

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INTRODUCTION

Coronary artery bypass graft (CABG) surgery increases survival in patients with severe coronary artery disease (CAD) and still remains one of the most common surgical procedures in the world (1). Both arterial and venous conduits can be used in this procedure, but patency rates of saphenous vein grafts (SVGs) are lower compared to arterial conduits. Patency rates at 1st, 5th and 10th years after CABG were reported to be 93%, 74% and 41%, respectively (2). Most common mechanisms for saphenous vein graft disease (SVGD) are thrombosis (first month), neointimal hyperplasia (1–12 months), and atherosclerosis (>12 months) (3). Despite technical and medical advances, SVGD remains a significant problem that is associated with high morbidity and mortality rates.

Epicardial adipose tissue (EAT) that has key roles in the regulations of cardiovascular physiology and pathophysiology, is located in atrioventricular and interventricular grooves, surrounding the major branches of coronary arteries, atria, right ventricular free wall, and apex of the left ventricle (4). EAT communicates locally with coronary vessels and myocardium through paracrine or vasocrine pathways, and also secretes pro-atherogenic and pro-inflammatory cytokines which affects cardiac local functions (5).

Endothelial dysfunction and structural changes of the coronary microcirculation are well established features of patients with increased EAT (6-8). Although the relationship between EAT and CAD is well known, there is not any sufficient information about the effect of EAT on SVG stenosis. Therefore, we aimed to investigate the relationship between EAT thickness and SVG stenosis.

MATERIALS AND METHODS

Study population

The study population consisted of 124 consecutive patients who underwent elective coronary angiography (CAG) between October 2017 and May 2018 more than one year (mean 6.4 years) after CABG surgery, which involved the use of at least one SVG for bypass. The indications of elective coronary angiography were either the presence of typical angina or positive or equivocal results of noninvasive screening tests for myocardial ischemia. The patients were divided into two groups depending on the extent of SVG patency. Stenosis of 50% or greater within the SVG was categorized as SVGD (+) group (58 patients) (9,10). Patients with stenosis below 50% were defined as SVGD (-) group (66 patients).

Exclusion criteria were history of chronic renal and hepatic failure, previously known inflammatory/autoimmune disorders, thyroid dysfunction, malignancy, and receiving radiotherapy treatment. The study was approved by the local ethics committee. Informed consent was obtained from all of the patients included in the study.

Baseline clinical and demographic characteristics of the study population were recorded. Hypertension (HT) was defined by a previous diagnosis of HT or the presence of systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg. Diabetes Mellitus (DM) was defined as fasting plasma glucose ≥126 mg/dl or plasma glucose level ≥ 200 mg/dl 2 hours after the 75 mg oral glucose tolerance test or glycated hemoglobin ≥6.5% or patients using antidiabetic medications. Hyperlipidemia (HLP) was defined as a baseline total cholesterol level >200 mg/dL or current treatment with statins and/or lipid-lowering agents. Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m2). Cigarette smoking was defined as smoking ≥ 1 packet of cigarettes a day. Blood samples were taken from all participants after 12-14 hours fasting.

Measurement of EAT thickness by echocardiography

The echocardiographic evaluations were done in the left lateral decubitus position with one-lead ECG monitoring. All patients underwent 2-dimensional transthoracic echocardiographic (HD11 XE Ultrasound system, Philips, Canada) evaluation equipped with a 1.5- 4.0 MHz transducer. LVEF was obtained by using modified Simpson's method as specified by current guideline of chamber quantification by American Society of Echocardiography (11).

EAT thickness measurements were determined from the low echogenic density area perpendicular to lines drawn from the parasternal long and short axes to the free wall of the right ventricle, using 2-dimensional and M-mode measurements. The aortic annulus was considered to be an anatomical landmark. Average values were measured in three separate cardiac cycles and recorded (12). The measurement of EAT thickness was performed by the same cardiologist who was unaware of the clinical and coronary angiographic data.

Angiographic assessment

CAG was performed by the Judkins technique without the use of vasodilating agents using 6-French right and left heart catheters using Siemens AXIOM Artis (Erlangen, Germany). Two blinded interventional cardiologists analyzed the coronary angiograms without knowledge of the clinical status, and echocardiographic results. Saphenous vein grafts were visualized from at least two angles after selective injection of contrast agent. SVGD was defined as stenosis of 50% or greater within the SVG.

Statistical analysis

Normally distributed continuous data were expressed as mean ± standard deviation (minimum–maximum). Continuous variables that are not normally distributed were expressed as median (minimum–maximum), and categorical variables were expressed as n and percentages. The normal distribution of the data was evaluated by Lilliefors-corrected Kolmogorov-Smirnov test and Shapiro-Wilk test and the variance homogeneity was evaluated by the Levene test. The Independent-Samples T test was used with the Bootstrap results when comparing two independent groups with one according to the quantitative data, and the Mann-Whitney U test was used together with the Monte Carlo results. To compare categorical variables, Pearson chi-square and Fisher Exact tests were tested using exact results. Multivariate logistic regression test was used with Forward Stepwise (Wald) method in order to determine the relationship between the explanatory variables which were significant in other analyses. Receiver operator characteristic curve (ROC) was used to analyze the sensitivity of EAT thickness for predicting SVG stenosis. Variables were examined at 95% confidence level. A p-value < 0.05 was considered as statistically significant. SPSS 25.0 (IBM Corp., Armonk, NY, USA) program was used for variable analysis.

RESULTS

A total of 124 patients were included in the study. The mean age of the patients was 66.8 ± 9.5 years, and 68.7% were male. The demographic, echocardiographic, and laboratory characteristics of the study population were presented in Table 1. The number of patients with a history of HT, DM, and HLP were significantly higher in the SVGD (+) group than the SVGD (-) group (Table 1). There were not any significant differences between groups for age, gender, body mass index, smoking, systolic and diastolic blood pressure (Table 1). Left ventricular ejection fraction was lower in the SVGD (+) group than the SVGD (-) group ($p = 0.01$) (Table 1).

TC, TG, and LDL-C were significantly higher in the SVGD (+) group than in the SVGD (-) group ($p = 0.017$; $p < 0.001$; $p = 0.001$, respectively); and HDL-C was significantly lower in the SVGD (+) group than in the SVGD (-) group ($p = 0.032$) (Table 1).

Mean platelet volume (MPV) was significantly higher in the SVGD (+) group than in the SVGD (-) group ($p = 0.002$) (Table 1).

EAT thickness was significantly higher in the SVGD (+) group than in the SVGD (-) group (p <0.001) (Table 1).

Table 1. Demographic, echocardiographic, and laboratory characteristics

	SVGD (-) group (n = 66)	SVGD (+) group (n = 58)	P value
Age	65.6 ± 9.7	67.5 ± 9.1	0.242
BMI (kg/m^2)	28.1 ± 4.2	28.8 ± 4.5	0.376
Male gender, n (%)	45 (68.1)	41 (70.6)	0.312
Hypertension, n (%)	40 (60.6)	43 (74.1)	0.008
Diabetes Mellitus, n (%)	28 (42.4)	30 (51.7)	0.014
Hyperlipidemia, n (%)	36 (54.5)	39 (67.2)	0.011
Smoking, n (%)	27 (40.9)	28 (42.4)	0.097
LVEF (%)	54.6 ± 6.5	51.8 ± 7.7	0.01
EAT thickness (mm)	6.2 ± 1.8	8.9 ± 2.7	< 0.001
Systolic BP (mmHg)	121.4 ± 9.3	128.6 ± 8.5	0.085
Diastolic BP (mmHg)	73.4 ± 7.6	74.1 ± 6.9	0.284
Fasting Glucose (mg/dl)	150.6 ± 62.7	164.3 ± 78.2	0.112
Creatinine (mg/dl)	0.89 ± 0.7	0.95 ± 0.6	0.505
TC (mg/dl)	210.7 ± 38.4	252.4 ± 48.5	0.017
HDL-C (mg/dl)	41.8 ± 9.4	38.5 ± 8.6	0.032
LDL-C (mg/dl)	138.2 ± 38.5	158.2 ± 35.1	0.001
TG (mg/dl)	175.4 ± 82.5	286.8 ± 114.6	< 0.001
Hemoglobin (g/dL)	13.8 ± 1.2	12.9 ± 1.6	0.415
Platelet (K/uL)	248000 ± 112000	256000 ± 128000	0.121
MPV (fL)	9.18 ± 0.9	10.8 ± 1.1	0.002

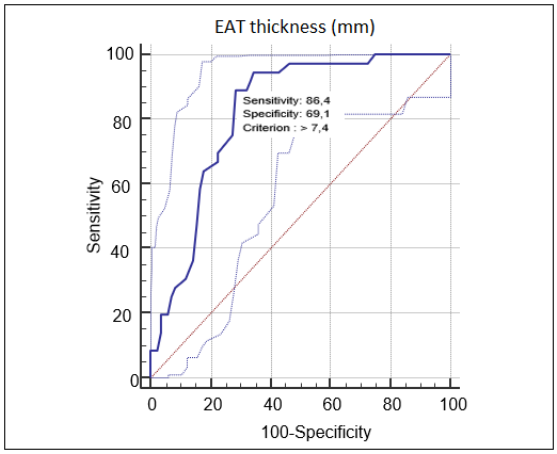
The multivariate logistic regression models revealed that EAT thickness (p < 0.001, Odds ratio (OR) = 3.65, 95% Confidence interval (C.I.) = 2.52–8.12), TG (p = 0.001, OR = 2.26, 95% C.I. = 1.98–3.82), and MPV (p = 0.011, OR = 2.05, 95% C.I. = 1.67–3.16) were found to be independent factors for predicting SVG stenosis (Table 2).

To find out the ideal EAT thickness cut-off value for predicting the SVG stenosis, ROC analysis was performed. An EAT thickness value of > 7.4 mm has 86.4 % sensitivity, 69.1 % specificity for the prediction of SVG stenosis [AUC 0.755, (p < 0.001)] (Figure 1).

Table 2. The independent predictors of SVG stenosis in multivariate regression analysis

Variable	P	Odds Ratio (%95 C.I.)
EAT thickness	< 0.001	3.65 (2.52 – 8.12)
TG	0.001	2.26 (1.98 – 3.82)
MPV	0.011	2.05 (1.67 – 3.16)
Hypertension	0.072	1.24 (1.12 – 2.18)
LDL-C	0.095	0.96 (0.73 – 1.97)
TC	0.102	0.88 (0.64 – 1.75)
HDL-C	0.126	0.71 (0.52 – 1.13)

EAT: epicardial adipose tissue, TG: triglyceride, MPV: mean platelet volume, LDL-C: low density lipoprotein cholesterol, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, C.I.: Confidence interval



Şekil 1. ROC analysis for predicting the SVG stenosis. An EAT thickness value of > 7.4 mm has 86.4 % sensitivity, 69.1 % specificity for the prediction of SVG stenosis [AUC 0.755, (p < 0.001)]

DISCUSSION

In the present study, we showed that the EAT thickness was significantly higher in the SVGD (+) group than in the SVGD (-) group. This association remained significant after multivariate analysis, thereby indicating increased EAT thickness as an independent predictor of SVG stenosis. To the best of our knowledge, this is the first report to evaluate the relationship between EAT thickness and SVG stenosis.

SVG stenosis is an important problem in the CABG patients and is related to major cardiovascular events. Many risk factors related to the SVG stenosis such as surgery-related factors, smoking, HT, HLP, DM, and others have been determined previously. Kim et al. have shown that surgery related factors such as vein acquisition technique or use of extracorporeal circulation were independent predictors of SVG stenosis (13).

The previous studies have shown that TC, TG, LDL-C, and LDL/HDL ratios are significantly greater in coronary heart disease (CHD) patients than in healthy people (14), and also shown that atherogenic indices and atherogenic coefficient are major risk factors for atherosclerotic disease and its complications (15). Also, in the present study, it was shown that dyslipidemia has a negative effect on SVG. It was found that TC, TG, and LDL-C were significantly higher in the SVGD (+) group than in the SVGD (-) group; and HDL-C was significantly lower in the SVGD (+) group than in the SVGD (-) group. In our study, high TG level was found to be an independent risk factor for SVG stenosis.

DM has previously been shown to be a major cause of CAD in many studies (16). DM can cause SVG stenosis as a result of vascular endothelial dysfunction caused by immune and non-immune pathophysiological mechanisms (17). In the present study, similar to previous studies, it was shown that history of DM was significantly higher in the SVGD (+) group than the SVGD (-) group.

MPV, an indicator of platelet activation, has an independent effect on the pathophysiology of atherosclerosis in the presence of other risk factors. It has been shown that MPV is increased in acute coronary syndrome and congestive heart failure (18,19). Kaya et al. retrospectively reviewed the records of 128 patients who underwent emergency or elective coronary angiography after CABG surgery, and who died at an early stage (20). Patients were divided into three groups as early death, no SVG disease (SVGD), and SVGD group. MPV, PDW, and platelet count were evaluated at different times. MPV was significantly higher in the stenotic group than in the non-stenotic group. MPV values were also found to be higher in patients who died during the early stage than in surviving patients. In the present study, similarly, MPV values were significantly higher in the SVGD (+) group than the SVGD (-) group. And also, in our study, MPV was found to be an independent risk factor for SVG stenosis.

EAT is a type of visceral adipose tissue functioning as a metabolically active endocrine organ. The relationship between EAT thickness and components of cardiovascular diseases have been described in several studies (21-23). It has been shown that EAT 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 (24). Iacobellis et al. were the first to report a significant association between increased epicardial fat and metabolic syndrome, insulin resistance, LDL-C, adiponectin, and arterial blood pressure (25). On the basis of these facts, EAT may be associated with the pathophysiological processes causing SVG stenosis. The activation of immune system and endothelial dysfunction can play key roles in terms of SVG stenosis development. The present study shows an association between EAT thickness and the presence of SVG stenosis. EAT thickness emerged as an independent predictor of SVG stenosis among other well-known risk factors. We think that EAT is part of active adipose tissue that mediates graft circulation like coronary circulation via secretion of inflammatory mediators and adipokines.

STUDY LIMITATIONS

The main limitation of our study is the limited number of patients. Operator dependency of the echocardiographic measurements, two-dimensional measurements and difficulty in differentiating epicardial fat, and absence of other imaging modalities may also be considered as other limitations. EAT thickness assessment could potentially be ameliorated by using 3D echocardiography.

CONCLUSION

To the best of our knowledge, this is the first study to assess the relationship between EAT thickness and SVGD. EAT thickness is related to the presence of SVG stenosis. EAT thickness therefore could serve as an easily measurable non-invasive adjunctive marker to classical risk factors for the prediction of SVG stenosis. Further studies are needed to demonstrate the pathophysiology of SVG stenosis.

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