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Original article

Association between epicardial adipose tissue and Duke treadmill score

Levent Cerit[1], *Zeynep Cerit*[2]

[1]Department of Cardiology, Near East University Faculty of Medicine, Nicosia, Cyprus - E-mail: drcerit@hotmail.com; [2]Department of Pediatric Cardiology, Near East University Faculty of Medicine, Nicosia, Cyprus

Summary. Duke treadmill score (DTS) is a well-known prognostic tool in patients with suspected coronary artery disease (CAD). DTS is a stronger predictor than ST-segment response alone in a treadmill test. Epicardial adipose tissue (EAT) has anatomical and functional contiguity with myocardium and coronary arteries. Increased EAT thickness (EATT) is strongly associated with CAD. This study aimed to evaluate the association between EAT and DTS. The data of patients were retrospectively analysed for the demographic features, echocardiographic parameters including ejection fraction, EATT, biochemical parameters, and DTS. The study population consisted of 698 patients admitted to the outpatient clinic with chest pain. DTS was calculated as originally described: DTS = exercise time − (5 × ST deviation) − (4 × exercise angina). Patients were divided into two groups according to the DTS values: low risk (DTS≥ +5), intermediate to high risk (IHR) (DTS< +4). According to the EATT, the patients were divided into two groups: increased EATT (≥5.1), normal EATT (<5.1). Hypertension (HT), hyperlipidemia (HL), smoking history, diabetes mellitus (DM), and increased EATT were more frequent in IHR. On univariate analysis HT, HL, DM, smoking history, and increased EATT were associated with IHR. On multivariate analysis DM, smoking history, and increased EATT were independent predictors for IHR (OR 2.358; 95% CI: 1.739–4.793; p < 0.001, OR 1.817; 95% CI: 1.218-2.539; p<0.001, OR 2.143; 95% CI: 1.693-3.581; p<0.001; respectively). In our study, we have found a significant relationship between increased EATT and IHR. Combination of increased EATT and DTS might be beneficial to predict of future cardiovascular events in patients with chest pain.

Key words: epicardial adipose tissue, Duke treadmill score, diabetes mellitus, smoking

Background

Coronary artery disease (CAD) is one of the main causes of mortality and morbidity worldwide. Therefore the predictive role of diagnostic tools is crucial in terms of prevention to CAD. Although exercise testing is a well established noninvasive stress test for the evaluation of the patients with suspected CAD, its sensitivity and specificity are not satisfactory (67% and 71%, respectively) (1).

The Duke treadmill score (DTS) provides valuable diagnostic and prognostic knowledge for the evaluation of the patients with suspected CAD. DTS might be beneficial to evaluate prognosis in patients with a moderate to high-risk (IHR). DTS calculated by using parameters including ST-segment depression, chest pain, and exercise time [exercise time − (5 × ST deviation) − (4 × exercise angina)](2-3). The patients were classified as low-, intermediate-, or high-risk according to the scores (low-risk DTS ≥ +5, intermediate-risk −10 ≤ DTS ≤ +4, and high-risk DTS ≤ −11).

According to the DTS, patients categorised as follows, low risk (LR);<0.5%/year, intermediate risk; 0.5% to 5%/year and high risk; >5%/year of cardiovascular events with a 4-year follow-up. Shaw et al. (3) reported that cardiac event rates for low-, moderate-, and high-risk grouping of DTS, annual cardiac death rates were 0.6%, 2%, and 7%, respectively.SYNTAX score was developed to assess the extensity and complexity of coronary artery. All lesions with >1.5 mm segment length and >50% stenosis was taken into consideration in scoring system. Erkan et al. (4) found a significant and positive correlation between EAT thickness and the extent of CAD, as evidenced by the Gensini score (r =0.82; P <0.001). A similarly strong correlation existed between EAT thickness and CAD complexity, as evidenced by the Syntax score (r =0.825; P <0.001).

Recently, Kalaycı et al. (5) showed a close association between Fractional flow reserve and DTS values. Therefore, DTS levels might be useful to determine patients who require invasive management. Additionally, decreasing of DTS associated with increased angiographic CAD severity. Furthermore, DTS was found an independent predictor of higher SYNTAX score (6).

Epicardial adipose tissue (EAT) is the visceral fat depot of the heart, and covers 80% of the heart's surface and constitutes 20% of total heart weight. EAT has anatomical and functional contiguity with myocardium and coronary arteries. EAT is composed of adipocytes, inflammatory, stromovascular, and immune cells. EAT is a metabolically active endocrine and paracrine organ that generates several pro-inflammatory and pro-atherogenic cytokines and hormones resulting in vascular, immunologic, and inflammatory responses (7). EAT might interact locally with coronary arteries through paracrine secretion mechanisms. Cytokines from peri-adventitial EAT may pass through the coronary wall by diffusion from the outside to the inside, interacting with cells. In vivo studies have shown that the external application of inflammatory cytokines such as interleukin (IL)-1β and monocyte chemoattractant protein 1 (MCP-1) to coronary arteries of pigs increases intimal thickness and causes arterial remodelling. EAT was found to be strongly associated with metabolic syndrome and showed a significant correlation with metabolic risk factors such as waist circumference, hyperlipidemia (HL), blood pressure, and insulin resistance (8,9). Increased EAT thickness (EATT) was demonstrated to be strongly associated with not only a CAD, coronary plaque vulnerability but also arrhythmogenesis, major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death (10-12). Kaya et al. [13] reported that there was a relationship between EAT volume and advanced CAD in those undergoing coronary artery bypass grafting, and also higher EAT volume might be a predictor for serious coronary lesions.

Therefore, the relationship between EATT and DTS was evaluated in this study because of the evaluation of EATT might be beneficial to increase of the predictive value of treadmill test.

Methods

The study group was derived from a population of 698 consecutive patients, who underwent exercise stress test due to chest discomfort (including typical and atypical angina, non-anginal chest pain) between November 2016 and December 2017. Thirty-six patients were excluded due to severe valve disease, prosthetic valve diseases, heart failure, acute coronary syndromes, haematological disorders, previous myocardial infarction, prior revascularization procedures, congenital heart disease, left bundle branch block, left ventricular hypertrophy, Wolff-Parkinson-White syndrome, digoxin therapy, and chronic kidney disease. Finally, the remaining 662 patients were evaluated. The association between DTS and EATT was investigated.

The data of patients were retrospectively analysed for the demographic features, echocardiographic parameters including ejection fraction, EATT, biochemical parameters, and DTS. The study was approved by the local ethics committee.

Echocardiographic Examination

All patients underwent transthoracic echocardiography using Vivid S5 (GE healthcare) echocardiography device and Mass S5 probe (2-4 MHz). Standard two-dimensional and colour flow Doppler views were acquired according to the guidelines of American Society of Echocardiography and European Society of Echocardiography (14). The ejection fraction was measured according to the Simpson's method.

EAT identified as an echo-free space on the right ventricle free wall beneath the visceral pericardium on two-dimensional echocardiography was measured from the parasternal long -axis views at the end systole. EATT was measured from the parasternal long-axis view at a point on the free wall of the right ventricle along the mid-line of the ultrasound beam, perpendicular to the aortic annulus as the anatomic reference point. According to the EATT, the patients were divided into two groups: increased EATT (≥5.1mm), normal EATT (<5.1mm).

Exercise treadmill testing

Symptom-limited Bruce protocol was performed to all patients. Resting heart rate, blood pressure, and 12-lead ECG were recorded before exercise. ECG was repeated every 3 min during the exercise test. Exercise testing was terminated if limiting chest pain, exertional hypotension, malignant ventricular arrhythmias, and marked ST depression (>3 mm) were observed. An abnormal exercise ST response was defined as ≥1 mm horizontal or downsloping ST depression (J point ± 80 ms) or ≥1 mm ST-segment elevation in all leads excluding aVR without pathological Q waves.

Duke Treadmill Score

DTS was as calculated as originally described (15): DTS = exercise time − (5 × ST deviation) − (4 × exercise angina). Exercise angina was assessed as one of three levels: 0, none; 1, non-limiting; and 2, exercise-limiting. The DTS typically ranges from −25 to +15. The patients were classified as low-, intermediate-, or high-risk according to the scores (low-risk DTS ≥ +5, intermediate-risk −10 ≤ DTS ≤ +4, and high-risk DTS ≤ −11). In our study, patients were divided into two groups according to the DTS values: LR (DTS≥ +5), IHR (DTS< +4).

Patients with diabetes mellitus (DM) were identified on admission as those with documented DM using either oral hypoglycemic agents or insulin treatment. HL was defined as total cholesterol at least 200 mg/dL or using antihyperlipidemic therapy on admission. Hypertension (HT) was defined as blood pressure above 140/90 mmHg or using antihypertensive therapy on admission.

Statistical Analysis

Statistical analysis was performed using the SPSS (version 20.0, SPSS Inc., Chicago, Illinois) software package. Continuous variables were expressed as the mean ± standard deviation (mean± SD), and categorical variables were expressed as a percentage (%). The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Student's t-test was used to evaluate continuous variables showing normal distribution, and Mann-Whitney U-test was used to evaluate variables that did not show normal distribution. A p-value < 0.05 was considered statistically significant. To identify predictors of IHR, the following variables were initially assessed in a univariate model: HT, DM, smoking history, HL, and EATT. Significant variables in univariate analysis were then entered into a multivariate logistic regression analysis using backwards stepwise selection.

Results

The baseline characteristics of two group are summarised in Table 1. Among them 214 (32.3%) had IHR, 448 (67.7%) had LR. There was no significant difference between both groups regarding age, gender, high-density lipoprotein cholesterol, triglycerides, creatinine, beta-blocker therapy, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers therapy (Table1). HT, DM, HL, LDL-C, smoking history, and EATT were found significantly higher in the IHR group (Table1).

The results of univariate analyses are presented in Table 2. On univariate analysis HT, HL, DM, smoking history, and EATT were associated with IHR (Table2). On multivariate analysis DM, smoking history, and EATT were independent predictors for IHR (OR 2.358; 95% CI: 1.739–4.793; p < 0.001, OR 1.817; 95% CI: 1.218-2.539; p<0.001, OR 2.143; 95% CI: 1.693-3.581; p<0.001; respectively)(Table3).

Discussion

In the present study EATT, DM, smoking history were found strongly associated with DTS. To the best

Table 1. Baseline characteristics

Patient Characteristics	Duke treadmill score		p
	Low (DTS≥ +5)	Intermediate to high (DTS< +4)	
Age	58.9±16.4	60.7±17.3	0.734
Male gender, %	38.3	36.9	0.627
Hypertension, %	21.6	68.7	**<0.001**
Diabetes Mellitus, %	16.2	48.5	**<0.001**
Hyperlipidemia, %	10,4	41.6	**<0.001**
LDL-C (mg/dl)	134.8	156.9	**0.04**
HDL-C (mg/dl)	44.6	42.8	0.726
Triglycerides (mg/dl)	139.6	146.8	0.527
Smoking history, %	21.7	49.6	**<0.001**
Creatinine, (mg/dl)	0.86±0.18	0.91±0.23	0.863
Beta-Blocker therapy, %	16.8	18.1	0.829
Statin therapy, %	16.8	20.7	0.428
ACE-I/ARB therapy, %	8.1	10.6	0.792
EATT (mm)	3.7	7.9	**<0.001**
Increased EATT (≥5.1mm), %	14.6	62.8	**<0.001**

ACE-I: angiotensin-converting enzyme inhibitor, **ARB:** angiotensin-receptor blocker, **HDL-C**: high-density lipoprotein cholesterol; **LDL-C**: low-density lipoprotein cholesterol, **EATT**: Epicardial adipose tissue thickness

Table 2. Univariate Analysis of Predictors for Intermediate to high risk

Predictor Variables	OR (95% C.I.)	p
Hypertension, n(%)	1.863 (1.237 – 2.864)	**<0.001**
Hyperlipidemia, n(%)	1.972 (1.348 – 3.086)	**<0.001**
Diabetes mellitus, n(%)	2.359 (1.893 – 4.267)	**<0.001**
Smoking history, n(%)	2.167 (1.738 – 3.829)	**<0.001**
EATT (mm)	2,472 (2.085 – 3.927	**<0.001**

Table 3. Multivariate analysis of predictors for intermediate to high risk

Predictor Variables	OR (95% C.I.)	p
Diabetes mellitus, n(%)	2.358 (1.739-4.793)	**<0.001**
Smoking history, n(%)	1.817 (1.218-2.539)	**<0.001**
EATT (mm)	2.143 (1.693 – 3.581)	**<0.001**

EATT: epicardial adipose tissue thickness

of our knowledge, our study is the first study to evaluate the association between EATT and IHR. Considering the valuable role of EATT for both CAD and coronary plaque vulnerability combination of DTS and EATT might be beneficial to predict future cardiovascular events.

DTS is an easy, non-invasive, practical, and well-validated method to evaluate in patients with chest pain. The DTS which is calculated via exercise testing, and can predict CAD better than the ST response alone (16). DTS classifies patients in LR (99% survival at four years), IR (95% survival at four years), and HR (79% survival at four years)(17). Association between CAD and DTS has been demonstrated in several studies (4,16). DTS predicts the presence of left main coronary disease, and three-vessel disease and two-vessel disease involving proximal left anterior descending artery, with high specificity (90.5%)(18). Consistently with previous studies, Günaydın et al. (19) demonstrated that DTS can predict the presence and severity of stable CAD before coronary angiography and may enable the estimation of the revascularisation method that will be required after the procedure. Additionally, Banerjee et al. (20) revealed that DTS were satisfactorily correlated with single-photon emission computed tomography myocardial perfusion imaging (MPI) scanning in low DTS subsets of patients. Although DTS is a well-established diagnostic tool for CAD nearly one-third of patients with high-risk DTS had normal MPI and could be managed more conservatively (21).

EAT is the visceral fat depot of the heart and generates adiponectin, adrenomedullin, and several proinflammatory cytokines, such as tumor necrosis factor-alfa, monocyte chemotactic factor-1, interleukin-1 beta, and interleukin-6 interact with coronary arteries via paracrine and autocrine mechanisms (7). Abnormalities of EAT secretory properties are associated with coronary atherosclerosis, left ventricular (LV) hypertrophy, LV diastolic dysfunction, and aortic stenosis (22-27). Additionally, Nohara et al. (13) demonstrated that EAT was strongly associated with coronary plaque vulnerability.

There is scarce data about the association between EATT and DTS in literature. In this study, there was a significant association between EATT and DTS. Considering both valuable roles of EATT for coronary plaque vulnerability and nearly one-third of patients with high-risk DTS had normal MPI combination of DTS and EATT might be beneficial to predict future cardiovascular events. Further and larger studies are needed on this topic.

Limitations of the study

Our study has some limitations. First, small sample size and retrospective design of the present study. Second, the predictive value of combination with EATT and DTS on severe CAD is scarce in this study; further studies are needed to clarify this topic.

Conclusion

In our study, we found a strong association between EATT and DTS. Combination of DTS and EATT might be beneficial to predict future cardiovascular events

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Correspondence:
Levent Cerit, MD
Associate Professor of Cardiology
Near East Hospital University Hospital, Near East Boulevard, Nicosia, Cyprus
Phone: 00903926751000
E-mail: drcerit@hotmail.com