The Relation Between Echocardiographic Epicardial Fat Thickness and CHA$_2$DS$_2$-VASc Score in Patients with Sinus Rhythm

Fatih Aksoy$^1$, MD; Serdar Guler$^1$, MD; Fatih Kahraman$^1$, MD; Tülay Oskay$^1$, MD; Ercan Varol$^1$, MD

Abstract

Objective: To evaluate the predictive value of epicardial fat thickness (EFT) in CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category) score risk groups.

Methods: A total of 158 consecutive patients (75 females, 83 males, mean age 70.8±6.3 years) admitted routinely for cardiologic control were divided into two groups according to their CHA$_2$DS$_2$-VASc scores (scores 0 and 1 were regarded as low risk, and score ≥2 as high risk). One hundred twenty-five of 158 patients had a high-risk score.

Results: Mean EFT was significantly higher in the high-risk group than in the low-risk group (4.34±0.62 vs. 5.37±1.0; $P<$0.001). EFT was positively correlated with CHA$_2$DS$_2$-VASc score ($r=0.577$, $P<$0.001). According to receiver operating characteristics (ROC) analysis, EFT value of 4.4 mm was found to be predictive of high risk in CHA$_2$DS$_2$-VASc score with 80% of sensitivity and 79% of specificity (C-statistic = 0.875, $P<$0.001, 95% confidence interval [CI] = 0.76-0.90). And according to multivariate logistic regression analysis, EFT was an independent predictor of high thromboembolic risk in terms of CHA$_2$DS$_2$-VASc score.

Conclusion: Our findings suggest that echocardiographic EFT measurement could provide additional information on assessing cardiovascular risks, such as thromboembolic events, and individuals with increased EFT should receive more attention to reduce unfavorable cardiovascular risk factors and the development of future cardiovascular events.

Keywords: Thromboembolism/Prevention & Control. Pericardium. Adipose Tissue. Risk Assessment.
INTRODUCTION

Ischemic stroke is a leading cause of death and long-term disability worldwide\(^1\). Control of risk factors is of particular importance for the prevention of cerebrovascular diseases. It is possible to stop progression or prevent these diseases by elimination or modification of modifiable risk factors in the light of treatment goals.

Epicardial adipose tissue (EAT), located between the myocardium and visceral pericardium, has emerged as an important cardiovascular risk predictor, in view of producing and releasing several adipocytokines\(^2,3\). The importance of epicardial fat thickness (EFT) has been shown in recent years. Increased EFT is associated with hypertension, insulin resistance, and thromboembolic processes such as stroke and acute coronary syndrome\(^4-6\).

The CHA\(_2\)DS\(_2\)-VASc risk score is used to predict the thromboembolism risk in non-valvular atrial fibrillation (NVAF) patients\(^7\).

The present study aimed to determine whether EFT is more closely associated with high-risk patients according to the CHA\(_2\)DS\(_2\)-VASc score risk.

METHODS

The 158 consecutive patients (75 females, 83 males, mean age 70.8±6.3 years) admitted to the outpatient clinic of the Suleyman Demirel University Hospital, Department of Cardiology, and referred to our echocardiography laboratory due to suspicion of heart disease between June 2014 and May 2015 were enrolled in this prospective study. All patients underwent medical history assessment, physical examination, anthropometric measurements, electrocardiogram, and echocardiographic evaluation. The study was approved by the institutional ethics committee and all patients gave their informed consent. Exclusion criteria were pericardial effusion, the presence of mitral and aortic insufficiency was evaluated by Doppler color flow mapping. EFT was identified echocardiographically as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium. EFT was measured at the end of diastole.

The M-mode, two-dimensional, and Doppler echocardiographic examinations were obtained by an ultrasound machine (Philips iE 33 xMatrix) to assess left atrial (LA) diameter, interventricular septum (IVS) thickness, left ventricular posterior wall (LVPW) thickness, left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), and left ventricular EF. LA and left ventricular dimensions and left ventricular EF were measured by M-mode echocardiography in the parasternal long axis view by using the American Echocardiography Society M-mode technique\(^8\). The present study aimed to determine whether EFT is more closely associated with high-risk patients according to the CHA\(_2\)DS\(_2\)-VASc score risk.

Blood Sampling

Blood samples were drawn from the antecubital vein by careful venipuncture in a 21 G sterile syringe without stasis at 08.00-10.00 AM after a fasting period of 12 h. Glucose, creatinine, and lipid profiles were determined by standard methods.

Hemogram parameters were measured in a blood sample collected in dipotassium ethylenediaminetetraacetic acid (EDTA) tubes (Vacutette). An automatic blood counter (Beckman-Coulter Co, Miami, FL, USA) was used for whole blood counts.

Statistical Analysis

SPSS software package program, version 16.0, was used in this study’s statistical analyses. Categorical variables were expressed as frequency (%) and compared using the χ\(^2\) test. A Kolmogorov-Smirnov test was used to test the distribution of numeric variables, and those with normal distribution were expressed as mean ± standard deviation and were compared using the Student’s t-test. Data without normal distribution were expressed as median (inter-quartile range [IQR] of 25%-75% percentiles) and were compared using the Mann-Whitney U test. In all statistical analyses, P values <0.05 were considered as statistically significant. Univariate analysis of binary logistic regression was carried out to identify which factors were
associated with high risk according to CHA$_2$DS$_2$-VASc risk score. After including each of these potential confounding factors, backward conditional binary logistic regression analysis was performed to estimate the odds ratio (OR) and 95% confidence interval (CI) for high risk according to CHA$_2$DS$_2$-VASc risk score. Receiver operating characteristics (ROC) curve analysis was used to analyze the prognostic value of EFT for high risk according to CHA$_2$DS$_2$-VASc risk score. C-Statistic (area under the curve [AUC]) was presented as a unified estimate of sensitivity and specificity. According to the cut-off value that was obtained by a ROC curve analysis, the study population could be segregated into two groups, as low risk and high risk. The correlations between CHA$_2$DS$_2$-VASc risk score, EFT, and other clinical, laboratory, and echocardiographic parameters were performed with Pearson and Spearman correlation analysis when appropriate.

RESULTS

Baseline clinical features of the study population were summarized in Table 1. Age, female gender, hypertension, and diabetes mellitus were seen more often in high CHA$_2$DS$_2$-VASc score group than in low CHA$_2$DS$_2$-VASc score group. Only β-blocker and clopidogrel usages were significantly higher in the high CHA$_2$DS$_2$-VASc score group. Laboratory findings of the study population were summarized in Table 2. There was no statistically significant difference between the two groups except for fasting glucose ($P=0.04$). Cholesterol levels were similar between high- and low-risk groups according to CHA$_2$DS$_2$-VASc score. Echocardiographic findings of the study population were summarized in Table 3. LA diameter was significantly higher in patients with high-risk score than in low-risk score subjects in terms of CHA$_2$DS$_2$-VASc score (33±5.6 vs. 36±4.3 mm, respectively; $P<0.001$). IVS thickness was significantly higher in patients with high risk than in low-risk subjects (10±1.0 vs. 11±1.4 mm, respectively; $P<0.001$). LVEDD was significantly higher in patients with high risk than in low-risk subjects (44±1.7 vs. 45±3.7 mm, respectively; $P<0.001$). LVESD was significantly higher in patients with high risk than in low-risk subjects (27±1.7 vs. 28±3.3 mm, respectively; $P<0.001$). EFT was significantly higher in patients with high risk than in low-

| Parameter               | Low CHA$_2$DS$_2$-VASc score (n=33) | High CHA$_2$DS$_2$-VASc score (n=125) | $P$   |
|-------------------------|------------------------------------|-------------------------------------|-------|
| Age, years              | 64±4.1                             | 72±5.9                              | <0.001|
| Female gender, n (%)    | 9 (26)                             | 66 (53)                             | <0.001|
| Hypertension, n (%)     | 5 (14)                             | 85 (70)                             | <0.001|
| Diabetes mellitus, n (%)| 4 (11)                             | 58 (46)                             | <0.001|
| Hyperlipidemia, n (%)   | 18 (52)                            | 56 (47)                             | 0.359 |
| Smoking, n (%)          | 7 (20)                             | 53 (42)                             | 0.014 |
| CAD, n (%)              | -                                  | 31 (24)                             | <0.001|
| Stroke/TIA, n (%)       | -                                  | 11 (8)                              | 0.069 |
| BMI (kg/m$^2$)          | 29±3.5                             | 30±7.0                              | 0.209 |
| SBP (mmHg)              | 109±9                              | 122±17                              | <0.001|
| DBP (mmHg)              | 73±6                               | 76±10                               | 0.109 |
| Heart rate (beat/min)   | 70±12                              | 71±13                               | 0.623 |
| ASA, n (%)              | 17 (51)                            | 49 (39)                             | 0.183 |
| Clopidogrel, n (%)      | -                                  | 20 (16)                             | <0.001|
| OA/NOA, n (%)           | -                                  | 8 (6)                               | 0.146 |
| Statin, n (%)           | 8 (24)                             | 32 (25)                             | 0.535 |
| ACEi, n (%)             | 4 (12)                             | 34 (27)                             | 0.053 |
| ARB, n (%)              | 5 (15)                             | 32 (25)                             | 0.159 |
| β-blocker, n (%)        | 6 (17)                             | 55 (44)                             | <0.001|

ACEi=angiotensin-converting enzyme inhibitors; ARB=angiotensin II receptor blockers; ASA=Acetylsalicylic acid; BMI=body mass index; CAD=coronary artery disease; CHA$_2$DS$_2$-VASc=congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category; DBP=diastolic blood pressure; OA/NOA=Oral anticoagulant/New oral anticoagulant; SBP=systolic blood pressure; TIA=transient ischemic attack
All patients were divided into two risk groups: low and high risk subjects (4.34±0.62 vs. 5.37±1.0 mm, respectively; P<0.001). Correlation analysis between EFT and CHA₂ DS₂-VASc score with other clinical and echocardiographic parameters was shown in Table 4. EFT was positively correlated with CHA₂ DS₂-VASc score (r=0.577, P<0.001). Also, EFT was positively correlated with age (r=0.520, P<0.001), LA (r=0.264, P<0.001), IVS (r=0.356, P<0.001), LVESD (r=0.262, P=0.011), and aorta diameter (r=0.22, P<0.001). Negative correlation was found between EFT and left ventricular EF (r=−0.199, P=0.012). CHA₂ DS₂-VASc score was positively correlated with age (r=0.578, P<0.001), LA (r=0.235, P=0.003), IVS (r=0.386, P<0.001), LVESD (r=0.337, P<0.001), and aorta diameter (r=0.229, P=0.004). Negative correlation was found between CHA₂ DS₂-VASc score and left ventricular EF (r=-0.154, P=0.05). Univariate and multivariate regression analyses results were shown in Table 5. Older age, LA diameter, aorta diameter, left ventricular EF, IVS diameter, and EFT achieved statistical significance in the univariate logistic analysis. Then, multivariate analysis was carried out with these variables; age and EFT were found to be independent predictors of high risk for CHA₂ DS₂-VASc classification. According to ROC analysis, EFT value of 4.4 mm was predictive of high risk of CHA₂ DS₂-VASc score with 80% of sensitivity and 79% of specificity (C-statistic = 0.875, P<0.001, 95 % CI= 0.76-0.90; Figure 2).

### DISCUSSION

In the present study, we examined EFT in patients with high- and low-risk CHA₂ DS₂-VASc scores. We found out that EFT was significantly higher in patients with high CHA₂ DS₂-VASc score than in those with low CHA₂ DS₂-VASc score and that EFT was positively correlated with CHA₂ DS₂-VASc scores.

### Table 2. Laboratory findings of the study population.

| Parameter              | Low CHA₂ DS₂-VASc score (n=33) | High CHA₂ DS₂-VASc score (n=125) | P       |
|------------------------|---------------------------------|----------------------------------|---------|
| Hemoglobin, g/L        | 12.1±1.1                        | 11.9±1.0                         | 0.201   |
| Platelet count (x 10⁹/µL) | 238±58                          | 245±71                           | 0.603   |
| White blood cell count (x 10⁹/µL) | 8251±2344                    | 7730±2400                        | 0.264   |
| Fasting glucose, mg/dL | 111±34                          | 128±62                           | 0.04    |
| HDL-cholesterol, mg/dL | 45±15                           | 47±12                            | 0.444   |
| LDL-cholesterol, mg/dL | 114±43                          | 111±36                           | 0.763   |
| Triglycerides, mg/dL   | 178±131                         | 148±83                           | 0.109   |

### Table 3. Echocardiographic findings of the study population.

| Parameter              | Low CHA₂ DS₂-VASc score (n=33) | High CHA₂ DS₂-VASc score (n=125) | P       |
|------------------------|---------------------------------|----------------------------------|---------|
| Left ventricular EF, % | 60±1.9                          | 59±3.7                           | <0.001  |
| Aorta (mm)             | 24±1.5                          | 25±2.4                           | <0.001  |
| LA (mm)                | 33±5.6                          | 36±4.3                           | <0.001  |
| IVS (mm)               | 10±1.0                          | 11±1.4                           | <0.001  |
| LVFW (mm)              | 9.3±0.5                         | 10±0.8                           | <0.001  |
| LVESD (mm)             | 27±1.7                          | 28±3.3                           | <0.001  |
| LVEDD (mm)             | 44±1.7                          | 45±3.2                           | <0.001  |
| EFT (mm)               | 4.34±0.62                       | 5.37±1.0                         | <0.001  |

CHA₂ DS₂-VASc=congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category; HDL=high-density lipoprotein; LDL=low-density lipoprotein
EAT is a true visceral fat tissue, deposited around the heart and particularly around the subepicardial coronary vessels. EAT is a complex organ, mainly composed of adipocytes, but it also includes a neuronal network, stromavascular, immune and inflammatory cells, all nourished by a rich microcirculation. EFT is associated with thromboembolic diseases, including cardiovascular and neurovascular diseases. Akil et al. showed that EFT was significantly higher in patients with ischemic stroke than in healthy controls. Akdag et al. investigated the association of EFT, inflammatory, and thrombosis parameters with CHA2DS2-VASc score in NVAF patients. They determined that EFT, inflammatory, and thrombosis parameters were associated with the thromboembolic risk exhibited by CHA2DS2-VASc score in NVAF patients. In our study, we investigated the association of EFT with CHA2DS2-VASc score in patients with sinus rhythm. Our results were similar with those from that study. EFT was significantly higher in high CHA2DS2-VASc score than in low CHA2DS2-VASc score among patients with sinus rhythm. CHA2DS2-VASc score is considered an endocrine and metabolically active organ. It is a source of several bioactive molecules that can influence the myocardium and coronary arteries. Epicardial fat expresses and secretes a number of cytokines, pro- and anti-inflammatory adipokines, vasoactive factors, and growth factors. Accordingly, inflammation appears to play an important role in thromboembolic events, such as acute coronary syndrome and stroke. As a result, increased inflammatory mediators from EAT may have an important role in the pathogenesis of stroke and atherosclerosis. As also mentioned before, EAT is strongly associated with the pathogenesis of atherosclerosis due to sharing the same risk factors. In the present study, we have

Table 4. Clinical and echocardiographic parameters showing the significant correlation with EFT and CHA2DS2-VASc score.

|                          | With EFT |       |          | With CHA2DS2-VASc score |       |          |
|--------------------------|----------|-------|----------|-------------------------|-------|----------|
|                          |          |       | r        | P          |       | r        | P          |
| Age                      | 0.520    | <0.001| 0.578    | <0.001     |
| LA                       | 0.264    | 0.001 | 0.235    | 0.003      |
| IVS                      | 0.356    | <0.001| 0.386    | <0.001     |
| LVESE                    | 0.262    | 0.011 | 0.337    | <0.001     |
| LVEDD                    | 0.188    | 0.018 | 0.202    | 0.011      |
| LVEF                     | -0.199   | 0.012 | -0.154   | 0.05       |
| Aorta                    | 0.22     | 0.004 | 0.229    | 0.004      |
| Waist circumference      | 0.184    | 0.02  | 0.151    | 0.05       |
| BMI                      | 0.156    | <0.001| 0.172    | 0.03       |
| CHA2DS2-VASc score       | 0.577    | <0.001| 0.577    | <0.001     |

BMI=body mass index; CHA2DS2-VASc=congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category; LVEF=left ventricular ejection fraction; EFT=epicardial fat thickness; IVS=interventricular septum; LA=left atrium; LVEDD=left ventricular end diastolic diameter; LVESE=left ventricular end systolic diameter.

Table 5. Predictors of CHA2DS2-VASc risk classification in univariate and multivariate analyses.

|                          | OR      | (95 % CI)     | P value | OR      | (95 % CI)     | P value |
|--------------------------|---------|----------------|---------|---------|----------------|---------|
| Age (years)              | 1.318   | 1.17-1.47      | <0.001  | 1.270   | 1.11-1.44      | <0.001  |
| Epicardial tissue thickness | 7.01   | 2.89-16.9      | <0.001  | 4.0     | 1.61-10.28     | 0.003   |
| Left ventricular ejection fraction (%) | 0.876 | 0.76-0.997    | 0.045   |         |                |         |
| Left atrial length (mm)  | 1.161   | 1.05-1.27      | <0.001  |         |                |         |
| Aorta diameter           | 1.341   | 1.10-1.62      | <0.001  |         |                |         |
| IVS                      | 1.770   | 1.27-2.45      | <0.001  |         |                |         |

OR=odds ratio; CI=confidence interval; IVS=interventricular septum.
shown that high thromboembolic risk according to CHA$_2$DS$_2$-VASc score was positively correlated with EFT.

It has been shown that EAT is related to cardiovascular risk factors[11]. The studies using echocardiography to measure EFT on the right ventricle showed relations with waist circumference and left ventricular measurements[15-18]. Our findings were similar to these studies. We reported a strong relationship between EAT and age, diabetes mellitus, and hypertension. CHA$_2$DS$_2$-VASc score includes these risk factors. Similarly, Cetin et al.[19] reported a significant association between EFT and type 2 diabetic subjects with subclinical atherosclerosis. Dogan et al.[20] showed that in patients with newly diagnosed hypertension, increased EFT was significantly linked to impaired aortic elastic properties. Iacobellis et al.[21] showed a correlation between cholesterol levels and EFT. However, the relationship between EFT and CHA$_2$DS$_2$-VASc score was independent of cholesterol levels in our study.

In the echocardiographic evaluation, EFT, LA length, aorta diameter, and IVS length were correlated with CHA$_2$DS$_2$-VASc score and they are independent risk factors for high thromboembolic risk in CHA$_2$DS$_2$-VASc score, based on a multivariate analysis. Accordingly, Altun et al.[21] have shown a significant association between EFT, N-terminal pro b-type natriuretic peptide (NT-proBNP) levels, and arterial dysfunction in patients who had sustained acute ischemic stroke.

Stroke is one of the most important causes of death and long-term disability. Control of the risk factors can prevent the development of stroke[20]. Recent studies have shown a relation between EFT and stroke[6,22]. Akil et al.[6] demonstrated for the first time the association between EFT and cerebral ischemic stroke.

As mentioned before, EAT has the same blood supply as the adjacent myocardium and also shown paracrine functions. This causes risk for cardiac structures due to local pathogenic inflammatory effects[2,11,12]. A computed tomography (CT) evaluation from the Framingham Heart study showed that pericardial fat volume could predict atrial fibrillation (AF) risk independently of other measurements of adiposity[23]. Tsao et al.[22] showed that periatrial EAT was increased and was correlated with atrial dysfunction in patients with AF-related stroke.

EAT, a metabolically active tissue can induce fibrotic changes on the atrial myocardium by releasing proinflammatory cytokines and adipo-fibrokines. EAT can be an infiltrated adipocyte on the atrial myocardium. This can cause blockage of local conduction and promote the micro-reentry circuit. As a result, the occurrence of AF increases. Two potential mechanisms can be proposed for this association: firstly, the actions of proinflammatory cytokines and adipo-fibrokines released from EAT, such as activin A, adiponectin, and resistin, which can induce fibrotic changes on the atrial myocardium[2,4,11]; and secondly, adipocyte infiltration on the atrial myocardium, which can cause blockage of local conduction and promote the micro-reentry circuit; and potential modulations of the autonomic nervous system by the ganglionic plexus within the EAT, which may influence the occurrence of AF. In this study, we comprehensively assessed the relationship between the CHA$_2$DS$_2$-VASc score and EFT around the right ventricle. They were independently associated with each other, based on a multivariate analysis. Consequently, we can say that EFT is a risk indicator for stroke.

Study Limitations

The relatively limited number of patients could limit the strength of the results and the conclusion obtained from this study. Echocardiographic EAT is a linear measurement, and thus it may not assess the total epicardial fat volume that varies at several myocardial locations. As a result of EAT being a metabolically active tissue, inflammatory cytokines and inflammatory markers could be investigated in future studies.

CONCLUSION

In conclusion, our findings suggest that echocardiographic EFT measurement could provide additional information on assessing cardiovascular risks, such as thromboembolic events, and individuals with increasing EFT should receive more attention to reduce unfavorable cardiovascular risk factors and the development of future cardiovascular events.
Authors’ roles & responsibilities

FA  Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; final approval of the version to be published

SG  Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; final approval of the version to be published

FK  Drafting the work or revising it critically for important intellectual content; final approval of the version to be published

TO  Drafting the work or revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published

EV  Drafting the work or revising it critically for important intellectual content; final approval of the version to be published

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