Evaluation of Atrial Conduction Times and Epicardial Adipose Tissue Thickness in Patients with Ankylosing Spondylitis

Ankilozan Spondilit Hastalarında Atriyal İleti Sürelerinin ve Epikardiyal Yağ Dokusu Kalınlığının Değerlendirilmesi

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ABSTRACT

Introduction: In this study, we aimed to evaluate whether atrial electromechanical delay (EMD) and epicardial adipose tissue (EAT) thickness differed between ankylosing spondylitis (AS) patients and healthy subjects.

Methods: This prospective, cross-sectional study included 43 consecutive AS patients followed up in the Physical Medicine and Rehabilitation Department of the University of Health Sciences Turkey, İstanbul Training and Research Hospital, between June 2019 and January 2020. The control group consisted of 42 age-and gender-matched healthy participants. The PA atrial EMD was accepted as the beginning of the P wave on the electrocardiograph and the begining of late diastolic wave (Am wave) on the tissue Doppler obtained by transthoracic echocardiography, and all EMD parameters, including lateral mitral annulus (lateral PA), septal mitral annulus (septal PA) and right ventricular tricuspid annulus (tricuspid PA), were calculated. The thickness of EAT was obtained from the thickest part of the right ventricular free wall at the end of diastole in the parasternal long axis window.

Results: In AS patients, tissue Doppler measurements of PA lateral, PA septal and PA tricuspid were longer than the measurements in the control group. In addition, EAT thickness was significantly higher in AS patients than in the control group. There was a moderate correlation between interatrial EMD and C-reactive protein (r=0.445, p<0.001) and EAT thickness (r=0.451, p<0.001).

Conclusion: In this study, interatrial EMD and intraatrial EMD were significantly higher in AS patients. In addition, the thickness of EAD was significantly greater in patients with AS. These findings suggest a higher tendency toward coronary artery disease and atrial fibrillation in patients with AS.

Keywords: Ankylosing spondylitis, electromechanical delay, epicardial adipose tissue, atrial fibrillation

ÖZ

Amaç: Bu çalışmada, ankilozan spondilit (AS) hastaları ile tamamen sağlıklı kişiler arasında atriyal elektromekanik gecikme (EMG) ve epikardiyal yağ dokusu (EYD) kalınlığı bakımından fark olup olmadığını değerlendirmeyi amaçladık.

Yöntemler: Bu prospektif kesitsel çalışmaya, Haziran 2019-Ocak 2020 tarihleri arasında Sağlık Bilimleri Üniversitesi, İstanbul Eğitim ve Araştırma Hastanesi Fiziksel Tıp ve Rehabilitasyon bölümünde takip edilen 43 ardışık AS hastası dahil edildi. Kontrol grubu, yaş ve cinsiyete göre eşleştirilen 42 sağlıklı katılımcıdan oluşuyordu. PA atriyal EMG elektrokardiyografide P dalgasının başlangıcı ve transtorasik ekokardiyografik ile elde edilen geç diyastolik dalga (Am dalgası) başlangıcı olarak kabul edildi ve tüm EMG parametreleri olan lateral mitral anulus PA, septal mitral anulus PA ve sağ ventrikül triküspit anulus PA hesaplandı. EYD kalınlığı, parasternal uzun eksen penceresindeki diyastolün sonundaki sağ ventrikül serbest duvarının en kalın kısmından elde edildi.

Bulgular: AS hastalarında PA lateral, PA septal ve PA triküspit doku Doppler ölçümleri kontrol grubuna göre daha uzundu. Ek olarak, AS hastalarında EYD kalınlığı kontrol grubuna göre anlamlı olarak daha yüksekti. İnteratriyal EMG ile C-reaktif protein (r=0,445, p<0,001) ve EYD kalınlığı (r=0,451, p<0,001) arasında orta derecede bir korelasyon vardı.

Sonuç: Bu çalışmada, AS hastalarında interatriyal EMG ve intraatriyal EMG AS hastalarında anlamlı derecede yüksekti. Ayrıca, EYD kalınlığı AS hastalarında anlamlı olarak daha fazlaydı. Bu bulgular, AS'li hastalarda koroner arter hastalığı ve atriyal fibrilasyon eğiliminin daha yüksek olduğunu gösterebilir.

Anahtar Kelimeler: Ankilozan spondilit, elektromekanik gecikme, epikardiyal yağ dokusu, atriyal fibrilasyon

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease that mainly affects the sacroiliac joints and axial skeleton (1). Extra-articular involvement in AS includes cardiovascular involvement findings such as aortic valve regurgitation, aortic root pathologies, and transmission disorders (2). In addition to AS patients, increased cardiovascular morbidity and mortality have been reported compared to the general population. Although the reason for this increase is not known exactly, the idea that chronic inflammation and autoimmunity play a role comes to the fore (3).

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia that causes increased mortality. The various pathophysiological mechanisms that lead to AF include structural and electrical abnormalities, tissue remodeling, and inflammation (4). Previous studies have shown that prolonged atrial transmission time or electromechanical delay (EMD) may predispose to AF in chronic inflammatory diseases such as systemic sclerosis, psoriasis vulgaris (5,6). The gold standard in the evaluation of atrial transmission time is invasively applied electrophysiological studies. Another simple and non-interventional method can be obtained by measuring the time (PA) from the beginning of the P wave in electrocardiography (ECG) to the beginning of the Doppler A wave on transthoracic echocardiography (TTE) (7). Inter and intraatrial EMD can be evaluated using this method.

Epicardial adipose tissue (EAT) located between the myocardium and visceral pericardium is the actual visceral adipose tissue of the heart. EAT is a metabolically active tissue and a source of various local inflammatory mediators. Echocardiography can be used as the most appropriate low-cost and non-radiation imaging method to evaluate EAT. Many studies have shown an association between EAT and the development of atherosclerotic cardiovascular diseases, metabolic syndrome, and AF, including coronary artery disease (CAD) (8,9). In this study, we aimed to evaluate whether there was a difference in atrial EMD and EAT thickness between AS patients with a complex inflammatory structure and fully healthy people.

Methods

Data Collection

Fourty three consecutive patients with AS who were followed in the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation between June 2019 and January 2020 were included in this prospective, cross-sectional study. The control group of 42 healthy participants was matched with the patient group in terms of age and gender. All patients enrolled in the study met the modified New York criteria for AS. The exclusion criteria in the study are as follows; atherosclerotic cardiovascular disease, left ventricular (LV) systolic or diastolic (> grade II) dysfunction, moderate-to-severe heart valve disorder, diabetes mellitus, thyroid dysfunction, chronic lung disease, poor display quality, conduction abnormalities and/or the presence of branch block in ECG, electrolyte disorder, the use of antiaritmic and/or antipsychotic medication. Key clinical features such as age, gender and body mass index (BMI), duration of disease and drugs used in treatment for all patients were recorded. For each patient, pain conditions, movement restrictions and disease activity were assessed by using Bath Ankylosing Spondylitis Disease Activity index, Bath Ankylosing Spondylitis Functional index and chest expansion (Table 1).

This forward-looking, cross-sectional study protocol has been approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 1849, date: 24.05.2019). A written informed consent form was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Transthoracic Echocardiography Evaluation

TTE examinations were performed in all patients with echocardiography device using 5-1 MHz S5-1 ultrasound probe (EPIQ 7; Philips Medical Systems, Bothell, WA, USA) in accordance with the standards of the

Table 1. Clinical features and laboratory findings of patients in the ankylosing spondylitis and control group

	AS patient group (n=43)	Control group (n=42)	p
Age, years	42.8±9.2	41.5±8.9	0.491
Male Gender, n (%)	31 (72.1)	30 (71.4)	0.946
BMI, kg/m²	27.3±4.9	28.5±4.3	0.261
Smoking, n (%)	24 (55.8)	18 (42.9)	0.232
Heart rate, pulse/min	77.3±10.2	74.6±9.0	0.215
Duration of disease, year	9.19±5.54	-	-
NSAID use, n (%)	17 (39.5)	-	-
Sulfasalazine use, n (%)	13 (30.2)	-	-
Anti-TNF-alfa use, n (%)	20 (46.5)	-	-
BASMI	7.84±2.22	-	-
BASDAI	2.91±1.86	-	-
BASFI	2.03±2.34	-	-
Chest expansion, cm	4.23±0.86	-	-
Leucocyte, 10³ u/L	7.98±2.2	7.16±1.8	0.068
Hemoglobin, g/dL	13.9±1.6	14.3±1.6	0.213
Thrombocyte, 10³ u/L	254.6±64.5	244.0±56.8	0.425
Fasting blood glucose, mg/dL	96.0±19.4	94.4±16.6	0.848
Blood urea nitrogen, mg/dL	31.2±11.4	28.6±7.0	0.286
Creatinine, mg/dL	0.77±0.35	0.75±0.16	0.520
Total cholesterol, mg/dL	194.7±29.1	198.1±40.6	0.653
LDL cholesterol, mg/dL	122.8±25.3	123.6±33.6	0.899
HDL cholesterol, mg/dL	47.9±10.8	46.1±12.4	0.341
Triglyceride, mg/dL	119.8±61.1	142.3±83.7	0.305
ESR, mm/hr	15.5±13.6	11.3±12.2	0.067
CRP, mg/dL	7.28±9.49	3.53±5.96	<0.001
ASDAS-ESR	2.30±0.81	-	
ASDAS-CRP	2.38±0.77	-	

Nominal variables (%) and continuous variables presented frequently are shown as mean ± standard deviation.

AS: Ankylosing spondylitis, BMI: body mass index, NSAID: non-steroid antiinflammatory drugs, TNF: tumor necrosis factor, BASMI: Bath Ankylosing Spondylitis Metrology index, BASDAI: Bath Ankylosing Spondylitis Disease Activity index, BASFI: Bath Ankylosing Spondylitis Functional index, LDL: low density lipoprotein, HDL: high density lipoprotein, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ASDAS: ankylosing spondylitis disease activity score

American Echocardiography Association. During the examination, D2 derivation ECG was recorded continuously and the average of 3 consecutive measurements was calculated.

Conventional Echocardiography Measurements

From the parasternal long axis view window, LV end-systolic diameter, end-diastolic diameter, interventricular septum, posterior wall thickness, left atrial anteroposterior diameter, aortic root and ascending aortic diameter were measured by M-mode echocardiography. LV ejection fraction was measured by the Simpson's method. Left and right atrium mediolateral and apicobasal diameters as well as left and right atrium areas were measured from the apical-4 space window. In pulsed wave Doppler echocardiographic examination, the sample volume was placed at the tip of the mitral valve and the mitral early diastolic filling rate (E), late diastolic filling rate (A), E/A ratio and deceleration time were measured from the apical 4-chamber image. Systolic movement of the tricuspid valve annular plane towards the apex was measured by placing the M-mode cursor at the junction point of the tricuspid valve and the free wall of the right ventricle in the apical 4-chamber view.

Tissue Doppler Parameters

Tissue Doppler evaluation was performed with the same device, using a spectral pulse Doppler signal filter at a Nyquist limit of 15-20 cm/sec, with an optimal gain. The monitor flow rate was adjusted to 50-100 mm/s to optimize the image of myocardial velocities. A pulse Doppler volume sample from the apical 4 gap window was taken from the systolic volume (SV) lateral mitral ring, septal mitral ring, and right ventricular tricuspid ring, and peak systolic (Sm), peak early diastolic (Em), and peak late diastolic (Am) velocities were measured from these samples.

Electromechanical Delay Measurement

The time between the onset of the P wave on the superficial ECG and the onset of the tissue Doppler late diastolic wave (Am wave) was defined as PA atrial EMD (atrial conduction time), and all atrial EMDs were measured from lateral mitral annulus (lateral PA), septal mitral annulus (septal PA) and right tricuspid annulus (tricuspid PA) (Figure 1). The difference between the PA durations measured from the SV lateral mitral annulus
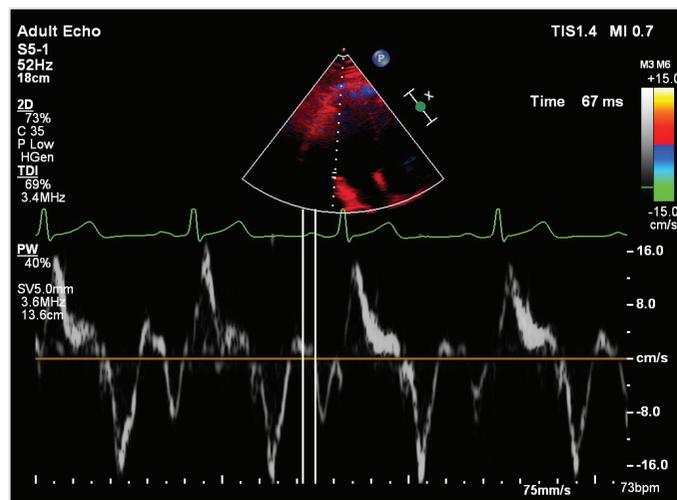
(ML) and the right ventricular tricuspid annulus (TL) regions was defined as interatrial EMD, the difference between the PA durations measured from SV lateral mitral annulus and septal mitral annulus (MS) was defined as intra-left atrial EMD, the difference between the PA durations measured from septal mitral annulus and right ventricular tricuspid annulus was defined as intra-right atrial EMD.

Epicardial Adipose Tissue Thickness

EAT thickness was obtained from the thickest part at the end of the diastole from the right ventricular free wall in the parasternal long axis window (Figure 2).

Laboratory Analysis

Blood values of the patients including erythrocyte sedimentation rate, C-reactive protein (CRP) and lipid values were obtained after 8 hours of fasting. The hematology analyzer (Beckman Coulter LH 780, FL, USA) was used to obtain the results of the full blood samples, while the CRP was measured using a biochemical analyzer (Beckman Coulter AU 680).

Statistical Analysis

SPSS statistical software version 22.0 (IBM, Chicago, IL, USA) was used to analyze the data. Kolmogorov-Smirnov tests were used to test whether the data was normal distribution. Mean $\pm$ standard deviation was used to express quantitative variables, while categorical variables were expressed in numbers and percentages. When comparing two groups for numerical variables, independent t-tests were used if there was a normal distribution. If there was no normal distribution, Mann-Whitney U tests were used. Chi-square tests were used to evaluate differences in categorical variables. Spearman correlation analysis was used to show the relationships between continuous variables. The power analysis of the study was evaluated using the G*power 3.1 program. The power of the study was 0.956 and the effect size was 1.413. $P<0.05$ was found to be statistically significant.

Results

Fourty three AS patients and age and gender matched 42 healthy control subjects were included in our study. Clinical characteristics and laboratory findings for AS patients and healthy people and various
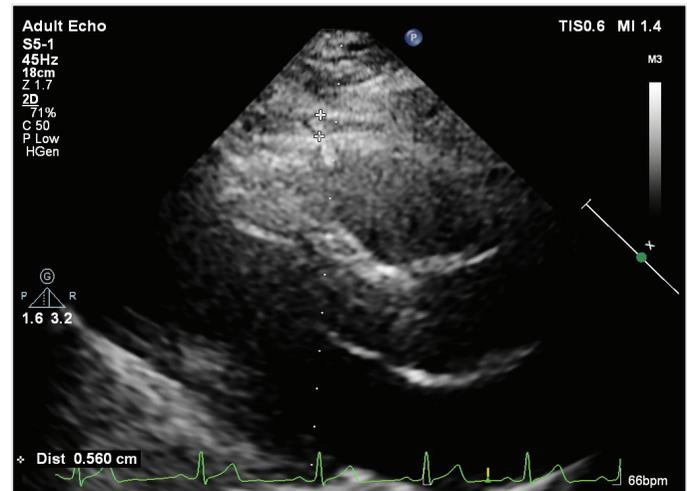

Figure 1. Evaluation of atrial conduction times with Doppler echocardiography

Figure 2. Evaluation of epicardial adipose tissue thickness by echocardiography

disease activity parameters of AS patients are given in Table 1. In terms of laboratory findings, CRP was significantly higher in AS patients (p<0.05). Other laboratory parameters were similar between groups.

Analysis of Conventional Echocardiographic and Tissue Doppler Parameters

There was no significant difference between many conventional echocardiographic parameters in which the diameter and functions of the right and left spaces were evaluated and tissue Doppler parameters (Table 2). However, diameters and volumes of the right and left atria were significantly higher and septal annulus systolic myocardial velocity (Sm) was significantly lower in AS patients.

Atrial Electromechanical Delay and Epicardial Adipose Tissue Thickness

Doppler tissue measurements showed that PA lateral, PA septal and PA tricuspid in AS patients were more elongated than the control group (p<0.05 for each). With all Doppler findings indicating EMD, EAT thickness was significantly higher in AS patients than in the control group (Table 3).

Correlation Between Electromechanical Delay, Epicardial Adipose Tissue, Echocardiographic Parameters and Working Variables

A significant moderate correlation was found between interatrial EMD and CRP (r=0.445, p<0.001) and EAT thickness (r=0.451, p<0.001). Atria dimensions and correlation results between BMI and interatrial EMD are given in Table 4.

Table 2. Echocardiographic findings of ankylosing spondylitis and control group patients

	AS patient group (n=43)	Control group (n=42)	p
Conventional echocardiography			
LV EF, %	64.60±2.95	64.67±2.47	0.961
Ascending aorta diameter, mm	3.19±0.36	3.23±0.33	0.587
Sinus of valsalva diameter, mm	3.24±0.30	3.29±0.29	0.293
Aortic root width, mm	2.14±0.16	2.15±0.17	0.676
LV end-diastolic diameter, mm	4.57±0.29	4.61±0.27	0.534
LV end-systole diameter, mm	2.68±0.27	2.69±0.24	0.961
Interventricular septum, mm	0.94±0.09	0.94±0.09	0.970
Posterior wall, mm	0.92±0.09	0.93±0.09	0.993
LA AP diameter, mm	3.55±0.28	3.41±0.23	0.008
LA ML diameter, mm	4.01±0.33	3.85±0.30	0.018
LA AB diameter, mm	5.03±0.40	4.79±0.30	0.003
LA volume, mL	17.10±2.41	15.42±1.61	<0.001
RA ML diameter, mm	3.61±0.38	3.49±0.25	0.035
RA AB diameter, mm	4.58±0.43	4.34±0.34	0.007
RA volume, mL	14.14±2.53	12.91±1.62	0.010
Mitral early (E) diastolic flow rate, cm/s	73.77±15.76	78.31±12.76	0.148
Mitral late (A) diastolic flow rate, cm/s	66.53±16.06	63.88±14.40	0.425
E/A	1.15±0.31	1.26±0.26	0.086
Deceleration time, ms	210.28±29.79	210.14±41.11	0.986
TAPSE, cm	2.63±0.15	2.68±0.18	0.133
Tissue Doppler parameters			
Lateral annulus Sm, cm/s	11.03±1.62	11.35±2.27	0.467
Lateral annulus Em, cm/s	13.82±3.20	14.44±2.42	0.316
Lateral annulus Am, cm/s	11.10±2.90	10.46±2.30	0.264
Septal annulus Sm, cm/s	8.12±1.01	9.05±1.46	0.002
Septal annulus Em, cm/s	10.45±2.12	11.30±2.11	0.070
Septal annulus Am, cm/s	9.86±1.91	9.46±2.03	0.354
Tricuspid annulus Sm, cm/s	14.01±1.57	14.32±1.62	0.377
Tricuspid annulus Em, cm/s	13.56±3.39	13.50±2.56	0.931
Tricuspid annulus Am, cm/s	13.97±2.96	14.79±2.69	0.183

Continuous variables are presented as mean ± standard deviation.

LV: Left ventricle, EF: ejection fraction, LA: left atrium, AP: anteroposterior, ML: mediolateral, AB: apicobasal, RA: right atrium, TAPSE: systolic displacement of the tricuspid valve in the annular plane, Sm: systolic myocardial velocity, Em: early diastolic myocardial velocity, Am: late diastolic myocardial rate, AS: ankylosing spondylitis

Table 3. Atrial electromechanical delay times and epicardial adipose tissue thickness findings of patients in the ankylosing spondylitis and control groups

	AS patient group (n=43)	Control group (n=42)	p
PA lateral, ms	60.07±6.62	52.14±4.51	<0.001
PA septal, ms	48.95±5.39	43.12±2.88	<0.001
PA tricuspid, ms	39.86±4.02	37.60±2.74	0.002
Interatrial EMD, ms	20.21±4.25	14.55±3.74	<0.001
İntra LA EMD, ms	11.12±2.80	9.02±2.94	0.001
İntra RA EMD, ms	9.09±2.62	5.52±1.93	<0.001
Epicardial fat tissue thickness, cm	0.46±0.15	0.33±0.12	<0.001

Continuous variables are presented as mean ± standard deviation.

PA: The duration from the onset of the P wave on electrocardiography to the onset of the A wave on echocardiography, EMD: electromechanical delay, LA: left atrial, RA: right atrial, AS: ankylosing spondylitis

Table 4. Correlation between electromechanical delay, epicardial adipose tissue, echocardiographic parameters and study variables

	Interatrial EMD, ms	
	r	p
Age, years	0.156	0.155
BMI, kg/m²	0.236	0.036
CRP, mg/dL	0.445	<0.001
LA AP diameter, mm	0.520	<0.001
LA ML diameter, mm	0.214	0.051
LA AB diameter, mm	0.460	<0.001
LA volume, mL	0.407	<0.001
RA ML diameter, mm	0.135	0.219
RA AB diameter, mm	0.406	<0.001
RA volume, mL	0.367	0.001
EAT	0.451	<0.001

BMI: Body mass index, CRP: C-reactive protein, LA: left atrium, AP: anteroposterior, ML: mediolateral, AB: apicobasal, RA: right atrium, EAT: epicardial adipose tissue, EMD: electromechanical delay

Discussion

In our study, atrial EMD and EAT thickness were evaluated in patients with AS, and three main findings were as follows: 1) Interatrial EMD and intraatrial EMD were significantly higher in AS patients; 2) EAT thickness was significantly greater in AS patients; 3) there was a significant correlation between interatrial EMD and CRP, atrial sizes and EAT.

Although AS primarily affects the axial skeleton, it is a systemic chronic inflammatory rheumatic disease affecting extra skeletal tissues such as ophthalmologic, cardiac and neurological. Cardiac complications occur especially after a long illness period (2,10). Cardiovascular complications seen in 5-10% of patients are aortic root diseases, diastolic dysfunction, intracardiac transmission disorders, myocardial fibrosis and more rarely arrhythmia. It is also recently reported a trend towards increased subclinical atherosclerosis in patients with AS without clinical evidence of cardiac involvement. Fibrosis in the atrial tissue that arises as a result of inflammation may also contribute to conduction abnormalities and impairment of atrial mechanical function in patients with AS (3,11). However, recent studies have shown that there is a relationship between chronic inflammation and the development of AF, and infiltration by inflammatory cells in the atrial tissue has been observed in AF patients (12). It has been reported that atrial conduction disorders due to electrophysiological and electromechanical abnormalities increase the risk of developing AF (4). In addition, it has been shown in recent studies that prolonged intraatrial and interatrial electromechanical conduction times increase the risk of AF (13,14). In this study, we observed that intraatrial and interatrial conduction times increased in AS patients. Although there is still no clear evidence, it has been suggested that AS patients may be at high risk for developing AF as a result of increased chronic inflammation and myocardial fibrosis.

EAT, located between myocardium and visceral pericardium, is a type of visceral adipose tissue. EAT secretes a wide variety of active biological molecules that regulate vascular smooth muscle contraction. Paracrine effects arise from its proximity to adventitia and extravascular bed (15). TTE provides non-invasive evaluation of EAT. EAT is thought to play an important role in CAD and AF pathogenesis (8,9). In a study conducted, it was shown that EAT is associated with hypertension, atherosclerosis and coronary heart disease (16). It has been shown by Yamashita et al. (17) that there is relationship between increased EAT thickness measured on computed tomography and especially left anterior descending and right coronary artery coronary plaque load. There are also studies explaining the relationship between EAT and the development and severity of AF. In the Framingham Heart Study, it was shown that higher pericardial fat volume was associated with approximately 40% higher AF rates, even after adjusting for risk factors such as age, myocardial infarction, heart failure, BMI, and gender associated with AF (18). Batal et al. (19) reported that increased EAT thickness is an important predictor of AF load independent of age, BMI, or left atrial area, and that patients with permanent AF have a significantly thicker EAT than patients with paroxysmal AF or without AF. Another study showed that EAT was associated with AF even after adding other risk factors, and that every 10 mL increase in EAT volume increased AF rates by 13% (20). In addition, the association of EAT with recurrence after AF catheter ablation has been demonstrated. It has been shown that in patients with increased EAT, recurrence is observed earlier after the ablation procedure and EAT independently predicts the presence, severity and recurrence of AF (21). All these evidences show that there is a close relationship between

EAT and CAD and AF. In our study, we observed significantly increased EAT thickness in AS patients. Our study had the following limitations. First, the main limitation was that there were a limited number of cases included in the study and that it was done in a single center. Therefore, multi-center studies involving large number of subjects are needed to validate the results of our study. Second, methods such as cardiac magnetic resonance or computed tomography for atrial remodeling and EAT evaluation were not used in this study. Therefore, it may be necessary to evaluate EAT and atrial remodeling with these methods in AS patients. Third, since a limited number of patients were included in the study, independent variables could not be evaluated by multiple analyses. Finally, the mean follow-up period of AS cases included in the study was relatively short. Since this time is not sufficient to show the development of AF and CAD, longer studies are required.

Conclusion

In this study, it has been shown that there is a prolongation in atrial EMG, that predicts AF in AS patients and an increase in EAT thickness, which also causes the development of CAD and AF. In addition, a significant positive correlation was found between interatrial and intraatrial EMD and EAT. These results suggest that it may cause increased CAD and AF development in AS patients. Therefore, AS patients should be followed closely in terms of cardiac involvement.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 1849, date: 24.05.2019).

Informed Consent: A written informed consent form was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept - A.Ö., B.A., T.K., E.A., S.Ç.E.; Design - A.Ö., B.A., T.K., H.C., E.A., S.Ç.E., N.Ö.; Data Collection or Processing - A.Ö., H.C., S.Ç.E.; Analysis or Interpretation - A.Ö., B.A., T.K., E.A., T.Ç., S.Ç.E., N.Ö.; Literature Search - A.Ö., T.Ç., N.Ö.; Writing - A.Ö.

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Predictors of Complex Aortic Plaques in Patients Undergoing Transoesophageal Echocardiography

Transözefajiyal Ekokardiyografik İnceleme Yapılan Hastalarda Kompleks Aort Plaklarının Öngördürücüleri

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ABSTRACT

Introduction: Atrial fibrillation (AF) is one of the most important causes of ischaemic stroke according to the TOAST classification. The CHA_2DS_2-VASc score is a widely used scoring system for estimating systemic thromboembolism in patients with non-valvular AF. TOAST classification indicates that an ischaemic stroke may also be due to large artery atherosclerosis. Since some of the atherosclerotic risk factors also occur in the CHA_2DS_2-VASc scoring system, we hypothesised that this scoring system can also predict the presence of complex aortic plaques and their stroke risk.

Methods: We retrospectively investigated 551 patients who underwent transthoracic echocardiography and subsequent transoesophageal echocardiography (TEE). Baseline characteristics of the patients were recorded, and the CHA_2DS_2-VASc score was calculated before the TEE examination. Aortic plaques are classified as complex when they are protruding more than 4 mm, mobile or have irregular boundaries.

Results: Among 551 patients, 110 complex aortic plaques (CAPs) were detected. Considering all the patients, higher CHA_2DS_2-VASc score [odds ratio (OR): 2.905], increasing age (OR: 1.056), and male (OR: 3.008) were significantly associated with CAP. CHA_2DS_2-VASc score was even more significantly associated with CAP in patients with a previous stroke [p<0.001, OR: 16.754 (4.196-66.894), confidence interval (CI): 95%]. After excluding complicated aortic plaques from the calculation, higher CHA_2DS_2-VASc score in patients with AF was also associated with the presence of CAPs (p<0.001, OR: 3.379 1.848-6.179, CI: 95%).

Conclusion: Although the CHA_2DS_2-VASc score has been validated to estimate thromboembolic risk in patients with non-valvular AF, the results of this study show that a high CHA_2DS_2-VASc score may also indicate an increased risk for CAP in patients with both sinus and non-valvular-AF rhythm.

Keywords: Complex aortic plaques, CHA_2DS_2-VASc score, ischaemic stroke

ÖZ

Amaç: Atriyal fibrilasyon (AF) TOAST sınıflamasına göre iskemik inmenin önemli bir nedenidir. CHA_2DS_2-VASc skor non-valvüler AF'li hastalarda iskemik stroke ve tromboemboli riskini belirlemek için sıklıkla kullanılan bir skorlama sistemidir. Bunun yanı sıra TOAST sınıflamasında, büyük arter aterosklerozu kardiyoembolizm gibi iskemik inmenin ayrı bir sınıfıdır. Biz bu çalışmamızda CHA_2DS_2-VASc skorunun kompleks aortik plaklar (KAP) ile olan ilişkisini incelemeyi amaçladık.

Yöntemler: Retrospektif olarak transtorasik ve sonrasında transözefajiyal ekokardiyografi (TÖE) uygulanmış 551 hasta analiz edildi. Hastaların demografik ve klinik özellikleri kaydedildi. CHA_2DS_2-VASc skoru TÖE incelemesi öncesinde hesaplandı. 4 mm'den büyük, hareket eden veya düzensiz sınırları olan plaklar KAP olarak kabul edildi.

Bulgular: Beş yüz elli bir hasta dahil edildi ve 110 KAP saptandı. Tüm hastalar göz önüne alındığında CHA_2DS_2-VASc skoru [olasılık oranı (OR): 2,905], yaş (OR: 1,056) ve ve erkek cinsiyet (OR: 3,008) anlamlı bir şekilde KAP ile ilişkili saptandı. Buna ek olarak daha önce iskemik inme geçiren [p<0,001, OR: 16,754 (4,196-66,894), güven aralığı (GA) %95] veya AF'li hastalarda da (p<0,001, OR: 3,379 1,848-6,179, GA: %95) KAP CHA_2DS_2-VASc skoru ile ilişkili saptandı.

Sonuç: Her ne kadar CHA2DS2-VASc skoru non-valvüler AF hastalarında tromboembolik riski hesaplamak için geliştirilmiş olsa da, bu çalışmanın sonucu CHA2DS2-VASc skorunun hem sinüs hem de AF ritmindeki hastalarda artmış KAP riskine işaret edeceğini de göstermiştir.

Anahtar Kelimeler: Kompleks aort plakları, CHA_2DS_2-VASc skoru, iskemik inme

Introduction

Ischaemic stroke is one of the leading causes of mortality and morbidity worldwide and it is related to multiple underlying aetiologies. Although the trial of ORG 10172 in acute stroke treatment (TOAST) ischaemic stroke classification has divided ischaemic strokes into five subgroups according to the underlying aetiology, the underlying aetiologies cannot be definitely diagnosed in the majority of the cases (1).

Cardioembolism is assumed to be the underlying cause in 30% of ischaemic strokes. Previous studies have demonstrated that the CHA$_2$DS$_2$-VASc score predicts cardioembolic stroke particularly in patients with non-valvular atrial fibrillation (NV-AF). Moreover, some studies suggested that it might also predict stroke risk even in patients with sinus rhythm (2-4). Current literature suggests that an increment in the CHA$_2$DS$_2$-VASc score is related to a higher stroke risk due to left atrial (LA) abnormalities, which create a favourable milieu for thrombus formation (5). Most of the risk factors that make up the CHA$_2$DS$_2$-VASc score are also traditional risk factors for atherosclerosis; therefore, an increased CHA$_2$DS$_2$-VASc score may also imply a higher atherosclerotic burden. Overwhelming evidence in the literature suggests that the presence of aortic atheroma plaques predicts future ischaemic stroke, especially when the thickness exceeds 4 mm. Sugioka et al. (6) have demonstrated a significant relationship between CHADS$_2$ score and complex aortic plaques (CAP). Since the CHA$_2$DS$_2$-VASc score predicts ischaemic stroke modestly better than the CHADS score (1), regardless of the underlying rhythm, we aimed to investigate the relationship between the CHA$_2$DS$_2$-VASc score and CAP.

Methods

Study Population

We retrospectively analysed 651 patients who underwent transoesophageal echocardiography (TEE) between January 2016 and January 2018 in our university clinic. Twenty-one patients were excluded due to the lack of prior transthoracic echocardiographic (TTE) data and 79 patients were excluded due to the absence of clinical variables. Finally, 551 patients (267 men and 284 women) were included in the analysis. The study protocol was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (decision no: 51436, date: 07.02.2018) and patients were included after their informed consent was obtained.

Patients' demographic characteristics such as age, sex and medical history including diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), peripheral arterial disease, ischaemic stroke and AF were recorded.

CHA$_2$DS$_2$-VASc score was calculated according to the recommendations of the current guidelines. In brief, one point was given for the history of heart failure, presence of diabetes, HT, age between 65 and 75 years, female sex, vascular disease and two points for age >75 years and history of previous stroke. History of myocardial infarction, symptomatic peripheral arterial disease and the presence of CAPs were considered to be vascular diseases as recommended.

Echocardiographic Data

TTE was performed prior to the TEE examination of each patient in accordance with the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines. TEE was performed for various clinical indications such as infective endocarditis, assessment of valvular diseases or identification of the aetiology of an ischaemic stroke. TTE and TEE findings that were suggested as potential sources of cardioembolism according to the TOAST classification were collected. In the TOAST trial, cardiac abnormalities, which are prone to be the source of embolism, were divided into two groups: high risk and medium risk.

TEE was performed to all the patients using a commercially available ultrasound imaging system with a 3-D matrix array transoesophageal transducer (Philips Medical systems, IE33, Andover, MA, USA and probe X7-2t). The thoracic aorta was screened when the probe was withdrawn gradually from the descending aorta after the routine assessment of the cardiac structures. Aortic plaques were considered complex if the plaque protruded more than 4 mm from intima to the lumen in the horizontal plane and perpendicular to the arterial wall. We also considered plaques as complex if the plaque had a mobile component or an ulceration. Plaque ulceration was defined as a 2 mm indentation of the plaque surface towards the arterial wall.

Statistical Analyses

SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used for the data analysis. MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium) was used for building the graphics. Data are presented as (i) mean $\pm$ standard deviation for continuous variables and (ii) counts with percentages for categorical variables. Normality of distribution for continuous variables was analysed using the Shapiro-Wilk test. Depending on the distribution pattern, independent samples t-test or Mann-Whitney U test was used for group comparisons of the continuous variables. Chi-square test or Fischer's Exact test was performed for the group comparisons of categorical variables as appropriate. Univariate and multivariate logistic regression analyses were used to assess the possible association among demographic, clinical, imaging findings, CHA$_2$DS$_2$-VASc scores and the presence of CAPs. Variables with p<0.05 in the univariate logistic regression were included in the multivariate logistic regression. Age, sex, HT, stroke, DM and CAD were included in the multivariate analysis regardless of their statistical significance in the univariate analysis. The statistical significance threshold in the multivariate analyses was adjusted using Bonferroni correction. Cochran-Armitage test was performed to test the trend between CHA$_2$DS$_2$-VASc scores and the prevalence of CAP. Unless otherwise stated, p<0.05 indicated statistical significance.

Results

Patients Demographics

The characteristics of all the 551 patients are shown in Table 1. Mean age was 55±18 years, and 49.1% of the patients were men. The prevalence of AF was high (33.4%). A total of 167 (30.3%) patients had a recent or previous ischaemic stroke. Echocardiographic findings that were supposed to be a potential source of cardioembolism according to TOAST classification are also shown in Table 1.

Potential Cardiac Source of Embolism

Fifty-two patients had LA/left atrial appendage (LAA) thrombi, three had left ventricular (LV) thrombi, 28 had a LV akinetic segment, three had an atrial myxoma, 97 had a diagnosis of dilated cardiomyopathy

Table 1. Demographic and echocardiographic characteristics of all patients

	Value (n=551)
Age	55±18
Gender	
Female	284 (51.5%)
Male	267 (48.5%)
HT	266 (48.3%)
Stroke	167 (30.3%)
DM	114 (20.7%)
CAD	106 (19.2%)
Atrial fibrillation	184 (33.4%)
LVEF	54±8
LA diameter	41±8
LAA thrombus	47 (8.5%)
LAA SEC	92 (16.7%)
LAA velocity	60±24
CAP	74 (18.3%)
PFO	93 (16.9%)
ASD	38 (6.9%)
ASA	34 (6.2%)
LV thrombus	3 (0.5%)
Dilated CM	97 (17.6%)
Akinetic segment presence	28 (5.1%)
LA thrombus	5 (0.9%)
Myxoma	2 (0.4%)
IE	28 (5.1%)
MR	443 (80.4%)
MR grade	
Mild	200 (36.3%)
Moderate	166 (30.1%)
Moderate to severe	39 (7.1%)
Severe	38 (6.9%)
MS	46 (8.3%)
MS grade	
Mild	27 (4.9%)
Moderate	16 (2.9%)
Severe	3 (0.5%)
MVP	19 (3.4%)
MAC	7 (1.3%)
CHA_2DS_2-VASc score	2±2

HT: Hypertension, DM: diabetes mellitus, CAD: coronary artery disease, LVEF: left ventricular ejection fraction, LA: left atrial, LAA: left atrial appendage, SEC: spontaneous echo contrast, CAP: complex aortic plaque, PFO: patent foramen ovale, ASD: atrial septal defect, ASA: atrial septal aneurysm, LV: left ventricle, CM: cardiomyopathy, IE: infective endocarditis, MR: mitral regurgitation, MS: mitral stenosis, MVP: mitral valve prolapse, MAC: mitral annular calcification

and 46 patients had a mitral stenosis with respect to the high risk for cardioembolism according to the TOAST classification. In addition, 184 patients had AF, of which 36 patients possessed a CHA_2DS_2-VASc score of 2, and CAP was detected in three of these 36 patients with AF. Therefore, the patients were deemed to have a high risk for future thromboembolism.

Complex Aortic Plaques

Patients were divided into two groups according to the presence or absence of CAP. CAP were detected in a total of 110 patients*. In univariate analyses, there was a statistically significant difference between the groups with respect to age (p<0.001), HT (p<0.001), CAD (p<0.001), DM (p=0.003) and AF (p<0.001). Mean CHA_2DS_2-VASc score was significantly higher in patients with CAP (2±1 in patients without CAP and 4±1 in patients with CAP, p<0.001). After multivariate analyses, male sex (p<0.001) and age (p=0.001) were independently associated with the presence of CAP. As expected, CHA_2DS_2-VASc score was also independently associated with the presence of CAP [p<0.001, odds ratio (OR): 2.905 (1.906-4.428), confidence interval (CI): 95%] (Table 2). Trend analyses of CHA_2DS_2-VASc score and presence of CAP demonstrated a significant linear relationship, which is depicted in Figures 1, 2 and 3.

The Relationship Between Cardiac Rhythm and Complex Aortic Plaques

Among the 551 patients, 184 patients had AF and AF patients had a higher percentage of CAP (28.1% vs 54.5%). Although there was a significant difference in the univariate analyses (p<0.001), AF was not independently associated with the presence of CAP in the multivariate analyses (p=0.307). CHA_2DS_2-VASc score was also significantly associated with CAP both in the univariate and multivariate analyses [p<0.001 and OR: 3.379 (1.848-6.179), CI: 95%]. Among the cases with sinus rhythm, 50 of them had CAPs. Although age, HT, DM, CAD, LV ejection fraction and CHA_2DS_2-VASc score were significant in the univariate analysis, only CHA_2DS_2-VASc score was independently associated with the presence of CAP after the multivariate analysis [p<0.001, 3.021 (1.620-5.623), CI: 95%] (Table 3).
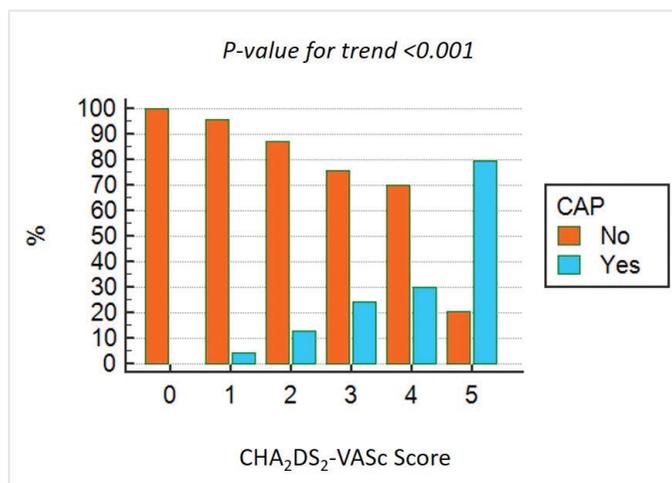
Figure 1. Trend analysis for CHA_2DS_2-VASc-VASc score and CAP in all patients
CAP: complex aortic plaque

Table 2. Group comparisons along with univariate and multivariate logistic regression analyses in all patients with or without complex aortic plaque

	Group comparisons			Univariate logistic regression		Multivariate logistic regression	
	CAP- (n=441)	CAP+ (n=110)	p	OR (95% CI)	p	OR (95% CI)	p
Age	51±17	71±10	<0.001	1.117 (1.091-1.144)	<0.001	1.056 (1.023-1.090)	0.001
Male	209 (47.4%)	58 (57.2%)	0.338	1.238 (0.815-1.881)	0.317	3.008 (1.526-5.391)	0.001
HT	180 (40.8%)	86 (78.2%)	<0.001	5.196 (3.181-8.487)	<0.001	0.609 (0.279-1.331)	0.214
Stroke	131 (29.7%)	36 (32.7%)	0.563	1.151 (0.736-1.801)	0.537	0.425 (0.188-0.960)	0.039
DM	76 (17.2%)	32 (34.5%)	<0.001	2.535 (1.593-4.032)	<0.001	0.533 (0.260-1.094)	0.086
CAD	65 (14.7%)	41 (37.3%)	<0.001	3.437 (2.153-5.487)	<0.001	0.409 (0.193-0.869)	0.020
AF	124 (28.1%)	60 (54.5%)	<0.001	3.068 (1.998-4.711)	<0.001	0.697 (0.348-1.394)	0.307
LVEF	55±7	51±10	<0.001	0.946 (0.924-0.968)	<0.001	1.015 (0.972-1.059)	0.506
LA diameter	40±8	43±6	<0.001	1.041 (1.015-1.068)	0.002	0.952 (0.909-0.997)	0.038
LAA thrombus	28 (6.3%)	19 (17.3%)	<0.001	3.080 (1.648-5.755)	<0.001	2-202 (0.881-5.503)	0.091
LAA spontaneous echo contrast	48 (14.5%)	27 (36.5%)	<0.001	2.775 (1.698-4.536)	<0.001	0.968 (0.454-2.066)	0.934
LAA velocity	63±23	50±23	<0.001	0.976 (0.966-0.986)	<0.001	0.991 (0.977-1.006)	0.231
PFO	81 (18.4%)	12 (10.9%)	0.065	0.544 (0.285-1.038)	0.065	-	-
ASD	32 (7.3%)	6 (5.5%)	0.674	0.737(0.300-1.810)	0.506	-	-
ASA	30 (6.8%)	4 (3.6%)	0.272	0.517 (0.178-1.500)	0.225	-	-
LV thrombus	2 (0.5%)	1 (0.9%)	0.488	2.014 (0.181-22.412)	0.569	-	-
Dilated CM	68 (15.4%)	29 (26.4%)	0.011	1.964 (1.195–3.227)	0.008	2.003 (0.835-4.803)	0.120
Akinetic segment	10 (3.0%)	5 (6.8%)	0.125	1.161 (0.979-1.375)	0.136	-	-
Akinetic segment number	4±2	5±3	0.561	1.192 (0.716-1.983)	0.500	-	-
LA thrombus	4 (0.9%)	1 (0.9%)	0.998	1.002 (0.111-9.058)	0.998	-	-
LA SEC	59 (13.4%)	33 (30%)	<0.001				
Myxoma	2 (0.5%)	0	0.479	-	0.999	-	-
IE	24 (5.4%)	4 (3.6%)	0.627	0.254 (0.223-1.980)	<0.001	1.308(0.482-3.555)	0.598
MR	342 (77.6%)	101 (91.8%)	<0.001	3.249 (1.585-6.658)	-	-	-
MS	37 (8.4%)	9 (8.9 %)	0.944	0.973 (0.455-2.081)	0.944	-	-
MVP	18 (4.1%)	1 (0.9%)	0.103	0.216 (0.028-1.633)	0.137	-	-
MAC	5 (1.1%)	2 (1.8%)	0.566	1.615 (0.309-8.436)	0.570	-	-
CHA$_2$DS$_2$-VASc score	2±1	4±1	<0.001	2.537 (2.114-3.046)	<0.001	2.905 (1.906-4.428)	<0.001

HT: Hypertension, DM: diabetes mellitus, CAD: coronary artery disease, AF: atrial fibrillation, LVEF: left ventricular ejection fraction, LA: left atrium, LAA: left atrial appendage, CAP: complex aortic plaque, PFO: patent foramen ovale, ASD: atrial septal defect, ASA: atrial septal aneurysm, LV: left ventricle, CM: cardiomyopathy, IE: infective endocarditis, MR: mitral regurgitation; MS: mitral stenosis, MVP: mitral valve prolapse, MAC: mitral annular calcification, OR: odds ratio , CI: confidence interval, LA SEC: left atrial spontaneous echo contrast

When the stroke patients were analysed according to presence of CAP, AF was found to be significantly more frequent in CAPs (+) patients.

Discussion

Our study demonstrated that the CHA$_2$DS$_2$-VASc score is strongly correlated with the presence of CAPs regardless of the underlying rhythm and that as the CHA$_2$DS$_2$-VASc score increased, the possibility of CAP detection also increased. After adjustment for atherosclerotic risk factors, LA abnormalities and cardiac rhythm, CHA$_2$DS$_2$-VASc score was still independently and significantly associated with the presence of CAPs. Moreover, trend analyses between CHA$_2$DS$_2$-VASc score and CAPs revealed that every 1 point increase in CHA$_2$DS$_2$-VASc score was significantly associated with an increased risk of the presence of CAPs. Although the CHA$_2$DS$_2$-VASc score was primarily developed to estimate

the stroke risk in patients with NV-AF, current studies suggest that these scores might also predict the future stroke risk even in patients without AF. This may be explained by the fact that most of the parameters included in the CHA$_2$DS$_2$-VASc scoring system are also the risk factors for stroke (7). Therefore, concomitance of a high CHA$_2$DS$_2$-VASc score, CAPs and stroke should be expected and the findings of our study provide evidence for this concomitance.

Although the aetiology and treatment modalities of ischaemic stroke are well defined in the literature, the precise cause of the ischaemic event in a particular patient cannot be established in most stroke cases (8). The TOAST classification system divides strokes into five subgroups according to the cause: cardioembolism, large artery atherosclerosis, small-vessel occlusion, stroke of other determined aetiology and stroke of undetermined aetiology. Strokes have an undetermined aetiology
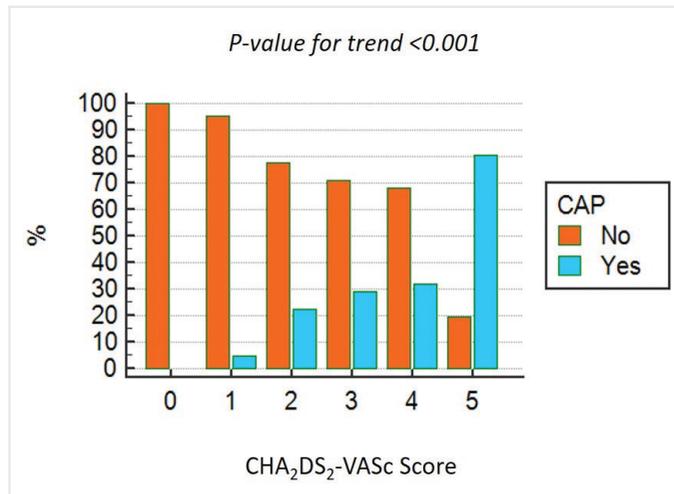
Figure 2. Trend analysis for CHA$_2$DS$_2$-VASc score and CAP in patients with atrial fibrillation

CAP: complex aortic plaque
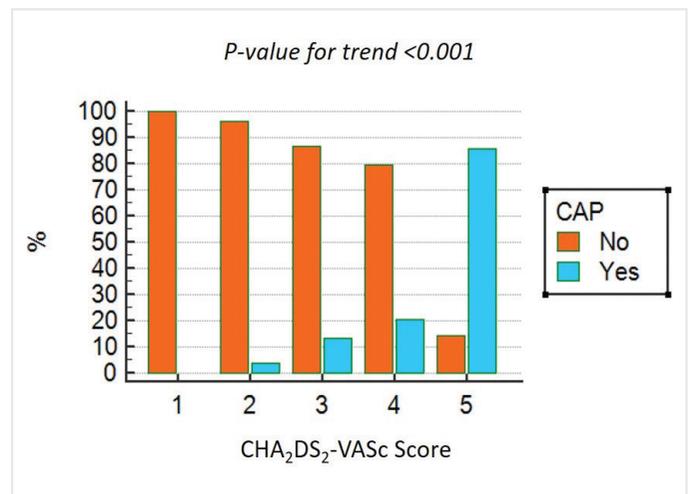
Figure 3. Trend analysis for CHA$_2$DS$_2$-VASc-VASc score and CAP patients with stroke

CAP: Complex aortic plaque

Table 3. Group comparisons along with univariate and multivariate logistic regression analyses in patients with atrial fibrillation

	Group comparisons			Univariate logistic regression		Multivariate logistic regression	
	AF+ & CAP- (n=124)	AF+ & CAP+ (n=60)	p	OR (95% CI)	p	OR (95% CI)	p
Age	61±11	75±8	<0.001	1.147 (1.094-1.202)	<0.001	1.032 (0.995-1.070)	0.089
Male	65 (52.4%)	33 (55.0%)	0.755	1.109 (0.598-2.060)	0.742	3.655 (1.453-9.199)	0.006
HT	80 (64.5%)	51 (85.0%)	0.005	3.117 (1.403-6.925)	0.005	0.530 (0184-1.521)	0.238
Stroke	24 (19.4%)	14 (23.3%)	0.299	1.268 (0.601-2.674)	0.553	0.112 (0.016-0.787)	0.028
DM	35 (28.3%)	20 (33.3%)	0.496	1.271 (0.654-2.470)	0.478	0.548 (0.188-0.1596)	0.270
CAD	36 (29.0%)	28 (46.7%)	0.021	2.139 (1.130-4.050)	0.020	0.518 (0.181-1.484)	0.221
LVEF	52±9	48±10	0.016	0.985 (0.955-1.015)	0.327	-	-
LA diameter	47±10	46±7	0.806	0.990 (0.952-1.029)	0.599	-	-
LAA thrombus	23 (18.5%)	16 (26.7%)	0.249	1.597 (0.770-3.313)	0.209	-	-
LAA SEC	43 (34.7%)	28 (46.7%)	0.109	1.648 (0.880-3.088)	0.119	-	-
LAA velocity	52±23	42±21	0.013	0.982 (0.967-0.998)	0.025	0.996 (0.979–1.013)	0.659
PFO	20 (16.1%)	4 (6.7%)	0.101	0.371 (0.121-1.140)	0.084	-	-
ASD	5 (4%)	1 (1.7%)	0.397	0.403 (0.046-3.532)	0.412	-	-
ASA	6 (4.8%)	1 (1.7%)	0.292	0.333 (0.039-2.833)	0.314	-	-
LV thrombus	2 (1.6%)	0	1.000	-	-	-	-
Dilated CM	39 (31.5%)	19 (31.7%)	0.326	1.010 (0.520-1.960)	0.977	-	-
Akinetic segment	7 (7.4%)	4 (8.9%)	0.747	0.968 (0.777-1.204)	0.767	-	-
Akinetic segment diameter	4±2	5±3	1.000	1.046 (0.596-1.834)	0.876	-	-
LA thrombus	1 (0.8%)	1 (1.7%)	0.598	2.085 (0.128-33.912)	0.606	-	-
Myxoma	1 (0.8%)	0	1.000	-	-	-	-
IE	0	0	-	-	-	-	-
MR	115 (92.7%)	57 (95.0%)	0.754	1.487 (0.388-5.705)	0.563	-	-
MS	10 (8.1%)	6 (10.0%)	0.781	1.267 (0.438-3.666)	0.463	-	-
MVP	1(0.8%)	1 (1.7%)	0.598	2.085 (0.128-33.912)	0.606	-	-
MAC	1 (0.8%)	1 (1.7%)	0.598	2.085 (0.128-33.912)	0.606	-	-
CHA$_2$DS$_2$-VASc score	3±1	5±1	<0.001	2.192 (1.662-2.892)	<0.001	3.379 (1.848-6.179)	<0.001

HT: Hypertension, DM: diabetes mellitus, CAD: coronary artery disease, AF: atrial fibrillation, LVEF: left ventricular ejection fraction, LA: left atrium, LAA: left atrial appendage, SEC: spontaneous echo contrast, CAP: complex aortic plaque, PFO: patent foramen ovale, ASD: atrial septal defect, ASA: atrial septal aneurysm, LV: left ventricle, CM: cardiomyopathy, IE: infective endocarditis, MS: mitral stenosis, MR: mitral regurgitation, MVP: mitral valve prolapse, MAC: mitral annular calcification, OR: odds ratio , CI: confidence interval

when the underlying cause cannot be established or more than one possible aetiologies are detected (1). In our study, we demonstrated that 39% of patients had at least two possible sources of embolism. Since the suggested strategy of treatment differs between TOAST groups, it is essential to precisely decide on the aetiology of the stroke. This scope of view is also valuable in patients with AF. Both the American College of Cardiology/American Heart Association and European Society of Cardiology (ESC) (9,10) guidelines on the treatment of AF strongly recommend anticoagulation in patients with a higher stroke risk; however, it has been demonstrated in previous studies that statin is more beneficial than anticoagulation in patients with stroke due to the CAPs. Di Tullio et al. (11) compared acetylsalicylic acid therapy with anticoagulation in patients with a previous stroke and aortic arch atherosclerosis. There was no difference between the groups in terms of recurrent stroke and death; however, in that study, although statin therapy was not given routinely to all patients, statin treatment was associated with improved outcomes with respect to recurrent stroke and death. In the light of these previous studies and ours, it would be fairly reasonable to administer statin therapy in patients with stroke and CAP regardless of antithrombotic therapies.

Sugioka et al. (6) demonstrated that the CHADS score is associated with the presence of CAPs, which is concordant with our findings. Although the CHADS score was used to estimate the stroke risk, current guidelines recommend the use of the CHA$_2$DS$_2$-VASc score, which has a modestly higher predictive ability for stroke. Sugioka had also shown a higher prevalence of CAPs in patients with AF. Although in our study, the univariate analysis suggested the same in our study, after adjustment for possible confounders, multivariate analyses have revealed that there is no independent association between CAPs and cardiac rhythm. Since most of the risk factors of AF and atherosclerosis are overlapping, one can expect the co-occurrence of AF and CAPs. However, there is no evidence in the literature regarding the accelerated atherosclerosis in AF patients, which is the case in our study as well.

Yang et al. (12) have also demonstrated a significant relationship between CHA$_2$DS$_2$-VASc score and CAPs. In that study, they concluded that the concomitance of AF and CAP may increase the risk of stroke by different mechanisms. In our study, 60 out of 184 AF patients had CAPs (32.6%), which eventually increased each patient's CHA$_2$DS$_2$-VASc score. There were 19 patients with a CHA$_2$DS$_2$-VASc score of 2. Among these patients, the score of two patients was 1 before the TEE examination and 1 point added as a result of the presence of CAPs, and consequently anticoagulation was indicated. Contrariwise to Yang et al. (12), there was a higher number of patients with CAP in our study (8.2% vs 19.9%). This may be explained by the higher CHA$_2$DS$_2$-VASc scores of the patients in our study (1.75±1.61 vs 2±2). Beside the CHA$_2$DS$_2$-VASc score, ESC considers the Turkish population as a very high-risk population for atherosclerosis (13). This may also explain the higher prevalence of CAP in our study.

Impact on the Treatment Strategy

In our study, 36 patients had AF with a CHA$_2$DS$_2$-VASc score of 2. Among these, three patients were considered as having an intermediate risk for stroke before the TEE examination; eventually, the presence of CAP

increased their CHA$_2$DS$_2$-VASc score and anticoagulant therapy was finally indicated. Among those with a previous stroke, 38 patients had AF (22.7%). If AF was considered as the primary underlying aetiology, anticoagulant therapy could be sufficient. However, 14 of 38 patients had CAP, which could well also be the obscure underlying aetiology. In conclusion, 14/167 (8.38%) patients with stroke were detected to possess multiple sources of embolism, which requires both anticoagulant and statin therapies.

The major limitation of our study is its retrospective design. We included patients who underwent TEE examinations within the last 16 months; therefore, it did not reflect the effect of treatment on any patient. Another limitation of our study is that it as a single centre study, which is the reason for the relatively small number of patients with AF or stroke. Furthermore, we did not make mention of the clinical consequences of CAPs in our study population.

Since it was previously well defined in the literature that CAPs were associated with ischaemic stroke, patients with AF and high CHA$_2$DS$_2$-VASc scores need to be treated with statins in addition to the anticoagulant therapy. Future studies are needed to evaluate the value of statin therapy in patients with a high ischaemic stroke risk.

Conclusion

Although the CHA$_2$DS$_2$-VASc score predicts ischaemic stroke in patients with NV-AF, it is also useful for the prediction of CAPs, which are related to the ischaemic stroke in the literature.

Ethics

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