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Original Article

Assessment of total cardiac repolarization's spatial distribution among patients with aortic sclerosis

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Abstract: Objective: To measure the Tp-e value, which shows the spatial distribution of cardiac repolarization and is defined as a possible predictor for ventricular arrhythmia among patients with aortic sclerosis (AS), and to compare this parameter's length to QTc length within the same population. Method: 60 patients that have been diagnosed with AS have been prospectively included in this study. Results: 60 AS and 64 control patients were evaluated as part of the study. The median age, prevalence for hypertension and diabetes, baseline medications and laboratory results of the groups were similar. The Electrocardiographic QT length of both groups were found similar. In the AS group Tp-e tangent and Tp-e tail values were more longer than control group ($P < 0.001$). Tp-e tangent index and Tp-e tail index values were also statistically higher among AS patients when compared to the control group. ($P < 0.001$). Conclusion: Our study showed that Tp-e durations had increased in AS patients with no structural coronary heart disease. AS causes local degeneration on the aortic root and also has a negative effect on the total cardiac spatial repolarization.

Keywords: Aortic sclerosis, cardiac repolarization

Introduction

Aortic Sclerosis (AS) is defined as calcification and thickening of the aortic root or leaflets without obstruction of the left ventricular outflow. AS prevalence increases with age and reaches 40% among adults aged over 75 years [1, 2]. Epidemiological studies have shown that patients with AS have a higher risk of developing cardiovascular diseases such as ventricular arrhythmia, myocardial infarction and systolic cardiac failure [3-5]. Ventricular arrhythmia occurrence as documented by electrocardiography (ECG) is approximately 20% [3]. However, no electrocardiographic parameter to be used for the assessment of elevated ventricular arrhythmia among this patient group was defined.

The total spatial distribution of cardiac repolarization (Tp-e) is an ECG parameter that shows the duration from the peak to the end of the T wave, as defined in the last period [6, 7]. It has been shown that any increase in Tp-e duration resulted in an increased development of malign ventricular arrhythmia and that this new parameter was more correlated with cardiac repolarization distribution than the QT interval [8]. In addition, it has been reported that the Tp-e length could also predict sudden cardiac death in cases with normal corrected QT lengths (QTc) [9]. Also, it has not yet been researched if the value of Tp-e and QTc has any additional benefit among the AS population with increased malignant ventricular arrhythmia. That is why this study aims to measure the Tp-e value as a possible predictor for ventricular arrhythmia among AS patients and to compare this parameter's length to QTc within the same population.

Method

Study population

The study population was prospectively included from patients diagnosed with AS at the car-

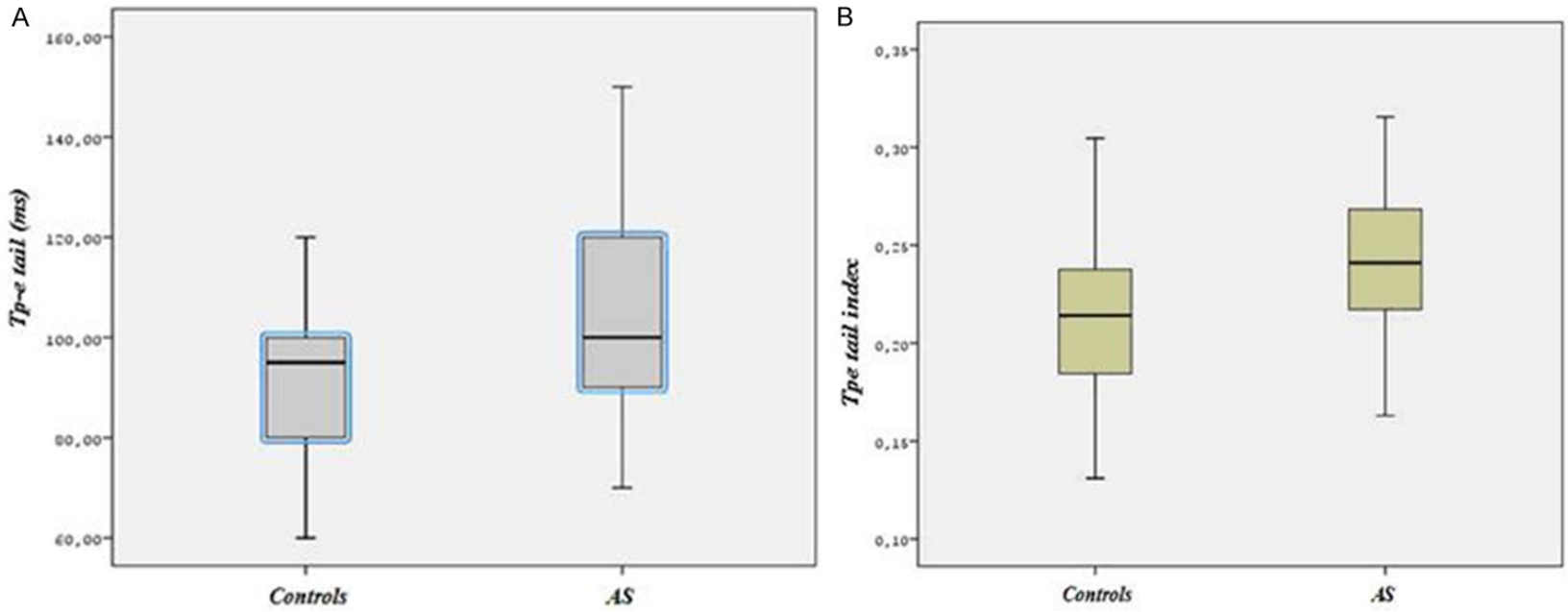

Figure 1. Distribution of Tp-e tail. A. Mean Tp-e tail (ms) in AS patients and controls (89.1 ± 14.8 vs 105.3 ± 16.4; P < 0.001); B. Mean Tp-e tail index in AS patients and controls (0.21 ± 0.034 vs 0.24 ± 0.038; P < 0.001).

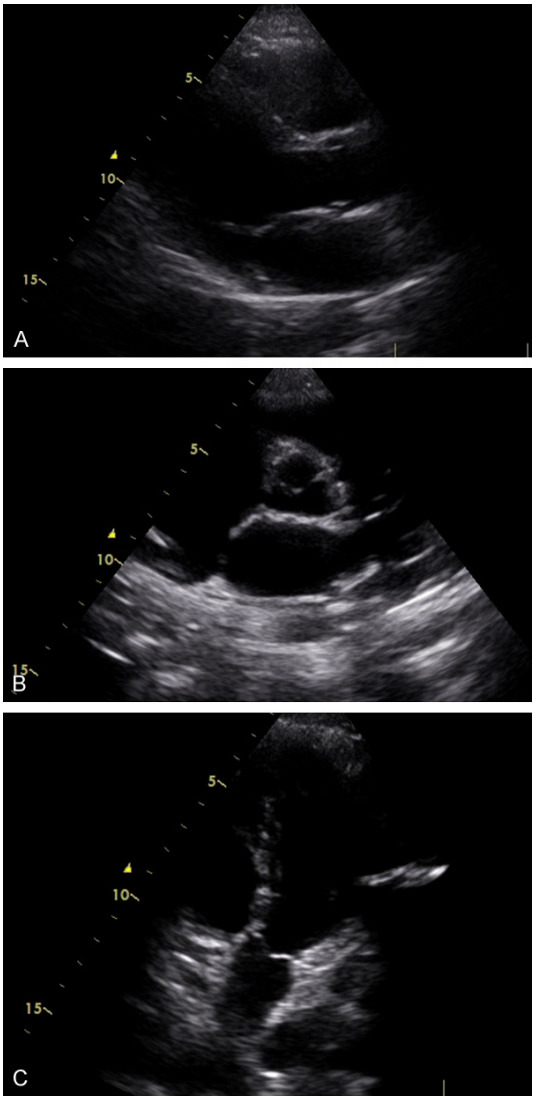

Figure 2. Parasternal long (A) short (B) axis and apical four chamber (C) view of control group. There were seen no thickening in the leaflets and aortic root and no obstruction observed of the left ventricular outflow tract.

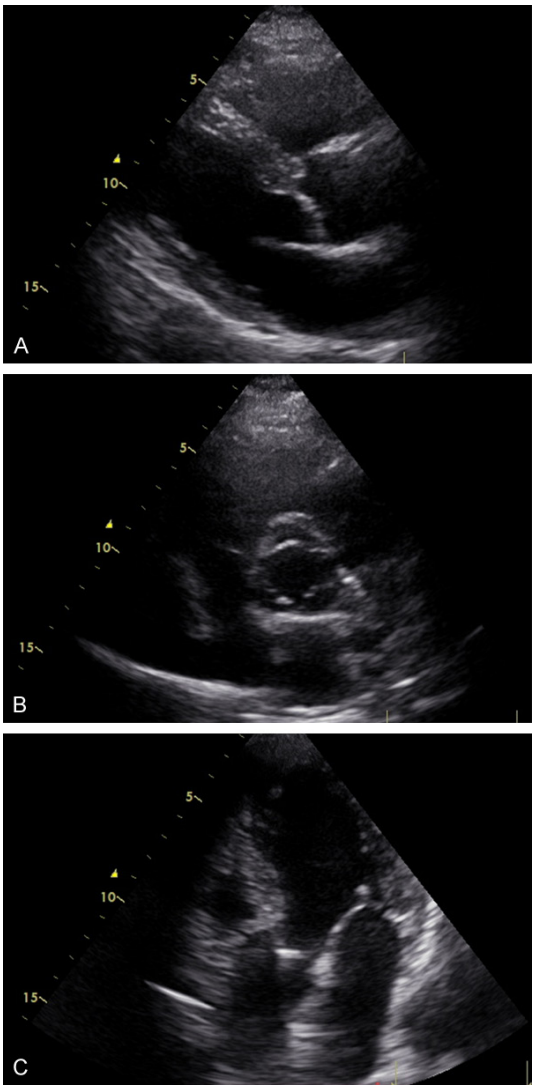

Figure 3. A. Parasternal short-axis images of the aortic sclerosis. Calcification and thickening of the aortic root and leaflets. B. Parasternal short-axis images of the aortic sclerosis. AS without obstruction of the left ventricular outflow. C. Apical four chamber view of the aortic sclerosis.

diology clinic between June 2011 and June 2013. Patients with known coronary artery disease, thyroid dysfunction, chronic renal disease, bicuspid aorta valve and moderate to severe cardiac valve disease were excluded from the study. Systemic hypertension was defined as having blood pressure of ≥ 140/90 mmHg or using antihypertensive medication, while diabetes mellitus was defined as having a fasting blood glucose of > 126 mg/dl or HbA1c ≥ 6.5%. Patients weight and lenght were measured and Body Mass Index (BMI) was calculated. Our study was approved by the local ethics committee.

Echocardiography

All echocardiographic analysis was performed using commercially available GE Healthcare Vivid devices and 4 s probes. All patients were examined using M-Mod and 2-D Doppler echocardiography. Left ventricular (LV) diameter and wall thickness was measured using M-Mod 2-D echocardiography. LV volumes were obtained using apical four and two chamber views. LV ejection fraction was calculated using modified Simpson method. Aortic valve's average and maximum gradients were calculated using

Table 1. Baseline characteristics of patients with aortic sclerosis and control

	Aortic Sclerosis	Control
Age (years)	65.6 ± 10.1	62.7 ± 10.6
Women (%)	33	51*
Hypertention (%)	70	55
Diabetes (%)	18	14
Smoking (%)	18	22
ACE inh-ARB (%)	61	45
B-blocker (%)	27	16
CCB (%)	20	16
SBP (mmHg)	134 ± 18.8	129 ± 16.6
DBP (mmhg)	80 ± 13.3	78.8 ± 9.3

ACE-inh: Angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium channel blockers, SBP: systolic blood pressure, DBP: diastolic blood pressure. Continuous data are shown as mean ± SD and categorical data are shown as percentages (*n = 60, n = 64 respectively*), *: $P < 0.05$ when compared with patients group.

Bernoulli's equation on the highest velocity measurements of apical four chamber view with continuous-wave Doppler. Echocardiographic aortic sclerosis was defined as the presence of calcification and thickening on the aortic valve that did not obstruct or minimally obstructed the ventricular outflow, with a valve Doppler velocity of ≤ 2.5 m/s [10] (**Figure 3A-C**). In addition, echocardiographic image of control groups were illustrated in **Figure 2A-C**. The LV mass was calculated using the "Penn Convention" method and the LV mass index was calculated by ratio of LV mass to body surface area.

Electrocardiographic assessment

For recording purposes, a 12-lead ECG (paper speed of 50 mm/s) was used. QT, QTc and heart rate was recorded. Tp-e was obtained using tangent and tail methods on chest derivations. Tangent method; calculated as the time interval between the T wave's peak point and downslope tangent intersecting with the isoelectric line [11]. Tail method; defined as the time interval between T wave's peak point and its downward endpoint to the isoelectric line [12]. Tp-e tail and tangent index were calculated as the ratio of Tp-e/QTc as described before [9]. The measurements were made by two independent cardiologists by taking the average of three consecutive beats. A third specialist was consulted for measurement when patients' beat difference exceeded 20 ms or more. Patients whose measurements continued to show discrepancies were excluded from the study.

Statistical analysis

Continuous variables were defined as mean ± standard deviation; categorical variables as percentages. Eligibility to normal distribution was evaluated using the Kolmogorov-Smirnov test. Mean Tp-e tail and mean Tp-e tail index were compared with Mann-Whitney U-test and other electrocardiographic and echocardiographic variables were compared with 2 sample t-test. Basal demographic variables were compared with chi square. A *P* value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (Version 14.0, SPSS, Inc., Chicago, IL).

Results

Basal demographic data for both groups were demostrated in **Table 1**. There was no significant difference between the two groups' age, hypertension and diabetes mellitus prevalence and basal medications; except for gender distribution. There were more women in control group ($P = 0.04$). Laboratory data were demostrated in **Table 2**. Serum electrolyte values such as sodium, potassium and calcium, which may be affect ventricular repolarization, were similar in both groups. Creatine levels, fasting serum glucose, total, low and high density cholesterol values were similar. Electrocardiographic and echocardiographic data were demostrated in **Table 3**. Echocardiographic image of aortic sclerosis were shown in **Figure 3A-C**. In Echocardiographic examination LV ejection fraction, LV mass-mass index, LV systolic and diastolic diameter were found to be similiar between two groups, only left ventricular systolic volume was higher than control group ($P < 0.001$). Electrocardiographic QT length were found to be similar in both groups but Tp-e tangent and tail values were longer in the AS group than in the control group ($P < 0.001$). Also, Tp-e tangent index and tail index were significantly higher in AS patients when compared to the control group ($P < 0.001$). Distrubition of Tp-e tail and tail index were shown in **Figure 1**.

Discussion

Our study evaluated QT, QTc, Tp-e tangent and Tp-e tail values, which are ECG parameters

Table 2. Laboratory parameters of patients with aortic sclerosis and control

	AS (n = 60)	Control (n = 64)
Sodium (mmol/l)	137.9 ± 3.7	138.9 ± 2.8
Potassium (mmol/l)	4.28 ± 0.5	4.35 ± 0.5
Calcium (mg/dl)	9.18 ± 0.78	9.43 ± 0.6
Total cholesterol (mg/dl)	209.7 ± 51.7	193.9 ± 51.1
LDL (mg/dl)	143 ± 34	146.8 ± 37.1
HDL (mg/dl)	51.2 ± 12.2	51.7 ± 16.4
Glucose (mg/dl)	110.3 ± 31.2	104.4 ± 25.3
Creatine (mg/dl)	0.76 ± 0.18	0.83 ± 0.18

HDL: High density lipoprotein, LDL: Low density lipoprotein. Data are shown as mean ± SD (n = 60, n = 64 respectively).

Table 3. Echocardiographic and Electrocardiographic datas in patients with aortic sclerosis and control

	Aortic sclerosis	Control
LV mass (g)	197.4 ± 47.6	183.7 ± 42.6
LV mass index (g/m^2)	104.1 ± 25.5	98.6 ± 21
LVSD (mm)	29.1 ± 10.1	29.9 ± 4.6
LVDD (mm)	47.2 ± 4.2	48.4 ± 4.6
LVSV (ml)	31.8 ± 4.02*	28.9 ± 11.8
LVDV (ml)	87.2 ± 11.5	79.6 ± 23.6
Ejection Fraction (%)	64.3 ± 5	64.6 ± 3.8
QT (ms)	400.3 ± 33.6	393.3 ± 27.8
QTc (ms)	431.7 ± 28.9	427.5 ± 30.3
Tp-e tail (ms)	105.3 ± 16.4*	89.1 ± 14.8
Tp-e tanjant (ms)	85.5 ± 13.8*	73.4 ± 10.4
Tp-e tail index	0.24 ± 0.038*	0.21 ± 0.034
Tp-e tanjant index	0.19 ± 0.03*	0.17 ± 0.024

LV: Left Ventricul, LVSD: Left ventricul systolic diameter, LVDD: Left ventricul diastolic diameter, LVSV: Left ventricul systoic volume, LVDV: Left ventricul diastolic volume. Data are shown as mean ± SD (n = 60, n = 64 respectively), *: $P <$ 0.001 when compared with control group.

used in the evaluation of cardiac repolarization in patient with AS. The standard parameters QT and QTc were similar in both groups but the newly defined Tp-e tangent and Tp-e tail values were longer in AS patients when compared to the control group.

Aortic valve sclerosis is the result of a complex pathological process that includes inflammation within the valve, endothelial dysfunction, fibrosis and microcalcification [14]. Histopathological studies have shown that focal subendothelial, plaque-like lesions extend from the aortic part to the fibrous tissue of the valves. It has been reported that atherogenic lipoproteins, inflammatory cells and micro-calcifications were present in these lesions, similar to atherosclerosis [15]. Clinically, aortic valve sclerosis has been associated with an increase in fatal and non-fatal cardiovascular endpoints such as increased incidence of ventricular arrhythmia, systemic atherosclerosis, myocardial infarction, systolic cardiac failure or stroke [1-3].

Tp-e is a recently defined ECG parameter used for the evaluation of cardiac repolarization. The action potential of myocardial cells is dependent on endocardial, epicardial and mid-myocardial M cells. A change in the repolarization timing of these three cell layers is responsible for T wave changes in the surface electrocardiogram [16, 17]. Recent studies have shown that the duration from the peak to the bottom of the T wave has an effect on the transmural dispersion of repolarization [18]. It has been shown that increased Tp-e duration is associated with malignant ventricular arrhythmia development [8]. Watanabe N et al. have shown through an electrophysiological study that Tp-e lengths of organic heart disease patients with inducible ventricular arrhythmia had prolonged [19]. Furthermore, it has been reported that the duration of Tp-e within normal QT and QTc duration can predict sudden cardiac death [9]. Also, it has not yet been researched if the value of Tp-e and QTc has any additional benefit among the AS population with increased malignant ventricular arrhythmia. That is why this study aims to measure the Tp-e value as a possible predictor for ventricular arrhythmia among AS patients and to compare this parameter's length to QTc within the same population.

Our study has shown that QT and QTc values, used during the basal echocardiographic data and classic repolarization assessment between AS patients and the control group, displayed no differences. But despite this, Tp-e tail, Tp-e tail index, Tp-e tangent and Tp-e tangent index values were significantly higher in the AS group. Ventricular arrhythmia occurrence as documented by electrocardiography (ECG) is approximately 20% in AS patients. Prior electrophysiological studies have shown that the majority of idiopathic ventricular tachycardia (VT) in patients with no structural heart diseases originated in the outflow tract and that the aortic

root was a frequent source for left sided idiopathic VTs [20]. Furthermore, in recent years it has been demonstrated that aortic root and aortic leaflets could act as a source for ventricular tachycardia or extrasystole [21]. Also, potential ethiopathogenesis and predictors have not been clearly identified for these patients with idiopathic VT. Considering our study data, it could be conceived that increased Tp-e in AS patients could indicate a repolarization disorder and that it could play a probable etiological factor for high occurrences of ventricular arrhythmia in these patients.

On the other hand, QTc is a traditional ECG parameter used for predicting ventricular arrhythmia and a lengthened QTc duration is associated with arrhythmia development. But when the QTc length is normal, its value is limited. Panikkath et al. have shown that even with normal QTc lengths, Tp-e is independently correlated with a rise of sudden cardiac death in patients with coronary artery diseases [9]. Milberg et al. have shown that an increase in the Tp-e duration in patients with long QT syndrome was a predictor for ventricular arrhythmia [22]. It has been shown that increased QTc and Tp-e in patients with Brugada syndrome is significantly correlated with the development of life threatening arrhythmia [23]. Our study has determined that AS patients Tp-e values had increased, despite normal QTc values. Therefore, it can be conceived that Tp-e duration could be more suitable for assessing ventricular repolarization disorder and predicting ventricular arrhythmia in this population, when compared to QTc duration.

Study limitations

An important limitation in our study was the small number of patients. This makes it necessary to substantiate our study data with a study that covers a larger patient population. Secondly, difficulties can arise when evaluating the end of the T wave during ECG because of the variability of the T wave. To counter this limitation and to minimize its effect on our results, the ECG derivation best showing the T wave end was chosen for analysis (usually the V2 derivation). In addition, analysis discrepancies among the analyzers exceeding 20 ms or more resulted in the patient data being excluded from the study. Lastly, ventricular arrhythmia presence was not documented using holter ECG because of the design of the study. That is why the clinical use of our study data could be questioned and it should be evaluated for clinical use in a study designed for this purpose.

Conclusion

Our study showed that Tp-e durations increased in AS patients with no structural heart disease. AS causes local degeneration on the aortic root and also has a negative effect on the total cardiac spatial repolarization. Studies that evaluate the correlation between increased Tp-e duration and increased ventricular arrhythmia occurrence in this population are needed.

Disclosure of conflict of interest

None.

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