Increased Ventricular Activation Time in Patients with the Diagnosis of Cardiac Syndrome X

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ABSTRACT

Introduction: Cardiac syndrome X (CSX) is defined as typical angina with detectable ischaemia on non-invasive stress tests without any evidence of coronary artery stenosis during coronary angiography. Impaired coronary microcirculation, inflammation and endothelial dysfunction are accepted aetiological factors for CSX. The ventricular activation time (VAT) has been reported to be prolonged in myocardial ischaemia due to the conduction delay in the Purkinje fibres and the myocytes. In this study, we aimed to investigate the electrocardiographic parameters including VAT in patients with CSX.

Patients and Methods: This study enrolled 120 patients (mean age, 54.7 ± 8.6 years; male, 53) diagnosed with CSX and 130 healthy controls (mean age, 53.3 ± 8.9; male, 66) without ischaemia. All patients underwent electrocardiography and transthoracic echocardiography. VAT was defined as the interval from the beginning of the QRS complex until the peak of the R or R' wave.

Results: There was no significant difference in terms of demographic, laboratory and echocardiographic parameters between CSX patients and controls. Comparison of electrocardiographic parameters yielded that there was no significant difference in terms of the heart rate, P-wave duration, PR interval, QT and corrected QT intervals between the groups. However, the QRS duration (95.1 ± 13.8 vs. 90.4 ± 12.7 msec; p= 0.006) and VAT (34.8 ± 5.7 vs. 29.2 ± 5.6 msec; p< 0.001) were significantly higher in patients with CSX.

Conclusion: The present study demonstrated that QRS duration and VAT were prolonged significantly in patients with CSX. This prolongation may be due to the presence of impaired microvascular perfusion and ischaemia-induced conduction delay.

Key Words: Cardiac syndrome X; electrocardiography; ventricular activation time

Kardiyak Sendrom X Tanılı Hastalarda Artmış Ventriküler Aktivasyon Zamanı

ÖZET

Giriş: Kardiyak sendrom X (KSX) noninvaziv stres testlerinde tespit edilebilen iskemi olmasına rağmen koroner anjiyografide koroner arter stenozu bulgularının olmadığı tipik anjina olarak tanımlanmaktadır. Bozulmuş koroner mikrosirkülasyon, inflamasyon ve endotel disfonksiyonu KSX için kabul edilmiş etyolojik faktörlerdir. Ventriküler aktivasyon zamanının (VAZ) miyokardiyal iskemi durumunda Purkinje liflerinde ve miyositlerdeki iletim yavaşlamasına bağlı olarak uzadığı bildirilmiştir. Bu çalışmada, KSX hastalarında aralarında VAZ'ın da bulunduğu elektrokardiyografik parametrelerin araştırılması amaçlanmıştır.

Hastalar ve Yöntem: Çalışmaya KSX tanısı alan 120 hasta (ortalama yaş: 54.7 ± 8.6 yıl , erkek: 53) ile iskemisi olmayan 130 sağlıklı kontrol (ortalama yaş: 53.3 ± 8.9 yıl , erkek: 66) dahil edildi. Tüm hastalar elektrokardiyografi ve transtorasik ekokardiyografi ile değerlendirildi. VAZ elektrokardiyografide QRS kompleksinin başlangıcından R veya R' dalgasının zirvesine kadar geçen zaman aralığı olarak tanımlandı.

Bulgular: KSX hastaları ile kontrol grubu arasında demografik, laboratuvar ve ekokardiyografik parametreler açısından anlamlı bir fark izlenmedi. Elektrokardiyografik parametreler karşılaştırıldığında gruplar arasında kalp hızı, P dalga süresi, PR aralığı, QT ve düzeltilmiş QT aralığı açısından anlamlı fark yok iken, QRS süresi (95.1 ± 13.8 ve 90.4 ± 12.7 msn, p= 0.006) ve VAZ (34.8 ± 5.7 ve 29.2 ± 5.6 msn, p< 0.001) KSX grubunda anlamlı olarak daha uzun olarak tespit edildi.

Sonuç: Bu çalışmada KSX hastalarında QRS süresi ve VAZ'ın anlamlı olarak uzadığı gösterilmiştir. Bu uzama KSX hastalarındaki bozulmuş mikrovasküler perfüzyon ve iskemiye bağlı iletim yavaşlamasına bağlı gelişmiş olabilir.

Anahtar Kelimeler: Kardiyak sendrom X; elektrokardiyografi; ventriküler aktivasyon zamanı

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INTRODUCTION

Angiographically normal coronary arteries have been detected in a significant proportion (20%-30%) of patients presenting with typical angina pectoris[1]. Despite non-cardiac causes that may be responsible for the chest pain, a considerable number of these patients have true angina due to myocardial ischaemia in the absence of angiographically significant coronary stenosis[2]. The term cardiac syndrome X (CSX) is used to describe patients with typical angina pectoris and a positive stress test (classic downsloping ST-segment depression on treadmill exercise test, and/or a reversible perfusion defect on radionuclear myocardial perfusion scan), in the absence of significant coronary stenosis on angiography and other cardiac diseases[3]. Coronary microvascular dysfunction was suggested to be the underlying pathophysiologic mechanism. Moreover, endothelial dysfunction with subsequent microvascular ischaemia has been implicated as an important contributing factor[4]. While several studies reported that patients with CSX supposed to have an excellent long-term clinical outcome[5], other clinical reports have found that a considerable percentage of those patients might have a higher risk of unfavourable clinical outcomes[6].

The ventricular activation time (VAT) (also known as the R-wave peak time) represents the time for the conduction of the electrical activity from the endocardium to the epicardium in the ventricles[7]. VAT has been reported to be prolonged in the presence of ventricular hypertrophy or dilatation, as well as disorders in the conduction system[8]. VAT is also prolonged in myocardial ischaemia due to the conduction delay in the Purkinje fibres and the myocytes[9]. In a previous study including patients with acute coronary syndrome treated with primary percutaneous coronary intervention, it was reported that the VAT prolongation was associated with impaired coronary reperfusion[10]. However, to the best of our knowledge, no previous study has examined VAT in patients with CSX. We hypothesised that the ischaemia-induced conduction delay in the Purkinje fibres and the ventricular myocytes would be more evident in patients with CSX as compared to controls without ischaemia. Thus, we aimed to investigate the electrocardiographic parameters including VAT in patients with CSX.

PATIENTS and METHODS

Study Population

This single-centre case-control study enrolled 120 patients (mean age, 54.7 ± 8.6 years; male, 53) diagnosed with CSX and 130 healthy controls (mean age, 53.3 ± 8.9; male, 66). Patients with left ventricular systolic dysfunction, arrhythmia, high-degree atrioventricular block, complete bundle branch block, cardiomyopathy, end-stage liver disorders, renal insufficiency, chronic inflammatory diseases, connective tissue diseases and malignancies were excluded from the study. Patients, who had angina pectoris with detectable ischaemia on non-invasive tests such as treadmill stress test or myocardial perfusion scintigraphy, and without any evidence of stenosis or vasospasm of epicardial coronary arteries during invasive coronary angiography, were diagnosed as CSX. Asymptomatic healthy controls without any detectable ischaemia on non-invasive tests constituted the control group. All patients underwent transthoracic echocardiography (TTE). Complete blood count and blood chemistry panel were carried out in all patients at the time of admission. All demographic, laboratory, electrocardiographic and echocardiographic parameters were recorded into a dataset and compared between the CSX patients and controls. All patients provided a written informed consent, and the study protocol was approved by the local ethics committee of the hospital in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Echocardiography

All patients underwent TTE performed by the same cardiologist using the Vivid 5 echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway) and a 3.2 mHz adult probe, with the patient in the left lateral decubitus position. In all patients, the left atrial diameter (LAD), interventricular septal thickness (IVST), posterior-wall thickness (PWT) and left ventricular end-systolic (LVESD) and end-diastolic diameters (LVEDD) were measured on the parasternal long-axis view. The early diastolic peak flow velocity (E wave) and late diastolic peak flow velocity (A wave) were measured using a colour-guided pulsed Doppler echocardiographic examination. Left ventricular ejection fractions (LVEF) of the patients were calculated using biplane Simpson's method. Left ventricular mass (LVM) was calculated based on the Devereux formula [$LVM = 0.8\ (1.04\ (IVST + LVEDD + PWT)^3 - (LVEDD)^3) + 0.6$], and the body surface area was estimated using the Mosteller formula [body surface area = (height (cm) × body weight (kg)/3600)$^{1/2}$]. Left ventricular mass was divided by the body surface area to estimate the left ventricular mass index (LVMI).

Laboratory Analysis

To perform complete blood count and blood chemistry panel, venous blood samples were collected after 12 hours of fasting by a clean puncture of an antecubital vein from all patients. Complete blood counts were measured on the Sysmex XT2000i analyser (Sysmex corporation, Kobe, Japan). Fasting blood glucose, urea, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, total cholesterol (TC), high-density lipoprotein (HDL) and triglyceride (TG) levels were also measured on an autoanalyser (Siemens

Advia 2400 Chemistry System, Siemens Diagnostic, Tarrytown, USA). Low-density lipoprotein (LDL) was calculated using the Friedewald formula [LDL(mg/dL) = TC - (HDL + TG/5)][11].

Electrocardiographic Analysis

A 12-lead high-resolution electrocardiography (ECG), which was recorded at a speed of 25 mm/s and a voltage of 10 mm/mV, was obtained from all patients after a 10-minute rest (Nihon Kohden Cardiofax ECG-9132). Patients were allowed to breathe freely, but not to speak or cough during recordings. All ECG papers were scanned, loaded to a computer, magnified sufficiently and analysed with a digital image-processing software (imagej. nih.gov/ij/). Measurements were calibrated on the underlying standard ECG graph paper. All measurements were calculated by 2 independent cardiologists blinded to other patients' clinical information. The onset and the end of the P-waves were marked with the cursor on a high-resolution computer screen to calculate P-wave duration in all leads. The beginning of the P wave was defined as the point where the initial deflection of the P wave crossed the isoelectric line, and the end of the P wave was defined as the point where the final deflection of the P wave crossed the isoelectric line. The QRS duration was defined as the interval from the start of the QRS complex until J point; and VAT was defined as the interval from the start of the QRS complex until the peak of the R or R' wave. The QT interval was defined as the interval from the onset of the QRS complex to the end of the T wave. The R-R interval was measured and used to compute the heart rate and to correct the QT interval (QTc) with the Bazett's formula (QTc = QT/√R-R interval in seconds). All durations were calculated in milliseconds, and the mean values were calculated from 12 leads.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp. Armonk, NY). Descriptive statistics were reported as the mean ± standard deviation for continuous variables with normal distribution or median (25^{th}-75^{th} percentiles) values for continuous variables without normal distribution and as frequency with percentages for the categorical variables. The Shapiro-Wilk and Kolmogorov-Smirnov test were used to test the normality of the distribution of continuous variables. Categorical variables were compared using the chi-squared or Fisher exact tests. Student's t-test or the Mann-Whitney U test was used to compare continuous variables as appropriate. The significance level was accepted as $p< 0.05$ in all statistical analyses. A logistic regression analysis was performed to identify any independent associates of CSX. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the sensitivity, specificity, area under the curve (AUC) and confidence interval (CI) of VAT for predicting CSX.

RESULTS

A total of 120 patients (mean age, 54.7 ± 8.6 years; male, 53) with the diagnosis of CSX and 130 healthy controls (mean age, 53.3 ± 8.9; male, 66) were enrolled in this single-centre case-control study. Demographic, laboratory and echocardiographic characteristics of the study population are presented in Table 1. Age and gender distribution were similar between patients and controls. There was no significant difference in terms of systolic and diastolic blood pressure measurements and body mass index values between the groups. The prevalences of hypertension, diabetes mellitus, dyslipidemia and smoking status were similar between the groups. Routine serum biomarkers such as fasting blood glucose, blood urea nitrogen, creatinine, uric acid, total bilirubin, ALT, AST, TC, HDL, LDL, TG and complete blood count paramemeters were similar between the patients and the controls (Table 1).

The echocardiographic parameters including LAD (33.1 ± 4.7 vs. 32.5 ± 3.9 mm, p= 0.356), LVEF (63.4 ± 6.7 vs. 64.5 ± 4.3%, p= 0.542), LVESD (28.2 ± 3.1 vs. 27.8 ± 4.6 mm, p= 0.625), LVEDD (43.7 ± 3.1 vs. 42.5 ± 4.2 mm, p= 0.337), IVST (10.1 ± 1.2 vs. 9.7 ± 0.9 mm, p= 0.143), PWT (9.9 ± 0.8 vs. 9.4 ± 1.1 mm, p= 0.176), left atrial E [0.6(0.5-0.8) vs. 0.7 (0.5-0.9) cm/s, p= 0.394] and A waves [1.0(0.8-1.1) vs. 0.95 (0.7-1.1) cm/s, p= 0.367], LVM (171.8 ± 24.7 vs. 166.9 ± 32.6 g, p= 0.283) and LVMI (91.3 ± 18.7 vs. 88.7 ± 21.3 g/m^2, p= 0.397) were found to be similar between the groups (Table 2).

A comparison of electrocardiographic parameters yielded that there was no significant difference in terms of the heart rate (75.7 ± 13.4 vs. 76.1 ± 10.3 bpm, p= 0.447), P-wave duration (103.8 ± 11.7 vs. 100.4 ± 13.9 msec, p= 0.628), PR interval (175.2 ± 48.5 vs. 172.6 ± 42.2 msec, p= 0.761), QT interval (370.1 ± 41.6 vs. 372.8 ± 35.7 msec, p= 0.718), and calculated QTc (417.6 ± 42.5 vs. 420.5 ± 38.1 msec, p= 0.576) between the groups (Table 2). However, the QRS duration (95.1 ± 13.8 vs. 90.4 ± 12.7 msec, p= 0.006) and VAT (34.8 ± 5.7 vs. 29.2 ± 5.6 msec, p< 0.001) were significantly higher in patients with CSX as compared to controls (Figures 1A and B, respectively).

The univariate associates of CSX were taken into multiple logistic regression analysis. An increased VAT was identified as an independent predictor of myocardial ischaemia (odds ratio, 1.223; 95% CI, 1.147-1.303; p< 0.001) (Table 3). In the ROC curve analysis, a VAT > 30.3 msec predicted myocardial ischaemia with a sentivity of 78% and a specificity of 71% (AUC, 0.798; 95% CI, 0.743-0.852; p< 0.001) (Figure 2).

Table 1. Comparison of demographic and laboratory parameters between patient and control groups

Variables	Cardiac syndrome X (n= 120)	Control group (n= 130)	p
Demographic parameters			
Age, years	54.7 ± 8.6	53.3 ± 8.9	0.219
Gender-male, n (%)	53 (44.2)	66 (50.8)	0.296
BMI (kg/m^2)	29.8 (25.3-31.7)	28.4 (26.2-32.1)	0.413
SBP (mmHg)	134.7 ± 13.2	132.5 ± 11.7	0.754
DBP (mmHg)	81.5 ± 7.8	79.7 ± 9.3	0.576
Hypertension, n (%)	34 (29.3)	28 (21.5)	0.214
Diabetes mellitus, n (%)	17 (14.2)	13 (10)	0.311
Dyslipidemia, n (%)	19 (15.8)	25 (19.2)	0.481
Smoking status, n (%)	25 (20.8)	20 (15.4)	0.263
Laboratory parameters			
White blood cell (x10^3/dL)	7.69 ± 1.57	8.19 ± 1.89	0.277
Haemoglobin (g/dL)	13.7 ± 1.4	14.1 ± 1.8	0.587
Platelet (x10^3/dL)	237.3 ± 45.6	243.1 ± 51.8	0.669
Glucose (mg/dL)	94.7 ± 10.7	95.3 ± 9.8	0.762
BUN (g/dL)	28.5 ± 9.1	32.2 ± 10.7	0.285
Creatinine (g/dL)	0.84 ± 0.17	0.79 ± 0.21	0.278
AST (U/L)	21 (17.8-26.3)	20.5 (18.7-23.9)	0.418
ALT (U/L)	18 (13.9-21.5)	17 (14.3-20.6)	0.846
Uric acid (mg/dL)	4.8 ± 0.9	4.7 ± 0.9	0.869
Total bilirubin (mg/dL)	0.6 (0.4-0.9)	0.7 (0.5-0.9)	0.679
LDL (mg/dL)	121.5 ± 23.7	128.6 ± 27.5	0.294
HDL (mg/dL)	42 (35-47)	44 (34-50)	0.253
Triglycerides (mg/dL)	157.9 ± 81.2	165.7 ± 74.6	0.742
Total cholesterol (mg/dL)	192.5 ± 27.3	199.3 ± 34.8	0.378

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, BUN: Blood urea nitrogen, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SBP: Systolic blood pressure.

DISCUSSION

In this observational case-control study, we have focussed on the effects of ischaemia-induced conduction delay on the electrocardiographic parameters in patients with CSX. The QRS duration and VAT were observed to be significantly higher in CSX patients as compared to healthy controls.

Epicardial coronary artery stenosis is usually responsible for myocardial ischaemia. However, with the technical advancements in the past 30 years, studies have shown that abnormalities in coronary microcirculation may also cause myocardial ischaemia in patients with normal coronary arteries[12]. In 1973, Kemp first described these patients as having CSX, defined as typical angina pectoris with abnormal stress test results indicative of myocardial ischaemia and normal coronary arteries on coronary angiography[13]. Since the original description of syndrome X over 30 years ago, a large number of studies have focussed on establishing an ischaemic origin for this condition. The pathophysiology of CSX is multifactorial and endothelial dysfunction with subsequent microvascular ischaemia has been implicated as an important contributing factor[4].

ECG is a simple, non-invasive and readily available tool in daily routine practice. A variety of ECG markers including ST-segment and T-wave abnormalities have been utilised to assess myocardial ischaemia. In addition, the QRS duration has been considered an important prognostic marker, and the

Table 2. Comparison of echocardiographic and electrocardiographic parameters between patient and control groups

Variables	Cardiac syndrome X (n= 120)	Control group (n= 130)	p
Echocardiographic parameters			
LV EF (%)	63.4 ± 6.7	64.5 ± 4.3	0.542
LAD (mm)	33.1 ± 4.7	32.5 ± 3.9	0.356
LVEDD (mm)	43.7 ± 3.1	42.5 ± 4.2	0.337
LVESD (mm)	28.2 ± 3.1	27.8 ± 4.6	0.625
IVST (mm)	10.1 ± 1.2	9.7 ± 0.9	0.143
PWT (mm)	9.9 ± 0.8	9.4 ± 1.1	0.176
E (cm/s)	0.6(0.5-0.8)	0.7 (0.5-0.9)	0.394
A (cm/s)	1.0(0.8-1.1)	0.95 (0.7-1.1)	0.367
LVM (g)	171.8 ± 24.7	166.9 ± 32.6	0.283
LVMI (g/m^2)	91.3 ± 18.7	88.7 ± 21.3	0.397
Electrocardiographic parameters			
Heart rate (beats/min)	75.7 ± 13.4	76.1 ± 10.3	0.447
P-wave duration (msec)	103.8 ± 11.7	100.4 ± 13.9	0.628
PR interval (msec)	175.2 ± 48.5	172.6 ± 42.2	0.761
QRS duration (msec)	95.1 ± 13.8	90.4 ± 12.7	0.006
QT interval (msec)	370.1 ± 41.6	372.8 ± 35.7	0.718
Corrected QT interval (msec)	417.6 ± 42.5	420.5 ± 38.1	0.576
R-wave peak time (msec)	34.8 ± 5.7	29.2 ± 5.6	< 0.001

A: Atrial A wave; E: Atrial E wave; IVST: Interventricular septal thickness, LAD: Left atrial diameter, LVEF: Left ventricular ejection fraction, LVESD: Left ventricular end-systolic diameter, LVEDD: Left ventricular end-diastolic diameter, LVM: Left ventricular mass, LVMI: Left ventricular mass index, PWT: Posterior-wall thickness.

significance of QRS duration is well known in patients with heart failure or myocardial infarction[14,15]. In recent studies, a prolongation of the QRS duration has also shown correlations with an interventricular conduction delay because of myocardial ischaemia[16,17]. The QRS duration is also increased in patients with left ventricular hypertrophy. The increased QRS duration may be attributed to the increased thickness of the left ventricular wall and to myocardial fibrosis, which distort and prolong the transmural conduction of electrical activity. The R-wave peak time, also known as VAT, was described as the duration from onset of the QRS complex to the peak of the R wave. Not only the QRS duration but also VAT has been reported to be prolonged in left ventricular hypertrophy, volume overload, conduction abnormalities and coronary artery disease causing ischaemia. In a previous study, Rencüzoğulları et al. demonstrated that the presence of a prolonged QRS duration and R-wave peak time were associated with the severity of coronary artery disease in patients with acute coronary syndrome. Furthermore, they described the R-wave peak time as a predictor of a high SYNTAX score in these patients[18]. In a different study, they also reported a significant correlation between the no-reflow phenomenon and R-wave peak time in patients with the ST-elevation myocardial infarction treated with primary percutaneous coronary intervention[10]. In the present study, there was no significant difference in terms of echocardiographic parameters related to left ventricular hypertrophy between the patients with CSX and controls. Thus, the prolongation in the QRS duration and VAT may be attributed to the presence of impaired microvascular perfusion and ischaemia-induced conduction delay in patients with CSX. In the present study, VAT was superior to QRS duration to predict myocardial ischaemia. Consistently, in previous studies, it was reported that VAT was more valuable than the QRS duration in the prediciton of coronary ischaemia and reperfusion in patients with acute coronary syndrome[10,19].

STUDY LIMITATIONS

The primary limitation was that our study was a nonrandomised and single-centre study with a relatively small number of patients. Secondly, coronary angiography was not

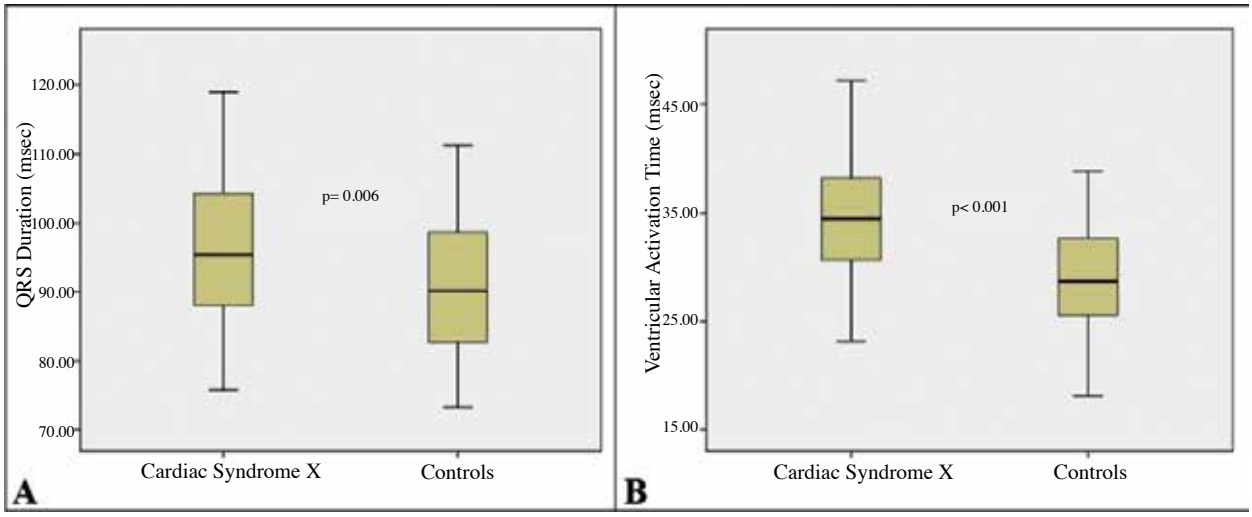

Figure 1. Box-plot graph comparing the QRS duration (A) and ventricular activation time (B) values between patients with cardiac syndrome X and the controls (B).

Table 3. Results for multivariate logistic regression analysis of univariate associates of myocardial ischaemia

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
QRS duration	1.029	1.007-1.052	0.009	1.020	0.991-1.050	0.171
Ventricular activation time	1.230	1.155-1.310	< 0.001	1.223	1.147-1.303	< 0.001

CI: Confidence interval, OR: Odds ratio.

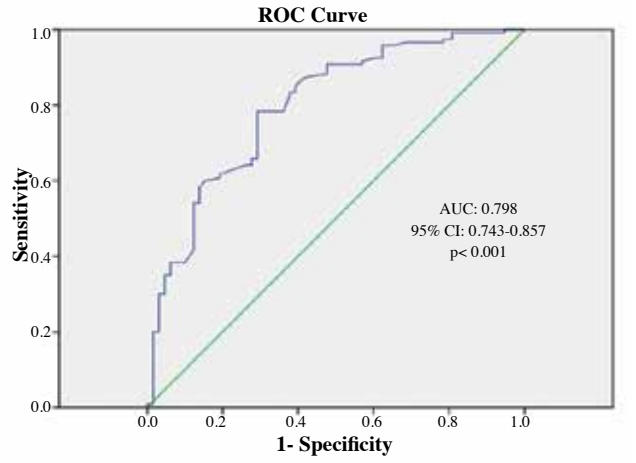

Figure 2. Receiver operating characteristic curve revealing the area under the curve for ventricular activation time to predict myocardial ischaemia (AUC, area under curve; CI, confidince interval).

performed in the control group, so this issue is also open to criticism. A control group without symptoms and with a negative stress and angiographically normal coronary arteries would have been ideal. However, it would be impossible to get approval from the ethics committee to perform coronary angiography in a patient group without symptoms and with a negative stress test in our country.

CONCLUSION

The present study demonstrated that the QRS duration and VAT prolonged significantly in patients with CSX. This prolongation may be due to the presence of impaired microvascular perfusion and ischaemia-induced conduction delay in patients with CSX. Electrocardiography may be an additional and easy diagnostic tool for risk stratification of patients with CSX. Those with an increased VAT may be particularly at risk for impaired coronary blood flow reserve, which is an early manifestation of atherosclerosis.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: MK, MY, OÇ
Analysis/Interpretation: AG, MY, YK
Data Acquisition: EB, AG, OÇ
Writting: MK, MY
Critical Revision: EB, MY
Final Approval: All of authors

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