Fragmented QRS frequency in patients with cardiac syndrome X

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Abstract

Objective: Cardiac syndrome X (CSX) is characterised by typical exertional chest pain, a positive response to exercise testing, and a normal coronary angiography. The relationship of CSX with myocardial fibrosis and ischemia has been clearly demonstrated in previous studies. In addition, fragmented QRS (fQRS) has been reported in the literature as an indicator of myocardial fibrosis. The aim of this study was to investigate the frequency of fQRS in patients with CSX.

Methods: This prospective case-control study included 37 patients (CSX group) with typical complaints of angina, ischemia on an exercise test, and normal coronary arteries as detected by angiography and 47 patients (control group) with normal coronary arteries. Echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography. Continuous variables were expressed as mean±standard deviation (SD), and the qualitative variables were expressed as a percentage or ratio. Data were compared statistically with Shapiro–Wilk test, Student's t-test, Mann-Whitney U, chi-square and Fisher exact test.

Results: There was no significant difference between the CRX and control groups with respect to basic characteristics such as age and sex. fQRS and the frequency of its presentation with stable angina pectoris at the clinic were significantly higher in the CSX group than in the control group (p values: 0.001 and <0.001, respectively).

Conclusion: A close follow-up would be useful in CSX patients in whom fQRS is detected in an electrocardiogram (ECG) because of the association between fQRS and poor prognosis with respect to the prevention of late complications. We believe that the presence of fQRS in the ECG aids in the diagnosis of CSX in clinical practice and in the recognition of this group of patients. *(Anatol J Cardiol 2016; 16: 616-20)*

Keywords: cardiac syndrome X, fragmented QRS, myocardial fibrosis

Introduction

Cardiac syndrome X (CSX) is defined angiographically as anginal symptoms associated with decreased heart tissue blood flow and no signs of coronary artery disease (1). CSX is thought to be due to many conditions, including microvascular angina and myocardial ischemia. Endothelial dysfunction, abnormal pain threshold, estrogen deficiency, inflammation, and abnormal autonomic control are the most involved mechanisms in the pathophysiology of the disease (1–4).

Fragmented QRS (fQRS) is thought to represent depolarization of the ventricles, which can be determined by an electrocardiogram (ECG) with 12 superficial channels, and it is caused by the slowdown of electrical conduction because of myocardial fibrosis. The slowdown of electrical conduction causes non-homogen ventricular activation, which can be observed in an ECG as notching on the QRS complex (5–7). It has been reported that the presence of fQRS in an ECG is associated with sclerotic systemic diseases, myocardial perfusion abnormalities, and myocardial scars (8–9).

Based on these data, we hypothesised that the ECG results of patients with CSX will show increased fQRS frequency compared with those of the normal population.

Methods

Study design

Patients who underwent coronary angiography in our center between January 2012 and December 2013 were evaluated in this prospective case-control study. This study included 37 patients (19 males, 18 females; mean age 51±7 years) with typical complaints of angina, ischemia on an exercise test and normal coronary arteries as detected by angiography (the CSX group) and 47 patients (24 males, 23 females; mean age 51±8 years) who met the following criteria: 1) their complaints were in line with a

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high probability of coronary artery disease (heavy chest pain or squeezing; a "burning feeling;" or difficulty in breathing, associated with radiation to the left shoulder, neck, or arm, builds in intensity over a period of a few minutes, and begins with exercise or psychological stress.), 2) their exercise tests were evaluated non-diagnostically, and 3) their coronary arteries were found to be normal as detected on coronary angiography. Echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography (10).

Approval for this study was obtained from the institution's Ethics Committee, and all the enrolled patients gave their informed consent. Patients with moderate-to-severe valvular heart disease; a prosthetic heart valve; a bundle branch block; atrial fibrillation; paced rhythm; an atrioventricular block; restrictive, hypertrophic, or dilate cardiomyopathies; congenital heart disease; coronary artery ectasia; a previous history of myocardial infarction; uncontrolled hypertension; hyperthyroidism; hypothyroidism; malignancy; and pulmonary, hepatic, renal, and hematological disorders were excluded from the study.

Diagnosis criteria for CSX

CSX is diagnosed based on the presence of the following conditions: persistent anginal symptoms, normal coronary angiography, and positive exercise test (11).

ECG criteria for fragmented QRS

The resting baseline 12-lead ECG (filter range, 0.05–150 Hz; AC filter, 60 Hz, 25 mm/s, 10 mm/mv) was analysed by two independent cardiologists blinded to the study. The fQRS was defined as the presence of an additional R wave (R'), notching of the R or S wave, or the presence of fragmentation (more than one R') in two contiguous leads corresponding to a major coronary artery (Fig. 1). There was 99% concordance for the ECG signs of fQRS.

Exercise test

All patients in both groups underwent an exercise test according to the Bruce test protocol using a Mortara treadmill (MI-REF 9501-001-50 REV G1, Mortara Instruments). Routine 12-lead electrocardiography of all patients was taken before they underwent the exercise test. The heart rate (HR), blood pressure, and ECG were recorded at the end of each derivation. The target HR was calculated using the 220-age (year) formula satisfying the maximum HR in beats/min. The test was considered positive for the following criteria: (i) observation of 1 mm or more down sloping or horizontal collapse or elevation on the ST segment 80 ms after the J junction in two or more consecutive derivations during the process; (ii) 10 mm Hg or more decrease in systolic blood pressure compared with the initial blood pressure, and (iii) bradycardia development during the process.

Coronary angiography

All patients underwent selective right and left coronary angiography through the right femoral artery using the standard Judkins technique with a MEGALIX Cat plus 125/40/90-121 GW model angiography device (Siemens Artis Zee, Forchheim, Germany). Iohexol 350/100 was used as a contrast agent, and approximately 6–8 ml of the contrast medium was injected manually for each exposure. The coronary arteries were imaged in the right and left oblique position using cranial and caudal angulations. The images were recorded digitally at 15 frames per second (Fig. 2; Panel A and Panel B).

Statistical evaluation

Continuous variables were expressed as mean±standard deviation (SD), and the qualitative variables were expressed as a percentage or ratio. Compliance of the variables with normal distribution was assessed using the Shapiro–Wilk test. Continuous variables were compared between groups using either the Student's t-test or the Mann–Whitney U test, depending on the variable's compliance with the normal distribution. For the qualitative variables, the chi-square test was used. Fisher's exact chi-square test was used in cases in which the expected values in the cross tables were less than 5. The Statistical Package for the Social Sciences software (Version15: SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. A p value of less than 0.05 was considered statistically significant.

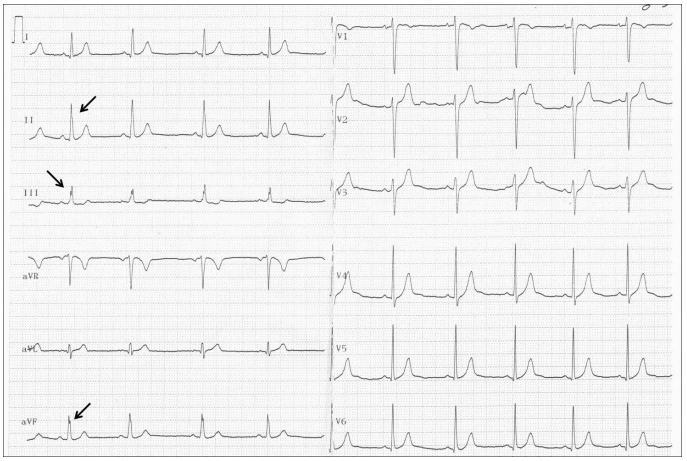

Figure 1. Twelve-Lead ECG of a patient with cardiac syndrome X. There are fQRS complexes in Lead II-III-aVF (arrow)

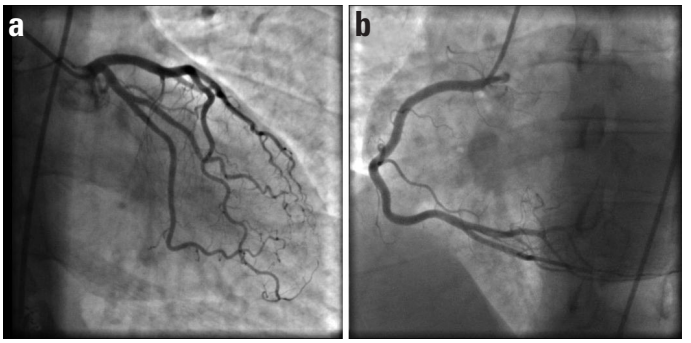

Figure 2. Coronary angiographic images of patients with cardiac syndrome X. Panel (a) left coronary angiography. Panel (b) right coronary angiography

Table 1. Basic characteristics of the study groups

	Control (n=47)	CSX (n=37)	*P*
Age, years	50±8	51±7	0.46
Sex, male/female	24/23	19/18	0.97
Body mass index, kg/m^2	30±4	30±5	0.53
Clinic presentation			
SAP, n (%)	11 (23.4)	33 (89.2)	<0.001
USAP, n (%)	7 (14.9)	1 (2.7)	0.06
Creatinine, mg/dL	0.8±0.2	0.8±0.2	0.85
Total cholesterol, mg/dL	205±41	204±27	0.90
LDL, mg/dL	138±38	140±29	0.80

Continuous variables are expressed as mean±standard deviation (SD), qualitative variables are expressed as percentage. CSX - cardiac syndrome X; LDL - low-density lipoprotein; SAP - stable angina pectoris; USAP - unstable angina pectoris

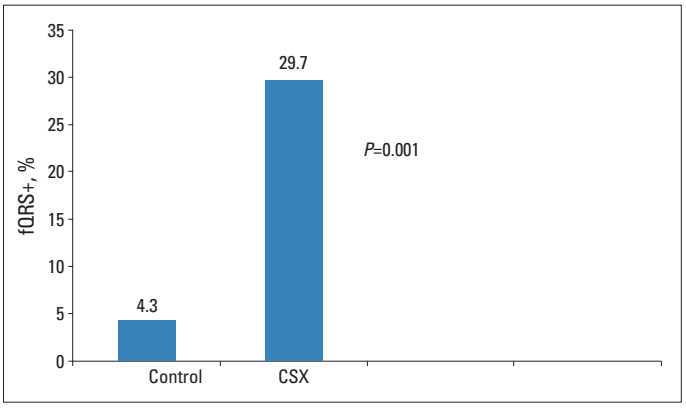

Figure 3. Fragmented QRS frequency between the study groups

Table 2. Echocardiographic and ECG findings of the study groups

	Control (n=47)	CSX (n=37)	*P*
LVEDD, cm	4.7±0.3	4.7±0.3	0.51
LVESD, cm	3.0±0.4	3.0±0.4	0.53
Left atrium, cm	3.3±0.4	3.3±0.5	0.71
EF (%)	61±5	61±5	0.86
Heart rate, /min	71±11	69±8	0.25
fQRS, n (%)	2 (4.3)	11 (29.7)	0.001

Continuous variables are expressed as mean±standard deviation (SD); qualitative variables are expressed as percentage. CSX - cardiac syndrome X; EF - ejection fraction; fQRS - fragmented QRS; LVEDD - left ventricular end-diastolic diameter; LVESD - left ventricular end-systolic diameter

Results

General characteristics of the study groups

There was no statistically significant difference between the CSX and control groups with respect to age, gender, uric acid, creatinine, total cholesterol, and low-density lipoprotein cholesterol values. Patients in both groups were obese, but there was no statistically significant difference between the CSX and control groups with respect to body mass index. The number of patients presenting with stable angina pectoris at the clinic was significantly higher in the CSX group (p<0.001). There was no significant difference between the two groups with respect to other presentations at the clinic, such as shortness of breath, unstable angina, and palpitations. The basic characteristics of both study groups are presented in Table 1.

Echocardiographic and ECG findings of the study groups

There was no significant difference between the study groups with respect to left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left atrial diameter, ejection fraction, and HR. fQRS was detected in the ECG in 2 (4%) of 47 patients in the control group compared with 11 (30%) of 37 patients in the CSX group. All of the patients in the control group, all were detected in the inferior leads. In the CSX group, one was detected in anterior leads and ten were detected in inferior leads. The fQRS frequency in the ECGs of the patients in the CSX group was significantly higher than in the control group (p=0.001) (Fig. 3). The echocardiographic and ECG findings of both study groups are presented in Table 2.

Discussion

In our study, the ECG-determined fQRS frequency was significantly higher in the CSX group than in the control group. This finding supports the presence of a myocardial perfusion defect in CSX pathophysiology. Many studies have reported that the presence of fQRS in ECGs is associated with sclerotic systemic diseases, myocardial perfusion abnormalities, and myocardial scarring (8–9,12–15). In a study conducted by Kaski et al. (16), temporary myocardial perfusion abnormalities were detected in 25% of patients with CSX. In studies on perfusion and left ventricular function using radionuclide agents, findings supporting myocardial ischemia have been obtained in 20%–30% of patients with CSX (16, 17). Moreover, it has been reported that changes detected in the ECG during chest pain in these patients support these findings (17–20). Bugiardini et al. (21) reported that in patients with microvascular dysfunction, the risk of major cardiovascular events was shown to be 2.5%. All these studies clearly demostrated the presence of myocardial ischemia in CSX patients and the relationship with mortality of this ischemia. Das et al. (11) reported that fQRS is significantly superior to Q-wave in detecting perfusion defects in two different studies investigating the specificity and sensitivity of fQRS in detecting myocardial perfusion defects (12, 22). Furthermore, studies conducted using magnetic resonance imaging determined that the presence of myocardial scarring is associated with fQRS in ECGs (11–14, 20, 22) and an adverse cardiac outcome (5, 13, 23, 24). Considering all these studies, we hypothesise that the presence of a myocardial scar and a myocardial perfusion defect increases the likelihood of fQRS in patients with CSX.

Studies have presented different data on the prevalence of CSX based on sex. Although 79% of patients with CSX were females in the study conducted by Kaski et al. (16), the percentage of female patients was lower in the studies conducted by Pasternak (24) and Kemp (18). There was no significant difference with respect to sex in our study. This situation may result from differences in the study design and contains a different number of post-menopausal female patients.

Kaski et al. (16) reported that chest pain in patients with CSX have similar pain in patients with obstructive coronary artery disease. Studies show that transient myocardial ischemia may indeed be the cause of chest pain in CSX (24). In our study, the percentage of patients presenting with stable angina pectoris at the clinic in the CSX group was significantly higher than that in in the control group.

Study limitations

This study has several limitations. First, relatively few patients were included in this study. In the future, the number of participating centres should be increased, and the results should be confirmed by more comprehensive studies. Second, the presence of myocardial scarring could be confirmed by magnetic resonance imaging.

Conclusion

Based on our study's findings, we conclude that a close follow-up would be useful in patients diagnosed with CSX in which fQRS is detected in ECGs because the presence of fQRS in electrocardiography has been found to be associated with poor prognosis with respect to the prevention of late CSX complications. We believe that the presence of fQRS in the ECG provides significant support for the diagnosis of CSX in clinical practice and in the recognition of this group of patients. We think that earlier detection, via the identification of fQRS in ECGs, may help address those issues, prevent late complications, and improve the quality of life for these patients.

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