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Assessment of the relationship between a narrow fragmented QRS complex and coronary slow flow

Huseyin Altug Cakmak[1], Serkan Aslan[2], Mehmet Gul[2], Ali Kemal Kalkan[2], Derya Ozturk[2], Omer Celik[2], Omer Tasbulak[2], Muhammet Hulusi Satilmisoglu[2]

[1]Department of Cardiology, Rize Kackar Government Hospital, Rize, Turkey
[2]Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Education and Training Hospital, Istanbul, Turkey

Abstract

Background: *The coronary slow flow (CSF) phenomenon is a delayed antegrade progression of contrast agent to the distal branch of a coronary artery in the absence of obstructive coronary artery disease (CAD). A narrow fragmented QRS (fQRS) has been reported as a significant predictor of sudden cardiac death in patients with idiopathic dilated cardiomyopathy. The present study aimed to investigate the relationship between a narrow fQRS on the admission electrocardiogram (ECG) and CSF on coronary angiography.*

Methods: *This study included 165 consecutive patients (112 CSF, 53 controls) who underwent first-time diagnostic conventional coronary angiography for suspected CAD. Coronary flow was quantified by thrombolysis in myocardial infarction (TIMI) frame count (TFC). The patients were divided into two groups according to the presence or absence of a narrow fQRS complex on the admission ECG.*

Results: *Forty four patients were in the fQRS group (mean age, 52.97 ± 3.13 years). There was no difference between the two groups with respect to age, gender, body mass index, family history, hyperlipidemia, hypertension, or diabetes mellitus. The extent of CSF was significantly greater in the fQRS group compared to the non-fragmented group ($p < 0.001$). A significant correlation was also found between mean TFC values and fQRS ($p < 0.001$). On multivariate analysis, only CSF ($p = 0.03$) was a significant independent predictor for narrow fQRS, after adjustment for other parameters.*

Conclusions: *The narrow fQRS is a simple, inexpensive, and readily available noninvasive ECG parameter that may be a new potential indicator of myocardial damage in patients with CSF.* (Cardiol J 2015; 22, 4: 428–436)

Key words: coronary slow flow, narrow fragmented QRS, thrombolysis in myocardial infarction frame count, electrocardiography

Introduction

The coronary slow flow (CSF) phenomenon is an angiographic finding characterized by a delayed antegrade progression of contrast agent to the distal branch of a coronary artery in the absence of obstructive epicardial coronary artery disease (CAD), coronary ectasia, coronary vasospasm, or acute coronary syndrome [1]. It is not a rare angiographic finding, having a reported incidence of

Address for correspondence: Huseyin Altug Cakmak, MD, Department of Cardiology, Rize Kackar Government Hospital, Rize, Turkey, tel: +90 5333286329, e-mail: altugcakmak@hotmail.com

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1–7% in patients undergoing coronary angiography for suspected CAD [2]. Although neither the exact etiologies nor the pathophysiological mechanisms are yet fully understood, several potential mechanisms have been proposed, including microvascular and endothelial dysfunction, small-vessel disease, diffuse atherosclerosis, increased platelet aggregability, and inflammation [3–7]. CSF has been linked to various clinical manifestations, such as hypertension, stable and unstable angina pectoris, acute myocardial infarction, life-threatening arrhythmias, and sudden cardiac death [8].

Fragmented QRS (fQRS), which has attracted great interest as a new, easy to assess, and reliable electrocardiographic (ECG) finding in clinical practice, has been defined as the presence of notched R or S waves without accompanying typical bundle branch block, or the existence of an additional wave resembling an RSR' pattern in the original QRS complex (with a duration of < 120 ms) [9]. It reflects impaired ventricular depolarization due to heterogeneous electrical activation of ischemic and/or infarcted ventricular myocardium. A narrow fQRS, caused by non-specific electrical deviation and/or deformation of QRS morphology, has recently been associated with a high risk of sudden cardiac death in patients with idiopathic dilated cardiomyopathy [10]. Furthermore, a wide or narrow fQRS on the admission ECG strongly predicts event-free survival rates in patients with dilated cardiomyopathy and a left ventricular ejection fraction (LVEF) < 40% [11].

Since there is no information in the literature concerning the relationship between the presence of a narrow fQRS on the admission ECG and the occurrence and extent of CSF on coronary angiography, we aimed to investigate this association in the present study.

Methods

Patient selection and study protocol

This is a cross-sectional observational study. Coronary angiography was performed on 5,856 consecutive patients between July 2010 and October 2014, and 165 (2.8%) patients who had angiographically proven normal coronary arteries and slow coronary flow were included in the study. During this period, of 482 (8.2%) patients who had normal coronary arteries and normal coronary flow, 53 were randomly enrolled as the control group by 3 different experienced cardiologists without knowledge of the patients' demographic, clinical and laboratory data. All patients had angiographically normal coronary arteries, with varying coronary flow rates and without any atherosclerotic lesion. Study participants were divided into two groups according to their coronary flow rates: 112 patients with isolated CSF and 53 control subjects with normal coronary flow.

All study patients had typical chest pain or angina-equivalent symptoms with positive results from either a treadmill test or a myocardial perfusion study. Demographic, clinical, and laboratory characteristics of the study groups, which were taken from each patient's history and physical examination, were recorded by systematic review of the patient files. In addition, the angiographic characteristics of the patient groups were obtained from the database of the cardiac catheterization laboratory.

The exclusion criteria for the present study were as follows: acute coronary syndrome, coronary vasospasm, coronary ectasia or anomaly, systolic (LVEF < 50%) and/or diastolic heart failure, moderate to severe heart valve disease, QRSd > 120 ms on the 12-lead admission ECG, acute or chronic renal disease (creatinine-based estimated glomerular filtration rate [GFR] calculated by the Cockcroft–Gault formula < 90 mL/min/1.73 m^2, serum creatinine > 1.4 mg/dL), obstructive CAD, and non-coronary atherosclerosis, including stroke, peripheral arterial disease, carotid artery disease, hematological disorders, chronic obstructive lung disease, impaired liver function (aspartate aminotransferase/alanine aminotransferase elevation to > 3 times the upper limit of normal), evidence of ongoing infection or inflammation, endocrine disorders such as metabolic syndrome, medications that affect coagulation pathways, known malignancy, autoimmune diseases, major trauma or surgery in previous 3 months, thyroid dysfunctions such as hypothyroidism and hyperthyroidism, inadequate electrocardiographic or echocardiographic images, and presence of bundle branch block, Wolff–Parkinson–White syndrome, Brugada syndrome, or paced rhythm. Any of the study participants who were taking vasoactive drugs underwent a 3-day "washout" before the coronary angiography procedure.

All study participants underwent a transthoracic echocardiographic examination using a Vivid S6 device with a 3.5 MHz phased array transducer (GE Medical Systems, Horten, Norway) to evaluate left ventricular morphology and function. Recordings were performed with the patients in the left lateral decubitus position. The LVEF was measured using the modified Simpson's rule, according to the most recent guidelines [12].

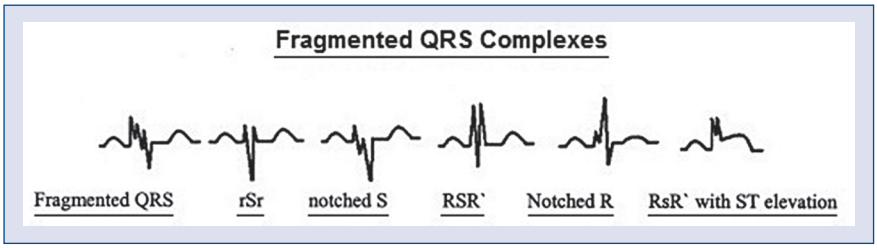

Figure 1. Different examples of an fragmented QRS complex and 12-lead electrocardiogram [9].

Written informed consent was obtained from all the participants and the study was approved by the local Ethics Committee and institutional Review Board. The study protocol complied with the Declaration of Helsinki.

Definitions

Smoking was defined as the current regular use of cigarettes. Hypertension was diagnosed if systolic arterial pressure exceeded 140 mm Hg and/or diastolic arterial pressure exceeded 90 mm Hg, or if the patient was taking antihypertensive drugs [13]. Hyperlipidemia was defined as fasting total serum cholesterol > 200 mg/dL, low-density lipoprotein cholesterol (LDL-C) > 130 mg/dL, serum triglycerides (TG) > 180 mg/dL, or use of lipid-lowering drugs because of a history of hypercholesterolemia [14]. Diabetes mellitus was defined as a previous history of the disease, use of diet, insulin or oral antidiabetic drugs, or a fasting venous blood glucose level ≥ 126 mg/dL on 2 occasions in previously untreated patients [15]. GFR for each patient was calculated using the measured plasma creatinine levels and the Cockcroft-Gault formula for the estimation of renal function [16]. The height and weight of the study participants were measured, and body mass index (BMI) was calculated as body weight in kilograms divided by the square of the height in meters (kg/m^2).

Data analysis

A 12-lead ECG was obtained from all patients (filter range 0.5 Hz to 150 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV). A narrow fQRS was described as a narrow QRS complex (duration < 120 ms) in addition to notching in the R' or QRS complex. For the diagnosis of fQRS, the presence of various RSR' patterns, including an additional R wave (R'), or notching of the R wave or S wave, or the presence of more than one R' (fragmentation), without typical bundle branch block, was sought in two contiguous leads corresponding to a major lead set for major coronary artery territory. A notch on an R or S wave was defined as a definite but transient reversal of direction of the main deflection (Fig. 1) [4, 9]. All ECGs were analyzed without using any magnification by 2 independent clinicians who were blinded to the study design and to the clinical and angiographic data. The inter-observer concordance rate in the detection of fQRS was 97%. In case of disagreement, the final diagnosis was arrived at by mutual agreement. The intra-observer concordance rate was 98%. The QRS duration was determined by measuring the longest QRS in any lead, both by manual reading and from the digital records obtained by the ECG machine.

Coronary angiography procedure and determination of CSF

Coronary angiography was performed via femoral approach using the standard Judkins technique with a monoplane cineangiography system. Coronary angiograms were recorded in right and left oblique planes using cranial and caudal angulations, at a rate of 30 Fr/s. During the coronary angiography procedures, iopromide (Ultravist 370, Schering AG, Berlin, Germany) was used as a contrast agent in all study participants. The patients were evaluated for the presence of CSF during coronary angiography. Coronary blood flow rates were measured quantitatively, using the thrombolysis in myocardial infarction (TIMI) frame count method (TFC), by 2 experienced interventional cardiologists who were totally blinded to the study [17]. The intra- and inter-observer coefficients of variation were 4.9% and 7.4%, respectively.

In this method, the number of cine frames required for the contrast to reach standard distal coronary landmarks in the left anterior descending (LAD), left circumflex (LCX), and right coronary (RCA) arteries is noted. Initial frame count is defined as the frame in which concentrated dye occupies the full width of the proximal coronary artery lumen, touching both borders of the lumen,

and having forward motion distal to the artery. The final frame is designated when the leading edge of the contrast column first reaches the distal end. Predefined distal landmarks are the distal bifurcation for the LAD, commonly referred to as the "moustache", "pitchfork" or "whale's tail", the distal bifurcation of the segment with the longest total distance for the LCX, and the first branch of the posterolateral artery for the RCA. Since the LAD artery is usually longer than the other major coronary arteries, the TFC for this vessel is often higher. To obtain the corrected TFC for the LAD, TFC was divided by 1.7 [17]. The mean TFC for each patient and control individual was calculated by totaling the TFC for the LAD, LCX, and RCA and then dividing by 3. The standard corrected mean values for normal visualization of the coronary arteries are 36.2 ± 2.6 Fr for the LAD, 22.2 ± 4.1 Fr for the LCX, and 20.4 ± 3 Fr for the RCA [17]. The standard corrected mean value for the LAD coronary artery is 21.1 ± 1.5 Fr. All study participants with a TFC that exceeded the previously published range for the particular vessel by more than 2 standard deviations (SDs) were considered to have CSF. In our study, values obtained above these thresholds in any of the 3 coronary arteries (not all 3) were considered to be CSF.

Statistical analysis

Continuous, normally distributed variables were expressed as mean ± SD and non-normally distributed variables as median (interquartile range). Categorical variables were expressed as frequencies and/or percentages. The Kolmogorov–Smirnov test was used to evaluate whether the continuous variables were normally distributed. Student's t-test was used for the comparison of normally distributed continuous numerical variables, the Mann–Whitney U-test was used for non-normally distributed numerical variables, and the χ^2-test was used for comparing categorical variables between the two groups. Any correlation between the data was tested by Spearman or Pearson correlation analysis. A univariate and backward stepwise multivariate Cox regression analysis, which included variables with a p-value less than 0.1, were performed to identify independent predictors of a narrow fQRS. A 2-sided p-value was considered for all comparisons. Statistical significance was defined as $p < 0.05$. Statistical analyses were carried out using the Statistical Package for Social Sciences for Windows 13.0 (SPSS Inc., Chicago, Illinois, USA).

Results

The baseline demographic, clinical and laboratory characteristics of the CSF and the control group are presented in Table 1. There were no statistically significant differences between the two groups in terms of age, male gender, hypertension, diabetes, hyperlipidemia, cigarette smoking, or family history, hematocrit, hemoglobin, white blood cell count (WBC), or total cholesterol (all $p > 0.05$). However, BMI ($p < 0.001$), systolic and diastolic blood pressure ($p = 0.001$ and $p = 0.008$, respectively), heart rate ($p = 0.001$), and the incidence of a narrow fQRS complex ($p = 0.007$), creatinine ($p < 0.001$), fasting glucose ($p < 0.001$), LDL-C ($p < 0.001$), and TG ($p = 0.001$) were significantly higher in the CSF group compared to the control group. Moreover, LVEF ($p = 0.001$), GFR ($p < 0.001$), and high-density lipoprotein cholesterol ($p < 0.001$) were significantly lower in the CSF group compared to the controls. There were no significant differences between the two groups with respect to the use of medications (all $p > 0.05$).

The baseline demographic, clinical and laboratory characteristics of the fragmented and non-fragmented QRS groups are presented in Table 2. There was no difference between two groups except diastolic blood pressure ($p = 0.02$) and hematocrit levels ($p = 0.03$), which were found to be increased in the fragmented QRS groups as compared to the non-fragmented QRS groups.

Those patients who were deemed to have CSF had slower coronary blood flow by TFC measurements when compared with the control group. Twenty-two (19.6%) patients had slow flow in all 3 vessels, 36 (32.1%) patients in 2 vessels, and 54 (48.2%) patients in 1 vessel. The distribution of CSF according to the coronary vessels was as follows: 70 (63%) patients had slow flow in the LAD, 57 (51%) had slow flow in the LCX, and 68 (61%) had slow flow in the RCA. All TFC values for the LAD, LCX, and RCA vessels, as well as the mean TFC, were found to be significantly higher in the CSF group than in the controls (all $p < 0.001$).

In the fQRS(+) group, 17 (38.6%) patients had slow flow in all 3 vessels, 12 (27.2%) patients in 2 vessels, and 8 (18.1%) patients in 1 vessel. In the fQRS(–) group, 5 (4.1%) patients had slow flow in all 3 vessels, 24 (19.8%) patients in 2 vessels, and 46 (38%) patients in 1 vessel. The extent of CSF was significantly greater in the fQRS(+) group compared to the non-fQRS group

Table 1. Baseline demographic and clinical characteristics of the coronary slow flow (CSF) patients and the control group (NCF).

	CSF (n = 112)	NCF (n = 53)	P
Age [years]	53.33 ± 3.0	53.67 ± 2.88	0.493
Gender, male	73 (65.1%)	27 (50.9%)	0.81
Body mass index [kg/m^2]	28.18 ± 1.14	27.12 ± 0.67	**< 0.001**
Family history	34 (30.3%)	9 (16.9%)	0.68
Smoking	31 (27.6%)	23 (43.3%)	0.70
Diabetes mellitus	23 (20.5%)	10 (18.8%)	0.80
Hypertension	63 (56.2%)	23 (43.3%)	0.12
Hyperlipidemia	46 (41%)	20 (37.7%)	0.68
Systolic BP [mm Hg]	131.49 ± 5.54	124.77 ± 7.38	**0.001**
Diastolic BP [mm Hg]	72.41 ± 4.32	70.56 ± 3.73	**0.008**
Heart rate [min]	76.08 ± 5.33	73.35 ± 3.99	**0.001**
Ejection fraction [%]	59.10 ± 4.11	61.33 ± 3.05	**0.001**
fQRS	37 (33%)	7 (13.2%)	**0.007**
GFR [mL/min/1.73 m^2]	109.14 ± 9.26	127.64 ± 7.37	**< 0.001**
Total cholesterol [mg/dL]	192.57 ± 36.62	191.15 ± 33.33	0.811
LDL-cholesterol [mg/dL]	148.36 ± 23.36	121.77 ± 16.31	**< 0.001**
HDL-cholesterol [mg/dL]	39.33 ± 5.68	44.62 ± 9.86	**0.001**
Triglyceride [mg/dL]	177.96 ± 44.07	154.77 ± 37.51	**0.001**
Fasting glucose [mg/dL]	112.07 ± 26.35	95.32 ± 13.33	**< 0.001**
Creatinine [mg/dL]	0.85 ± 0.16	0.73 ± 0.13	**< 0.001**
Hemoglobin [g/dL]	12.86 ± 1.85	12.64 ± 1.16	0.428
Hematocrit [%]	41.6 ± 2.36	40.9 ± 2.14	0.06
WBC [10^3/mm^3]	7.67 ± 1.39	7.48 ± 1.25	0.402
Acetylsalicylic acid	25 (22.3%)	10 (18.8%)	0.62
Beta-blocker	14 (12.5%)	7 (13.2%)	0.90
Ca channel blocker	15 (13.3%)	7 (13.2%)	0.97
Nitrate	18 (16%)	7 (13.2%)	0.63
ACEI/ARB	23 (20.5%)	8 (15.0%)	0.40
Statin	19 (16.9%)	7 (13.2%)	0.71

Values are presented as mean ± standard deviation or number (%), as appropriate; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; BP — blood pressure; fQRS — fragmented QRS complex; GFR — glomerular filtration rate; HDL — high-density lipoprotein; LDL — low-density lipoprotein; SBP — systolic blood pressure; WBC — white blood cell count

($p < 0.001$). The distribution of CSF according to the coronary vessels in the fQRS(+) group was as follows: 33 (75%) patients had slow flow in the LAD, 24 (54.5%) had slow flow in the LCX, and 26 (59%) had slow flow in the RCA. Furthermore, those patients who were deemed to have narrow fQRS complex also had slower coronary blood flow by TFC measurements when compared with the non-fQRS group. All TFC values for the LAD ($p < 0.001$), LCX ($p = 0.003$), and RCA ($p = 0.023$), as well as the mean TFC ($p < 0.001$), were found to be significantly higher in the narrow fragmented group than in the non-fragmented group (Table 3).

When the correlations between fQRS and baseline demographic, clinical and laboratory parameters were assessed, fQRS was found to be significantly negatively correlated with diastolic blood pressure ($p = 0.008$). Furthermore, there was a positive correlation between the presence of fQRS on the admission ECG and the blood flow in all 3 coronary vessels ($p < 0.001$, $p = 0.003$, $p = 0.016$, respectively, for TFC in the LAD, LCX, and RCA). The TFC of the LAD showed the strongest correlation with fQRS ($r = 0.416$, $p < 0.001$). A strong significant relationship was also seen between the mean TFC values and fQRS ($r = 0.383$,

Table 2. Baseline demographic and clinical characteristics of the fragmented QRS (+) and the non-fragmented QRS (–) groups.

	Fragmented QRS (+) (n = 44)	Non-fragmented QRS (–) (n = 121)	P
Age [years]	52.97 ± 3.13	53.61 ± 2.89	0.22
Gender, male	31 (70.4%)	69 (57%)	0.11
BMI [kg/m^2]	28.06 ± 1.28	27.76 ± 1.06	0.13
Family history	9 (20.4%)	34 (28%)	0.32
Smoking	13 (29.5%)	31 (25.6%)	0.61
Diabetes mellitus	9 (20.4%)	24 (19.8%)	0.93
Hypertension	24 (54.5%)	62 (51.2%)	0.70
Hyperlipidemia	16 (36.3%)	50 (41.3%)	0.56
Systolic BP [mm Hg]	130.15 ± 6.97	129.03 ± 6.91	0.35
Diastolic BP [mm Hg]	73.25 ± 4.90	71.30 ± 3.83	**0.02**
Heart rate [min]	75.31 ± 5.23	75.17 ± 5.23	0.86
Ejection fraction [%]	59.70 ± 4.03	59.86 ± 3.91	0.81
GFR [mL/min/1.73 m^2]	113.56 ± 11.30	115.63 ± 12.59	0.31
Total cholesterol [mg/dL]	189.84 ± 35.11	192.94 ± 35.76	0.61
LDL-cholesterol [mg/dL]	139.68 ± 20.44	139.87 ± 26.12	0.96
HDL-cholesterol [mg/dL]	39.63 ± 5.31	41.53 ± 8.33	0.08
Triglyceride [mg/dL]	163.43 ± 38.62	173.09 ± 44.81	0.17
Fasting glucose [mg/dL]	108.04 ± 20.79	106.19 ± 25.45	0.63
Creatinine [mg/dL]	0.81 ± 0.16	0,81 ± 0,17	0.89
Hemoglobin [g/dL]	12.79 ± 2.09	12.79 ± 1.48	0.98
Hematocrit [%]	41.9 ± 2.07	41.1 ± 2.3	**0.03**
WBC [10^3/mm^3]	7.43 ± 1.46	7.67 ± 1.31	0.33
Acetylsalicylic acid	8 (18.1%)	27 (22.3%)	0.56
Beta-blocker	5 (11.3%)	16 (13.2%)	0.75
Ca channel blocker	8 (18.1%)	14 (11.5%)	0.26
Nitrate	8 (18.1%)	17 (14.0%)	0.51
ACEI/ARB	11 (25.0%)	20 (16.5%)	0.21
Statin	10 (22.7%)	16 (13.2%)	0.13

Abbreviations as in Table 1

Table 3. Comparison of angiographic characteristics between the fragmented QRS (+) and the non-fragmented QRS (–) groups.

TIMI frame count measurements	Fragmented QRS (+) (n = 44)	Non-fragmented QRS (–) (n = 121)	P
Mean	36.93 ± 12.26	27.86 ± 8.63	**< 0.001**
Left anterior descending artery (corrected)	38.97 ± 12.89	27.97 ± 9.81	**< 0.001**
Left circumflex artery	34.54 ± 12.89	27.71 ± 12.62	**0.003**
Right coronary artery	33.88 ± 14.83	27.96 ± 13.40	**0.023**

$p < 0.001$). There was no correlation between fQRS and other parameters (Table 4).

On multivariate analysis, only CSF (OR 2.66, 95% CI 1.075–6.62, $p = 0.03$) was found to be

Table 4. Correlation analysis between the fQRS complex and clinical, laboratory and angiographic parameters of CSF patients.

Variables	r	p
Age	–0.096	0.220
BMI	0.117	0.134
SBP	0.072	0.357
DBP	0.204	**0.008**
Heart rate	–0.047	0.549
Ejection fraction	–0.018	0.815
Mean TFC	0.383	**< 0.001**
LAD TFC (corrected)	0.416	**< 0.001**
LCX TFC	0.233	**0.003**
RCA TFC	0.188	**0.016**
TC	–0.039	0.621
LDL-C	–0.003	0.965
HDL-C	–0.110	0.160
Triglyceride	–0.099	0.207
Glucose	0.034	0.667
Creatinine	0.010	0.894
GFR	–0.075	0.340

BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; TFC — TIMI frame count; LAD — left anterior descending artery; LCX — left circumflex artery; RCA — right coronary artery; TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; GFR — glomerular filtration rate

a significant independent predictor for a narrow fQRS complex, after adjustment for other parameters that univariate analysis had identified as significant predictors, such as age, male gender, systolic and diastolic blood pressure, hypertension, diabetes, hyperlipidemia, smoking, family history, heart rate, LVEF, GFR, BMI, WBC, and hemoglobin (Table 5).

Discussion

The present study demonstrated a significant relation between the presence of a narrow fQRS complex on the admission ECG and CSF confirmed by coronary angiography. Moreover, we found a significant positive association between narrow fQRS and the extent and severity of CSF. On multivariate analysis, only CSF was found to be a significant independent predictor of a narrow fQRS, after adjustment for other risk parameters. To the best of our knowledge, this is the first study to demonstrate a correlation between the presence of a narrow fQRS complex on the admission ECG and the presence of CSF. In addition, a strong relation between a narrow fQRS and the extent and severity of CSF is reported for the first time.

Although the precise etiology and underlying pathophysiological mechanisms of CSF have not been consistently determined, it is a well known angiographic finding, whose incidence has been reported as 1–7% in patients undergoing coronary angiography for suspected CAD. CSF has been demonstrated to be more common in males, smokers, and in individuals with hyperlipidemia, metabolic syndrome, or obesity [18]. However, we were unable

Table 5. Univariate and multivariate logistic regression analyses for predictors of a narrow fragmented QRS.

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.929 (0.82–1.04)	0.219		
Coronary slow flow	3.24 (1.33–7.87)	**0.009**	2.66 (1.07–6.62)	**0.034**
Male gender	1.79 (0.85–3.77)	**0.121**	0.67 (0.33–1.45)	0.331
Diastolic BP	1.11 (1.02–1.20)	**0.01**	1.08 (1.0–1.18)	0.051
Hypertension	1.14 (0.57–2.28)	0.70		
Smoking status	1.21 (0.56–2.61)	0.61		
Hyperlipidemia	0.81 (0.39–1.65)	0.56		
Diabetes mellitus	1.03 (0.44–2.45)	0.93		
GFR	0.98 (0.95–1.01)	0.33		
Ejection fraction	0.98 (0.90–1.08)	0.81		
Systolic BP	1.03 (0.97–1.07)	0.35		
White blood cell count	0.87 (0.66–1.13)	0.30		
Hemoglobin	0.99 (0.81–1.22)	0.98		

OR — odds ratio; CI — confidence interval; GFR — glomerular filtration rate; BP — blood pressure

to show any difference between the CSF and control groups in terms of age, gender, or other risk factors for CAD, including hypertension, diabetes, dyslipidemia, family history, and smoking; the exception was BMI, which was found to be higher in patients with CSF, consistently with some other previous studies [19, 20]. Several important mechanisms have been proposed for the development of CSF, including endothelial dysfunction, diffuse atherosclerosis, microvascular vasomotor dysfunction, small-vessel disease, imbalance of vasoactive substances, and raised platelet aggregability [3–6]. Inflammation has also been reported to play an important role in the development of CSF [7]. Furthermore, not only microvascular dysfunction, but also epicardial CAD was demonstrated by intravascular ultrasound studies to be an important pathophysiological factor for CSF [21]. Oxidative agents and free radical damage may also play a role in the pathogenesis of CSF. Hypertension, stable and unstable angina pectoris, acute myocardial infarction, life-threatening arrhythmias, and sudden cardiac death are among the main clinical sequelae of CSF [9].

The fQRS is a simple, inexpensive, and readily available noninvasive ECG parameter that can be easily identified by clinicians. It may occur because of the heterogeneous activation of ischemic or infarcted ventricles during ischemic or inflammatory heart disease. Scar or fibrotic tissue, resulting from cardiac remodeling after ischemic heart disease or cardiomyopathy, can lead to hemodynamically significant arrhythmias and congestive heart failure, and eventually to cardiovascular death. The presence of fQRS has been demonstrated to be an independent predictor of impaired myocardial perfusion and left ventricular function detected by myocardial single-photon emission computed tomography imaging in patients with ischemic heart disease [9, 22, 23]. Moreover, fQRS, which may be widened or narrowed, has been reported to be related with a high incidence of major adverse cardiovascular events, including mortality due to hemodynamically significant ventricular arrhythmic events in CAD, acute coronary syndromes [24, 25], hypertrophic obstructive cardiomyopathy [26], ischemic and non-ischemic cardiomyopathy [27, 28], and decompensated systolic heart failure [29]. Moreover, a significant relation between the presence of wide fQRS and the occurrence of CSF was demonstrated by Yilmaz et al. [30]. The fQRS was found to be significantly higher in patients with CSF compared to the control group. However, the investigators did not demonstrate any association between the fQRS and the extent and severity of CSF. In our study, for the first time, we report a significant relation between the presence of a narrow fQRS complex on the admission ECG and the occurrence of CSF, confirmed by coronary angiography. In contrast to the study by Yilmaz et al. [30], we demonstrated a strong association between a narrow fQRS and the extent and severity of CSF. The TFCs of all 3 coronary artery were found to be significantly positively related with the presence of a narrow fQRS. It seems that the presence of a narrow fQRS is affected by the degree of flow rate in the coronary arteries. Moreover, in our study, similarly to Yilmaz et al. [30], we found that only CSF was an independent predictor for fQRS on multivariate analysis, after adjustment for other parameters. Although the main underlying pathophysiological mechanisms linking a narrow fQRS and CSF were not elucidated in previous studies, cardiac arrhythmias and conduction disturbances, including fQRS, may be due to myocardial inflammation, myocardial ischemia or scar, which may lead to depolarization abnormalities of the myocardium at the cellular level.

Limitations of the study

The present study had some limitations. First, the study population was relatively small; however, we were still able to demonstrate an important association between the presence of a narrow fQRS on the admission ECG and the occurrence of CSF on coronary angiography. Second, since the patients did not undergo intravascular ultrasonography to detect atherosclerotic changes and plaque burden in the lumen and walls of the coronary arteries, the coexistence of non-obstructive CAD in patients with "isolated" CSF could not be established with certainty. Third, we did not perform analyses based on the number of leads with fQRS on the ECG, which might have decreased the predictive value of narrow fQRS for the presence of the CSF phenomenon. The final limitation of the present study was the lack of follow-up of the patients in terms of major adverse cardiac events, including mortality due to hemodynamically significant arrhythmic events, that could have helped to determine the significance of a narrow fQRS as a novel risk stratification tool.

Conclusions

The presence of a narrow fQRS on the admission ECG is associated with the occurrence of CSF confirmed by coronary angiography. Moreover, it is significantly related with the extent and severity of

CSF. The fQRS, which reflects impaired ventricular depolarization due to heterogeneous electrical activation of ischemic and/or injured ventricular myocardium, is a simple, inexpensive, and readily available noninvasive ECG parameter that could serve as a new potential indicator of myocardial damage in patients with CSF. Further studies with larger patient groups are needed to clarify the exact pathophysiological mechanisms and the relation between a narrow fQRS and CSF.

Conflict of interest: None declared

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