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The relationship between fragmentation on electrocardiography and in-hospital prognosis of patients with acute myocardial infarction

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDE Ersin Yıldırım
ABDE Denizhan Karaçimen
ACDE Kazım Serhan Özcan
ADF Damirbek Osmonov
BCDE Ceyhan Türkkan
BCE Servet Altay
ACF Ufuk Sadik Ceylan
BCE Murat Uğur
ADE Mehmet Bozbay
ACD İzzet Erdinler

Department of Cardiology, Siyami Ersek Cardiovascular and Thoracic Surgery Center, Istanbul, Turkey

Corresponding Author: Ersin Yıldırım, e-mail: ersinyil44@gmail.com
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Background: In patients with acute ST elevation myocardial infarction (STEMI), QRS fragmentation was determined as one of the indicators of mortality and morbidity. The development of fragmented QRS (fQRS) is related to defects in the ventricular conduction system and is linked to myocardial scar and fibrosis.

Material/Methods: We prospectively enrolled 355 consecutive patients hospitalized in the coronary intensive care unit of our hospital with STEMI between the years 2010 and 2012 and their electrocardiographic features and the frequency of in-hospital cardiac events were evaluated.

Results: There were 217 cases in the fQRS group and 118 cases in the control group. QRS fragmentation was found to be a predictor for major cardiac events. In the fragmented QRS group, the frequency of in-hospital major cardiac events (MACE) and death were higher (MACE p<0.001; death p<0.003). In the fragmented QRS group, the cardiac enzymes (Troponin-I, CK-MB) were significantly higher than in the control group (p<0.001). In subgroup analyses, apart from the presence of fragmentation, the presence of more than 1 type of fragmentation and the number of fragmented deviations were also found to be related with MACE. A significant negative correlation was observed with the ejection fraction and, in particular, the number of fragmented deviations.

Conclusions: Fragmented QRS has emerged as a practical and easily identifiable diagnostic tool for predicting in-hospital cardiac events in acute coronary syndromes. Patients who present with a fragmented QRS demonstrate increased rates of major cardiac events, death risk, and low ejection fraction. In patients with STEMI, the presence of fQRS on the ECG and number of fQRS derivations are a significant predictor of in-hospital major cardiac events.

Keywords: Fragmented QRS • Myocardial Infarction • MACE

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Background

The presence of fQRS on electrocardiogram is associated with myocardial scarring, ischemia, and fibrosis and originates from the deterioration in the process of signal transduction and ventricular depolarization [1,2]. The presence of fQRS in coronary artery disease is known to be significantly associated with major adverse cardiac events, left ventricular dysfunction, and impairment of myocardial perfusion [3–7]. Fragmentation originates from small abnormal myocardial areas where ventricular activation is delayed and asynchronous. Partial damage of the conducting system inside the ventricle causes the notching of the QRS segment on ECG [8].

In our study we aimed to investigate the effect of fQRS on major adverse cardiovascular events and mortality in patients with acute STEMI treated with primary percutaneous coronary intervention.

Material and Methods

This study was conducted at the Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital in Istanbul between December 2010 and November 2012. We prospectively enrolled 355 consecutive patients diagnosed with acute STEMI and treated with primary percutaneous intervention.

The ECGs of patients with percutaneous coronary interventions that were taken initially and during the intensive care follow-up at the first hour, 12th hour, 24th hour, 48th hour. ECGs were evaluated. The 48th hour ECG was finally interpreted for fragmentation. During the intensive care and hospitalization follow-up of patients, ventricular arrhythmia (ventricular fibrillation, ventricular tachycardia), cardiogenic shock, cardiopulmonary resuscitation (CPR), reinfarction, and death were regarded as MACE. Patients who received coronary angiography, primary angioplasty, stent implantation, and percutaneous coronary interventions were given 300 mg of acetylsalicylic acid (ASA) and a 600-mg loading dose of clopidogrel before the procedure. The angiographic data was obtained from the catheter laboratory records and evaluated by 2 expert interventional cardiologists. Emergency coronary angiography and angioplasty were performed through the femoral artery. Following femoral artery puncture, all patients were given an intravenous bolus of 100 U per kg of unfractionated heparin. The arterial flow related with the infarct was evaluated with the TIMI (Thrombolysis in Myocardial infarction) classification. According to the lesion type, primary angioplasty (balloon angioplasty and/or stent implantation) was performed only on the infarct-related artery. Success in the acute phase was defined as a less than 50% residual narrowing with TIMI II or TIMI III flow achieved in the infarct-related artery for each procedure. Following angioplasty, all patients were admitted to the coronary intensive care unit and were given 1 mg/kg of subcutaneous enoxaparin twice a day, daily 300-mg aspirin, and 75-mg clopidogrel. While the choice of Glycoprotein IIb/IIIa inhibitor treatment was left up to the primary physician, β-blockers, ACE inhibitors, and statins were given according to ACC/AHA guidelines. Information regarding in-hospital outcomes was obtained from face-to-face patient interviews and hospital records for the short- and long-term follow-up. The results of long-term follow-up of the patients were excluded from the study.

For STEMI, the following diagnostic criteria were used:

1. ST segment elevation in ≥2 consecutive derivations (in chest derivations ≥2 mm, extremity derivations ≥1 mm) or new-onset left bundle brunch block (LBBB),
2. Ischemic type chest pain lasting more than 30 minutes,
3. A 2-fold or greater elevation in serum creatine phosphokinase myocardial band (CK-MB) and troponin levels.

Analysis of data

The history, risk factors (smoking, hyperlipidemia, hypertension, diabetes mellitus, previous coronary artery disease), and the durations of pain-balloon and door-to-balloon time of patients were recorded. Initial and peak cardiac enzyme levels were examined. By evaluating the ECG records before and after the percutaneous coronary artery interventions, the type of myocardial infarction with ST elevation, the presence of fragmentation on ECG and the fragmentation type were determined. Global left ventricular systolic ejection fraction was measured by the modified Simpson method by using the System V (Vingmed, GE) echocardiography equipment and 2.5 MHz a "phased-array" transducer.

Determination of fragmentation on ECG

The determination of fragmentation by ECG records were taken by Nihon Kohden - cardiofax (Filter range 0.5 Hz to 150 Hz, AC filter 60 Hz, at a speed of 25 mm/s and an amplitude of 10 mm/mV) and defined as:

1. Presence of an additional R wave or,
2. Presence of a notch in the tip of the S wave or,
3. More than 1 large R' wave in 2 consecutive derivations, and divided into 8 types (Table 1).

Statistical analysis

Statistical evaluation was performed with the NCSS (Number Cruncher Statistics System) 2007 & PASS 2008 statistic software program (Utah, USA). Quantitative variables are expressed as mean ± standard deviation and qualitative variables

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Table 1. Types of fragmented QRS as described by Das et al. [3].

Type 1: Fragmented QRS	**Type 2:** Notches on the R wave
Type 3: Notches on the S wave	**Type 4:** RsR' ST elevation
Type 5: rSr'	**Type 6:** RSR'
Type 7: Fragmented RBBB	**Type 8:** Fragmented LBBB

are expressed as percent (%). For the comparison of numerical values between the groups, Student t-test, Mann Whitney U test, and one-way ANOVA test were used. To compare categorical variables, the chi-square test and Fisher's exact test were used. For all statistical interpretations, a p<0.05 value was accepted as being significant.

Results

The baseline characteristics of the study groups are shown in Table 2. Accordingly, there was a statistically significant difference between the ages of the fragmented and non-fragmented groups (p<0.01). The mean age of the fragmented group was significantly higher than that of the non-fragmented group. While the mean age of the fragmented group was 59.1±11.86, the mean age of the control group was 55.05±12.95. The relative risk of fragmentation among those over 55 years of age was found to be 2.083 (95% CI: 1.317–3.295) times more. There was no difference in terms of gender among the cases (p>0.05). The smoking rates of the non-fragmented cases were found to be significantly higher than the fragmented cases (p<0.01). There was no difference with regards to hypertension, diabetes, chronic renal failure, hyperlipidemia, coronary artery disease, peripheral arterial disease, and cerebrovascular event rates (p>0.05).

Table 2. Baseline and angiographic characteristics of study patients.

	Fragmentation (–) (n=118)	Franmentation (+) (n=217)	P value
Age, years, n (SD)	55.05±12.95	59.51±11.86	0.002**
Male, n (%)	95 (%80.5)	175 (%80.6)	0.976
Smoker, n (%)	90 (%76,3)	132 (%60.8)	0.004**
Alcohol, n (%)	0 (%0)	9 (%4.1)	0.025*
Hypertension, n (%)	46 (%39.0)	98 (%45.2)	0.275
Diabetes, n (%)	20 (%16.9)	53 (%24.4)	0.113
Chronic Renal Failure, n (%)	0 (%0)	6 (%2.8)	0.094
Hyperlipidemia, n (%)	11 (%9.3)	14 (%6.5)	0.340
History of CAD, n (%)	16 (%13.6)	42 (%19.4)	0.181
History of PAD, n (%)	0 (%0)	2 (%0.9)	0.542
Cerebrovasculer Event, n (%)	3 (%2.5)	5 (%2.3)	0.891
Atrial Fibrillation, n(%)	2 (%1.6)	14 (%6.4)	0.061
Culprit lesion			
LMCA, n (%)	0 (%0)	1 (%0.4)	1.000
LAD, n (%)	57 (%48.3)	94 (%43.3)	0.422
CX, n (%)	18 (%15.2)	45 (%20.7)	0.244
RCA, n (%)	42 (%35.5)	66 (%30.4)	0.392
SVG, n (%)	0 (%0)	2 (%0.9)	0.542
Other, n (%)	1 (%0.8)	9 (%4.1)	0.106
Reperfusion time, min (SD)	162.6±119.4	213.6±200.4	0.287

Student t Test, chi-square Test, Fisher'sExact Test * p<0.05; ** p<0.01. SD – standart deviation; CAD – Coronary Artery Disease; PAD – Peripheral Arterial Disease; LMCA – left main coronary artery; LAD – left anterior descending coronary artery; CX – circumflex coronary artery; RCA – right coronary artery; SVG – saphenous vein graft.

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Table 3. In hospital cardiac events and success of operation.

	Fragmentation (–)		Fragmentation (+)		P value
	n (%)		n (%)		
Thrombosis, n (%)	22	(%18.8)	44	(%21.6)	0.555
Slow flow, n (%)	10	(%8.5)	32	(%15.7)	0.068
No- reflow, n (%)	5	(%4.3)	16	(%7,8)	0.213
In hospital VT, n (%)	0		18	(%8.3)	**0.001**
In hospital VF, n (%)	9	(%7.6)	26	(%12)	0.263
Cardiogenic shock, n (%)	1	(%0.8)	18	(%8.3)	**0.005**
Cardiopulmonary arrest, n (%)	2	(%1.7)	33	(%15.2)	**0.001**
In hospital mortality, n (%)	0		14	(%6.5)	**0.003**
MACE, n (%)	9	(%7.6)	55	(%25.3)	**0.001**
TIMI					
0–1, n (%)	8	(%6.8)	21	(%9.7)	
2, n (%)	3	(%2.5)	12	(%5.5)	0.277
3, n (%)	107	(%90.7)	184	(%84.8)	
Post operation CABG, n (%)	4	(%3.4)	18	(%8.8)	0.02

Chi-square Test * p<0.05; ** p<0.01. VT – ventricular tachycardia; VF – ventricular fibrillation; MACE – major adverse cardiac events (cardiovascular mortality, reinfarction, target-vessel revascularization); TIMI – Thrombolysis In Myocardial Infarction.

The incidence of thrombosis, slow flow and "no-reflow" was not different (p>0.05) in terms of fragmentation. There was a significant difference detected for the incidence of MACE (p<0.01). In the fQRS group, 55 events were observed, compared to 13 events in the control group. Of the observed events in the fQRS group; 18 (8.3%) had VT, 26 (12%) had VF, 18 (8.3%) had cardiogenic shock, 33 (15.2%) had cardiopulmonary arrest, and 14 (6.5%) died in hospital follow-up. In the control group there were no VT or deaths observed in the in-hospital follow-up: 9 (7.6%) cases had VF, cardiogenic shock was observed in 1 case (0.8%), and cardiopulmonary arrest was observed in 2 cases (1.7%). In terms of the success rate, there was no significant difference detected among the fragmented and non-fragmented groups (p>0.05). In-hospital mortality rates were found to be significantly higher in the fragmentation group (p=0.03) (Table 3). There was a significant difference found between the results of the procedures according to the presence of fragmentation (p<0.05). The application rate of CABG in the fragmentation group was significantly higher than the non-fragmented group. The reason for this was the presence of multiple vessel disease and type C lesions in the fragmentation group. According to the presence of fragmentation, there was no statistically significant difference detected between the 2 groups in terms of TIMI flow (p>0.05).

The peak troponin levels of the non-fragmented group varied between 0.37 and 50, with a mean value of 33.90±18.31. Peak troponin levels of the fragmented group varied between 0.08 and 50, with a mean value of 41.39±14.80. There was a highly significant difference detected among groups for peak troponin levels (p<0.001). Peak CK-MB values in the non-fragmented group were between 18 and 735 ng/mL (mean 147.02±103.5). Peak CK-MB values of the fragmented group were between 8.5 and 1167 ng/mL (mean 211.87±172.3) (p<0.001). There was no statistically significant difference detected between the 2 groups for leucocytes, hemoglobin, and platelet values (p>0.05). However, there was a statistically significant difference in the creatinine and BUN values (p<0.014 and p<0.001, respectively).

Of the 217 patients in the fragmentation group, MACE was observed in 55 patients. As the number of fragmented derivations increased, and particularly in patients with ≥4 derivations, MACE occurrence was found to be significantly high and left ventricular ejection fraction was significantly low. There was a significant relationship between the presence of 2 or more types of fragmentation and MACE (Table 4).

The left ventricular functions were significantly impaired in fQRS group (p<0.01) (Table 5). Moreover, the left ventricular EF was negatively correlated with the number of fragmented

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Table 4. Relationship between fragmentation and the MACE.

	MACE (–)		MACE (+)		P value
	n (%)		n (%)		
Fragmentation	162	(%59.8)	55	(%85.9)	0.001
Number of fQRS derivations					
0	115	(%42.4)	9	(%14.1)	0.001
2	53	(%19.6)	14	(%21.9)	
3	56	(%20.7)	13	(%20.3)	
≥4	47	(%17.3)	28	(%43.8)	
0–2–3	224	(%82.7)	36	(%56.3)	0.001
≥4	47	(%17.3)	28	(%43.8)	
Various types of fragmentations	39	(%14.4)	26	(%40.6)	0.001

Chi-square Test ** p<0.01. MACE – major adverse cardiac events (cardiovascular mortality, reinfarction, target-vessel revascularization).

Table 5. Left ventricular functions according to the fragmentation on ECG.

	Fragmentation (–)		Fragmentation (+)		P value
	Mean ±SD (Median)		Mean ±SD (Median)		
Ejection fraction (%)	50.21±10.47	(50)	41.66±11.45	(40)	0.001**
Left ventricular systolic diamater	3.19±0.59	(3.2)	3.67±0.79	(3.6)	0.001**
Left ventricular diastolic diamater	4.87±0.42	(4.9)	5.17±0.61	(5.2)	0.001**

Student t Test, ** p<0.01.

Table 6. Exchange of left ventricular ejection fraction according to the number of fQRS derivations.

	Number of fragmented derivations				p
	0	2	3	≥ 4	
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	
LVEF (%)	49.93±10.48	43.84±10.90	42.79±11.23	38.54±11.84	0.001**

One Way Anova Test ** p<0.01.

derivations on ECG. A higher number of fragmented derivations was associated with a lower EF (Table 6).

In the fragmented group, there was no significant difference between the magnesium, potassium, creatinine, Troponin I, and CK-MB levels in patients with in hospital VT compared to patients without VT (p>0.05).

Discussion

The main findings of our study were, in patients with STEMI, the presence of fQRS and the number of fragmented derivations on 12-lead ECG significantly predicted in-hospital major cardiac events. Our findings show that in the fQRS group, during the short-term hospital follow-up, MACE and mortality were observed more frequently (MACE p<0.001; mortality p<0.003) and, in contrast to other studies, we show that the presence of various types of fragmentation in the same ECG was associated with MACE (p<0.001).

The reasons for the relationship between fQRS and increased morbidity, mortality, sudden cardiac death, and MACE have been investigated in earlier studies [9–12]. Similar findings were seen in the study conducted by Das et al. [13], in which 896 patients with acute coronary syndrome were evaluated. At the end of the 34±16-month follow-up period, the presence of fQRS was found to be significant in all causes relating to

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death (HR=1.68, p<0.003). Our study differs from the study by Das et al. [14] in that we included only STEMI patients and the control group consisted of non-fragmented STEMI patients.

Although various types of fragmentations have been defined in the literature, a common shared opinion has not been defined. In our study we included patients who have fragmentation types defined by Das et al. (RSR', rSr', rSR', notched S, notched R, fragmented QRS), and we included patients with ST-elevated fQRS, QRS fragmentation with right or left bundle branch block. In various studies found in the literature, predictors of the development of fragmentation have not been clearly defined. In our patient group we determined the primary end-point as being the in-hospital incidence of MACE and we evaluated the predictors of fragmentation development. When the demographic characteristics and the histories of the patients were evaluated, the incidence of elderly patient population (mean ±SD 59.5±11.8 years) and presence of previous coronary artery disease patients were more common. In a study by Das et al. [15] conducted with 479 patients, the mean age range was 58±13 years and number of patients with history of previous coronary artery disease was 234 (48%). These values were similar to the values of our study. When the blood samples of the patients with more major cardiac events were evaluated, we noticed that in the fQRS group, the cardiac enzymes (Troponin-I, CK-MB) were significantly higher than in the control group (p<0.001). Along with the cardiac enzyme level elevation, as in the same patient group, the ejection fraction measurements were found to be lower by echocardiographic evaluation. The association of these 2 conditions in STEMI suggests that the infarct size in fQRS is larger.

Presence of the fQRS was associated with mortality and MACE in our study. In a cohort study of 85 patients, Ari et al. [16] researched the presence of fQRS and its predictive value on major cardiac events on ECG in the 48th hour post-PCI that was conducted in acute MI (STEMI, NSTEMI). However, in this study the definition of major cardiac events was not clearly defined. In the 6.6±2.3-year follow-up, patients with fQRS had more major cardiac events than those without fQRS (29.4% *vs.* 5.9%). The fQRS was found to be an independent predictor of major cardiac events by multivariate analysis. This study suggests that in patients with STEMI, the presence of fQRS on the ECG performed at the 48th hour was a significant predictor of major cardiac events. In the subgroup analysis of our study, we determined that as the number of derivations increased, the incidence of major cardiac events increased. In particular, the presence of fQRS in ≥4 derivations was found to be associated with MACE. Similar results were observed in the study by Toriqoe et al. [17], who investigated the importance and significance of fQRS in patients with coronary artery diseases. An important difference of our study was that it included STEMI patients, and post-STEMI events were taken as major cardiac events. The ejection fractions (EF) of the fQRS group were observed to be lower in the in-hospital echocardiographic evaluations, suggesting that fQRS can determine the growth of infarct size. Similar findings have been determined in the study by Angue et al., in which the presence of fragmented QRS in patients with acute myocardial infarction was found to be associated with significant decrease in EF [18]. Also, the study by Erdem et al., performed on patients with acute ST elevation myocardial infarction, found a significant negative correlation between fragmented QRS and left ventricular ejection fraction, which supports our findings [19]. While the non-fragmented group's mean EF was 49.93±10.48 (%), the mean EF in patients with ≥4 fragmentations was 38.54±11.84 (%). In the study by Das et al., with 479 patients [15], the mean EF of the non-fragmented group was found to be 63±9 (%), while it was 52±14 (%) in the fragmented group. In our study, the sensitivity of fQRS in predicting major cardiac events was found to be compatible with other studies in the literature. Although significant results were obtained, particularly in STEMI, multicenter prospective studies with larger case numbers are needed. Also, to determine the frequency of major cardiac events, longer follow-up periods are required after STEMI.

Conclusions

Fragmented QRS is an easily identifiable and practical tool that can be used for predicting in-hospital cardiac events in acute coronary syndromes. In the presence of fQRS, it should be kept in mind that the patient may be at risk for adverse cardiac events. The most important risk factor for predicting in-hospital major cardiac events was found to be a fragmentation on ECG. In subgroup analyses, various types of fragmentation and number of fragmented derivations were found to be associated with MACE. Our data also shows the relationship between the fragmentation and extent of infarction in STEMI.

Limitations of the study

The limitations of this study included the absence of long-term follow-up and the absence of consensus among physicians in the literature for the diagnosis of fragmentation.

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