ORIGINAL ARTICLE

Significance and Usefulness of Narrow Fragmented QRS Complex on 12-Lead Electrocardiogram in Acute ST-Segment Elevation Myocardial Infarction for Prediction of Early Mortality and Morbidity

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Background: The presence of notched R or S waves without accompanying typical bundle branch blocks, or the existence of an additional wave like RSR′ pattern in the original QRS complex (with a duration of <120 ms) has been defined as narrow QRS fragmentation. Persistence of the fQRS found on the admission electrocardiogram (ECG) in patients with acute ST segment elevation myocardial infarction (STEMI) will have prognostic significance in the short term.

Methods: The study was carried out using retrospectively collected data of 296 consecutive patients diagnosed as acute STEMI .fQRS group had fQRS both in admission and latest ECGs (n = 80, 27%), and non-fQRS group had no fQRS in last ECG (n = 216, 73%). Primary end points were in-hospital cardiovascular mortality, hemodynamic instability, and electrical instability.

Results: MI localization, symptom duration, reperfusion therapy (RPT) rate, RPT modality, rate of successful reperfusion did not differ. Mean ejection fraction was lower and all end points were more frequent in the fQRS group. Irrespective of the RPT modality and success of RPT, mortality rate was higher in patients with persistent fQRS. GRACE score >120 points (OR = 4.765), age >70 years (OR = 4.041), anterior MI localization (OR = 3.148), and presence of fQRS (OR = 2.484) were significant predictors of primary end points. fQRS increased the predictive ability of GRACE score >120 about two folds (OR = 7.305, P < 0.001).

Conclusion: Persistent fQRS on ECG is associated with poor prognosis and there is a lack of expected mortality benefit of RPT, particularly that of fibrinolytic therapy, in STEMI patients with fQRS.

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fragmented QRS; ST elevation; myocardial infarction; mortality

The presence of notched R or S waves without accompanying typical bundle branch block, or the existence of an additional wave like RSR′ pattern in the original QRS complex (with a duration of <120 ms) has been defined as QRS fragmentation.[1] Fragmented QRS (fQRS) originates from abnormal ventricular depolarization due to nonhomogeneous electrical activation of ischemic and/or injured ventricular myocardium. fQRS is an electrocardiographic sign of heterogeneous ventricular conduction delay around myocardial scar tissue.[2] fQRS was first demonstrated in experimentally stimulated canine heart, convalescing after acute MI. It was encountered more frequently in healed infarctions with an age of >2 weeks.[3,4] The presence of fQRS has increased the diagnostic performance of ECG in the recognition of old MI, when added to Q wave analysis.[1]

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The presence of fQRS without accompanying Q waves on ECG, has been able to diagnose ischemic heart disease (IHD) with a sensitivity of 62% and a specificity of 94%, and the existence of additional Q waves has increased the sensitivity of fQRS to 92.4%.[5–8] The presence of fQRS in patients with IHD was demonstrated to be an independent predictor of decreased myocardial perfusion and functional deterioration, and a reflection of marked left ventricular (LV) dilatation and decreased ejection fraction (EF).[9–11] fQRS has been recognized as a predictor of high mortality and recurrence of cardiac events, irrespective of the presence or absence of Q waves.[12, 13]

fQRS has been found to be associated with high mortality and arrhythmic events in coronary artery disease (CAD) and acute coronary syndromes (ACS). The presence of narrow (<120 ms) or wide (≥120 ms) fQRS complex on ECG of patients with known or suspected CAD, has been shown to demonstrate myocardial scarring.[14] fQRS was also able to predict arrhythmic events in patients with ischemic or nonischemic cardiomyopathy.[3, 15]

The aim of this study was to investigate the prognostic significance of the persistence of the fragmentation of the original QRS complex (with a duration of <120 ms) found on the admission ECG in patients with acute ST segment elevation myocardial infarction (STEMI). The role of persistent fQRS in the prediction of early prognosis alone or in combination with established clinical risk scoring systems was also investigated.

METHODS

The study was carried out using retrospectively collected data of 296 consecutive patients diagnosed as acute STEMI and admitted to a university hospital between years 2007–2012. The study complies with the Declaration of Helsinki, and study protocol was approved by the local ethics committee. All patients had ST segment elevation of ≥2 mm in ≥2 contiguous precordial leads and/or ≥1 mm in ≥2 contiguous limb leads (II, III, aVF, and I, aVL). Patients with prior history of myocardial infarction, those with bundle branch blocks and/or evidence of prior myocardial infarction as depicted by Q waves in electrocardiograms prior to hospitalization for the index event were excluded from the study. The presence of notching in R or S waves or additional R waves in the original QRS complex (<120 ms) and without typical bundle branch block pattern in at least two contiguous leads related to a major coronary artery area was the definition used for fQRS. The presence of fQRS was also investigated using the last available in-hospital ECG and patients were divided into two groups as follows: fQRS group consisting of patients with persistent fQRS, that is, presence of fQRS both in admission and latest ECGs (n = 80, 27%), and non-fQRS group consisting of patients without persistent fQRS, that is, no fQRS in last ECG, irrespective of the initial ECG findings (n = 216, 73%).

The following parameters were investigated: demographic characteristics, localization of MI, LV EF measured by transthoracic echocardiography (TTE) performed within the week of hospital discharge, drug therapy given in the first 24 hours after admission, duration of symptoms suggestive of myocardial ischemia at presentation, mode of reperfusion therapy, presence of successful reperfusion, in-hospital MI complications (hemodynamic and electrical instability), mortality, and coronary angiography findings in terms of number of vessels with ≥70% stenosis. Successful reperfusion was defined as ≥70% resolution of baseline ST segment elevation 90–120 minutes after the onset of thrombolytic therapy or restoration of TIMI-3 flow in infarct-related artery in patients undergoing primary percutaneous coronary intervention (PCI). Standard TTE was carried out using a System V echocardiography machine (GE, Vingmed Ultrasound AS, Horten, Norway). LV EF value was determined with Simpson's method of discs using 2-dimensional images.

Primary end points were defined as in-hospital cardiovascular mortality, hemodynamic instability and electrical instability. Hemodynamic instability was defined as new onset acute heart failure or cardiogenic shock or hypotension (systolic blood pressure ≤95 mmHg) not due to vasodilator drugs and despite adequate fluid therapy. Electrical instability was defined as development of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and atrioventricular (AV) block.

GRACE and TIMI scores were calculated in order to evaluate the association between fQRS and risk factors predictive of study end points.[16, 17] The predictive utility of persistent fQRS was investigated alone and when fQRS was added to models incorporating TIMI or GRACE scores.

Statistical Analysis

All statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). A P value <0.05 was considered to be statistically significant. The values were expressed as mean ± standard deviation. Variables were analyzed for the presence of normal distribution using Kolmogorov–Smirnov test. Differences of variables between the groups were assessed using the independent samples Student's t or Mann–Whitney U test. Associations between categorical variables were evaluated using the chi-square or Fisher's exact tests. Multivariate regression (backward stepwise method) was used to evaluate the factors affecting the presence of primary end points. Hosmer and Lemeshow test ($P > 0.05$) was used to assess regression models.

RESULTS

The mean age of the study population was 60.98 ± 12.84 years and there were more males (76.4%). When the two groups were compared, there were no differences with respect to demographic characteristics except sex: number of female cases were significantly lower in the fQRS group (Table 1). The clinical, echocardiographic and angiographic characteristics of the patients are demonstrated (Table 2). There was no difference between the groups in terms of MI localization. When duration of chest pain was considered, 95.9% of the patients were admitted within 12 hours, and 91.2% were admitted within 8 hours of symptom onset. There was no difference between fQRS and non-fQRS groups with regard to the distribution of patients admitted with a chest pain duration of <8 hours.

No significant difference was found in terms of the standard medical therapy (aspirin, clopidogrel, beta-blockers, angiotensin converting enzyme [ACE] inhibitors) administered in the first day of admission (Table 2).

Acute reperfusion therapy (RPT) was administered to 94.25% of the patients. Seventeen patients (2 in the fQRS, 15 in the non-fQRS group) did not receive RPT of any form. Fibrinolytic treatment was given to 60.81% of the cases (accelerated tPA in 98.8%, streptokinase only two patients) and primary PCI was utilized in the rest.

There was no difference with regard to number of patients receiving RPT, and the RPT modality utilized. There was also no difference in terms of reperfusion success when fQRS and non-fQRS groups were compared (81.25% vs 87.12%)

In 27.4% of the cases, LV EF was found to be <35% by TTE. The percentage of patients with EF values <35% was significantly higher in the fQRS group. The mean EF value of the fQRS group was also significantly lower compared to the non-fQRS group (Table 2).

Coronary angiography was performed in 95% of the cases and three-vessel CAD was demonstrated in 44.9%. The frequency of three-vessel disease was significantly higher in the fQRS group, compared to the non-fQRS patients (Table 2).

Overall in-hospital mortality was demonstrated to be 9.5%. All the end primary end points of the study, including mortality, hemodynamic instability, and electrical instability, were observed to be significantly more frequent in the fQRS group (Table 3). There were 34 cases with electrical instability (21 VT, 3 VF, 10 AV block [5 first degree, two 2:1, 3 complete]) in the fQRS group and 40 cases with electrical instability (19 VT, 7 VF, 14 AV block [12 first degree, 2 complete]) in the non-fQRS group. When AV blocks were omitted, there were still significantly more patients with electrical instability in the fQRS group (30% vs 12%, $P = 0.0002$). When patients with anterior MI were compared to patients with inferior MI, there were no differences in terms of mortality, hemodynamic instability and electrical instability ($P = 0.20$, $P = 0.17$, $P = 0.61$, respectively). Similar findings with regard to mortality, hemodynamic instability and electrical instability were noted when prognosis of anterior MI was compared to inferior MI in fQRS and non-fQRS groups ($P = 0.79$, $P = 0.29$, $P = 0.12$, respectively in the fQRS group and $P = 0.12$, $P = 0.35$, $P = 0.50$, respectively in the non-fQRS group).

When mortality was evaluated in patients who had received any form of RPT, it was found to be significantly higher in patients with persistent fQRS, compared to the ones without persistent fQRS (Table 4). When mortality rate was investigated with respect to the utilized RPT method, it was found to be higher in the fQRS group among patients receiving FLT and also among patients undergoing primary PCI. Irrespective of the RPT modality utilized, mortality rate was higher in the fQRS group when only patients with successful reperfusion were considered (Table 4).

The frequency of persistent fQRS was found to be higher (71.4%) among patients who died

Table 1. Demographic Characteristics of the Patient Group

Parameter	fQRS Group (n = 80)	Non-fQRS Group (n = 216)	All Patients (n = 296)	P Value
Female sex (%)	12.5	27.8	23.6	0.006
Age (years)	60.90 ± 13.02	61.05 ± 12.89	60.98 ± 12.84	0.951
Diabetes mellitus (%)	35.0	22.2	25.7	0.114
Smoker (%)	65.0	62.0	62.8	0.74
Hypertension (%)	52.5	50.9	51.4	0.865
CAD (%)	22.5	22.2	22.3	0.971
CABG/PCI (%)	17.5	13.0	14.2	0.482

CAD = history of coronary artery disease; CABG/PCI = history of coronary artery bypass grafting or percutaneous coronary intervention; fQRS = narrow fragmented QRS complex on electrocardiogram.

Table 2. Clinical Characteristics of the Patient Group

Parameter	fQRS Group (n = 80)	Non-fQRS Group (n = 216)	All Patients (n = 296)	P Value
Anterior MI (%)	60	55	56.41	0.44
Inferior MI (%)	35	42.12	40.2	0.26
RV MI (%)	5	2.77	3.37	0.34
LV EF (%)	37±11	44±13	42±13	0.003
LV EF < 35% (%)	45	20.8	27.36	0.00003
Three-vessel disease (%)	50	33.3	44.9	0.009
Symptom onset < 8 hours (%)	87.5	92.6	91.2	0.331
Symptom onset < 12 hours (%)	97.5	95.4	95.9	0.994
Acetylsalicylic acid* (%)	100	98.14	98.64	0.22
Clopidogrel* (%)	100	96.29	97.29	0.08
Beta-blocker* (%)	70	69.44	69.59	0.92
ACE-I* (%)	65	53.7	56.75	0.08
RPT (%)	97.5	93.05	94.25	0.14
Primary PCI (%)	30	34.72	33.44	0.44
Fibrinolytic therapy (%)	67.5	58.33	60.81	0.15

fQRS = narrow fragmented QRS complex on electrocardiogram; MI = myocardial infarction; RV = right ventricle; LV EF = left ventricular ejection fraction; ACE-I = angiotensin converting enzyme inhibitor; RPT = reperfusion therapy; PCI = percutaneous coronary intervention; (*) = drugs administered within 24 hours of infarction.

Table 3. Clinical End Points of the Study

End Point	fQRS Group (n = 80)	Non-fQRS Group (n = 216)	All Patients (n = 296)	P Value
Hemodynamic instability (%)	62.5	32.4	40.5	<0.001
Electrical instability (%)	42.5	18.5	25	<0.0001
Mortality (%)	20	5.5	9.5	<0.001

fQRS = narrow fragmented QRS complex on electrocardiogram.

(P < 0.001). The mean TIMI and GRACE risk scores were also significantly higher among patients who died, compared to the rest of the patient group (TIMI scores: 8.00 ± 2.59 vs 3.57 ± 2.2, P < 0.001 and GRACE scores: 136.68 ± 33.1 vs 207 ± 44.7, P < 0.001, respectively). There were significantly more patients with TIMI score >7 (66.7%) and GRACE score >120 (93.3%) in patients who had any primary end point (P < 0.001 in either case).

In the regression model constructed from variables found to be related with occurrence of primary end points in the univariate analysis, GRACE score >120 points (OR = 4.765), age >70 years (OR = 4.041), anterior MI localization (OR = 3.148) and presence of fQRS (OR = 2.484) were demonstrated to be significant predictors of primary end points (Table 5). However, TIMI score >7 points, hospital admission <8 hours of the

Table 4. Reperfusion Therapy and Mortality

	Mortality (%)		
Reperfusion Therapy	fQRS Group (n = 78)	Non-fQRS Group (n = 201)	P Value
RPT	20.5	5.97	0.0002
Successful RPT	13.84	2.84	0.001
Unsuccessful RPT	53.84	28	0.11
FLT	25.9	9.52	0.004
Successful FLT	16.27	4.54	0.01
Unsuccessful FLT	63.63	43.75	0.3
PCI	8.33	0	0.01

fQRS = narrow fragmented QRS complex on electrocardiogram; RPT = mortality in patients who received reperfusion therapy; FLT = mortality in patients who received fibrinolytic treatment; PCI = mortality in whom primary percutaneous coronary intervention was performed (there were no unsuccessful percutaneous interventions).

Table 5. Predictors of Primary End Points (Hemodynamic Instability, Electrical Instability or Mortality)

Predictor	Odds Ratio	95% Confidence Interval	P Value
Presence of fQRS	2.484	1001–6162	0.05
Anterior MI localization	3.148	1403–7062	0.005
Age > 70 years	4.041	1477–11,058	0.007
GRACE score > 120 points	4.765	1922–11,813	0.001

fQRS = narrow fragmented QRS complex on electrocardiogram; MI = myocardial infarction.

onset of chest pain and administration of RPT were not independently predictive of clinical end points.

When the effect of the presence of fQRS in the constructed regression model on occurrence of primary end points was investigated, fQRS (OR = 2.617, P = 0.0029) increased the predictive ability of GRACE score >120 about two folds (OR = 7.305, P < 0.001).

DISCUSSION

In this study, the early prognostic significance of the presence of narrow (<120 ms) fQRS on admission ECG in patients with acute STEMI was investigated, for the first time according to the literature, to the best of our knowledge. Fragmented QRS complex frequency was found to be 27% in acute STEMI. Patients with fQRS had lower mean LV EF values and more three-vessel CAD compared to the non-fQRS group. The presence of persistent narrow fQRS on the ECG was found to be significantly correlated with in-hospital hemodynamic and electrical instability, as well as mortality. When added to traditional risk predictors such as GRACE score >120, age >70 years, and anterior localization of MI, fQRS was able to increase the predictive ability of models constructed. Interestingly, administration of RPT, duration of MI symptoms at presentation and TIMI score >7 were not found to be independent predictors of end points, contrary to expectations. Possible reasons for this finding may include the inability of reported symptom onset in reflecting the actual onset of MI, the actual presentation delays of the patients to be more than self-reported durations, and late administration of RPT.

The frequency of fQRS on ECG has been previously reported to be ranging from 34.9% to 60.1%, in patients with acute coronary syndrome.[1,2,18] The presence of fQRS has been reported to predict mortality in CAD patients in general, and NSTE acute coronary syndrome patients in particular.[13,14,18] fQRS has been demonstrated to form within about 24–48 hours of the symptom onset and persist thereafter, predicting cardiac events in CAD patients.[4,8,19] In acute MI patients, it has been reported to independently predict low LV EF and infarct burden by cine magnetic resonance imaging, and in patients receiving RPT, no-reflow phenomenon.[8,19]

The principal treatment strategies of STEMI, RPT rates and percentage of patients with reperfusion success did not significantly differ between fQRS and non-fQRS groups. However, although most of the patients (>90%) received timely RPT (<8 hours after symptom onset, in the period the therapy is expected to be most effective) surprisingly, the mortality benefit could not be observed in the fQRS group, especially in patients receiving FLT, to the anticipated extent. Furthermore, this finding was observed

irrespective of applied RPT modality or outcome of RPT in terms of reperfusion success, among patients in the fQRS group.

The acute MI mortality in our study was 9.5%. Although evidence-based reperfusion modalities with standard adjunctive and conjunctive STEMİ therapies were similarly used in both groups, the mortality of fQRS group was almost 3.5 times higher compared to the non-fQRS group (20% vs 5.5%).This may be explained by: (a) factors well-recognized in their association with increased mortality, like GRACE score >120, TIMI score >7, increased rate of three-vessel CAD, were present significantly more frequent in the fQRS group; (b) in 2/3 of patients, FLT, which is recognized to be less efficacious, was used in the place of primary PCI; (c) mortality in fQRS patients receiving RPT was higher irrespective of the presence or absence of successful reperfusion.

Although in >90% of the cases RPT was utilized, patients in the fQRS group had higher mortality irrespective of the RPT modality used or the treatment outcome. Probable explanations for this finding include: (a) three-vessel CAD was observed at a higher rate in the fQRS group, which may increase the area of myocardium at jeopardy; (b) occurrence of hemodynamic and electrical instability, which have been demonstrated to be associated with larger areas of ischemic and fibrotic myocardium characterized with its unstable nature in patients with acute coronary syndromes,[1] was significantly more frequent in the fQRS group; (c) failure of RPT, especially in cases of FLT, may be associated with onset of acute infarction taking place before the onset of reported symptoms, as demonstrated in experimental studies related to fQRS.[3,20] fQRS well may be a sign of previous non-Q wave MI or transmural infarction without the development of Q waves;[4,21] (d) application of FLT as a RPT strategy in about 60% of the cases with fQRS may be associated with increased mortality because FLT has been reported to be less efficacious in acute MI with rather delayed presentation and hemodynamic compromise.[22,23]

Presence of narrow fQRS on ECG of STEMI patients at admission may be a late electrophysiologic manifestation of a prior myocardial injury and/or scar rather than a new finding of index acute myocardial ischemia/infarction process, as generally considered. Narrow fQRS was found to be associated with larger infarcts and left ventricular dysfunction, which are indicative of increased mortality. The occurrence of narrow fQRS on ECG was found to be a significant predictor of malignant ventricular arrhythmias and hemodynamic compromise, as well as mortality, just like standard complex clinical risk scores like TIME and GRACE.

Remarkable finding of our study is the close association of fQRS with poor prognosis, and the lack of expected mortality benefit of reperfusion therapy, particularly with FLT, in STEMI patients with fQRS. This was observed even in patients with successful clinical reperfusion, a finding which may be explained by possibility of late presentation and presence of severe hemodynamic disturbances. We suggest that in STEMI patients with fQRS who receive FLT as RPT, the assessment of reperfusion success by clinical means may be suboptimal, possibly due to the high rate of no-reflow or slow flow phenomenon (malperfusion). Thus, in patients with fQRS, intensive therapies directed at myocardial preservation and stabilization should be used along with primary PCI, and keeping high probability three-vessel in mind, mechanical support and hybrid reperfusion strategies with coronary bypass grafting should be utilized in unstable patients as needed.

Limitations

RPT was administered only to 94.25% of the patients enrolled in the study. Although there was no difference with regard to number of patients receiving RPT, RPT modality utilized and RPT success between fQRS and non-fQRS groups, presence of patients with no RPT may be considered as a limitation during the interpretation of our findings.

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