ORIGINAL RESEARCH

Predictive value of the fragmented QRS complex in 6-month mortality and morbidity following acute coronary syndrome

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Background: Fragmented QRS encompasses different RSR' patterns showing various morphologies of the QRS complexes with or without the Q wave on a resting 12-lead electrocardiogram. It has been shown possibly to cause adverse cardiac outcomes in patients with some heart diseases, including coronary artery disease. In view of the need for risk stratification of patients presenting with acute coronary syndrome in the most efficacious and cost-effective way, we conducted this study to clarify the value of developing fragmented QRS in a cohort of patients presenting with their first acute coronary syndrome in predicting 6-month mortality and morbidity.

Methods: One hundred consecutive patients admitted to the coronary care unit at Shahid Madani Heart Center in Tabriz from December 2008 to March 2009 with their first acute coronary syndrome were enrolled in this prospective study. Demographic and electrocardiographic data on admission, inhospital mortality, and need for revascularization were recorded. Electrocardiography performed 2 months after the index event was examined for development of fragmented QRS. Mortality and morbidity was evaluated at 6-month follow-up in all patients.

Results: The patients were of mean age 57.7 ± 12.8 years, and 84% were men. The primary diagnosis was unstable angina in 17 (17%) patients, non-ST elevation myocardial infarction (MI) in 11 (11%), anterior or inferior ST elevation MI in 66 (66%), and postero-inferior MI in six (6%). Fragmented QRS was present in 30 (30%) patients during the first admission, which increased to 44% at the 2-month follow-up and to 53% at the 6-month follow-up. The presence of various coronary risk factors and drug therapy given, including fibrinolytic agents, had no effect on development of fragmented QRS. Mortality was significantly higher ($P = 0.032$) and left ventricular ejection fraction was significantly lower ($P = 0.001$) in the fragmented QRS group at the 6-month follow-up.

Conclusion: This study strongly suggests that fragmented QRS on initial presentation with acute coronary syndrome is not predictive of subsequent events but, if present 6 months later, could be predictive of an adverse outcome.

Keywords: acute coronary syndrome, fragmented QRS, electrocardiography, mortality, left ventricular function

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Introduction

Experimentally induced myocardial ischemic scarring in canine models gave rise to the first presentation of fragmented QRS on electrocardiography (ECG). Fragmented QRS was also more likely to be seen in areas of healed myocardial infarction (MI) 2 weeks after the index event than earlier.[1] Fragmented QRS complexes are defined as the presence of an additional R wave (R') or notching in the nadir of

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the S wave, or the presence of more than one R' in two contiguous leads, corresponding to a major coronary artery territory on the resting 12-lead ECG. Fragmented QRS is also defined as different RSR' patterns with or without Q waves on a resting 12-lead ECG.[2,3]

Previous studies have suggested that the regional myocardial scar may be associated with changes in QRS configuration, leading in turn to terminal conduction delay or fragmentation of the QRS complex on a 12-lead ECG.[4,5] Its association with scarring from prior MI is well documented.[6–8]

The fragmented QRS may be the sole evidence of previous silent myocardial infarctions, that has a significantly high incidence in females with atypical chest pain, diabetes mellitus, in elderly and those with dementia[6]. The presence of fragmented QRS in susceptible patients increases the risk of adverse cardiac events, including MI, need for revascularization, cardiac death, and all-cause mortality in patients with known ischemic heart disease.[9] It has also been suggested that fragmented QRS in patients with a history of Q wave MI heralds a higher risk of recurrent cardiac events, such as fatal or nonfatal MI.[10]

However, fragmented QRS is not specific for coronary artery disease, and is also seen in other myocardial diseases, including cardiomyopathy and congenital heart disease.[11,12] For instance, the presence of fragmented QRS is reported to be a predictor of episodes of ventricular fibrillation in patients with the Brugada syndrome.[12]

Unfortunately, relevant information is scarce from low and middle income countries, including Iran. Considering the simplicity and cost-effectiveness of distinguishing fragmented QRS on ECG and its potential prognostic value, more research in different populations is needed to develop a stronger body of knowledge. The aim of this study was to assess the role of fragmented QRS in predicting mortality and morbidity 6 months after the index event.

Materials and methods

One hundred consecutive patients admitted to the coronary care unit at Shahid Madani Heart Center in Tabriz from December 1, 2008 to March 1, 2009 with their first acute coronary syndrome (ACS) were enrolled in this prospective study. Patients with complete or incomplete bundle branch block, bradycardia, major comorbidity such as pulmonary or renal failure, a prior history of MI, a prior history of revascularization (coronary artery bypass grafting or percutaneous coronary intervention), or pacemaker implantation, as well as those receiving cardiac glycosides or being younger than 40 years of age were excluded.

The diagnosis of ACS was made on the basis of a history suggesting chest pain of cardiac origin, presence of risk factors for coronary artery disease, physical examination, echocardiographic findings, and/or ECG changes, with or without elevations of cardiac biomarkers. Patients were further categorized as having unstable angina (no cardiac enzyme rise), non-ST elevation MI (a rise in cardiac enzymes without ST elevation on a 12-lead ECG) and ST elevation MI (ST elevation on ECG). Acute non-ST elevation MI was defined by detection of elevated cardiac biomarkers (cardiac troponin I and creatine kinase MB), with ≥1 point above the 99th percentile of the upper reference limit, together with evidence of myocardial ischemia, which included typical symptoms of myocardial ischemia, and ST-T changes indicative of new ischemia or pathologic Q waves seen on ECG.

Diagnosis of acute ST elevation MI was made by detection of new or presumed new ST segment elevation at the J point in at least two contiguous leads of ≥0.2 mV in leads V1, V2, or V3 and ≥0.1 mV in other leads. ST elevation in anteroseptal MI (leads V1-V3), inferior MI (leads II, III, aVF), anterior MI (leads V1-V6), high lateral MI (leads I and aVL). Marked ST depression, which was maximal in leads V1–V3, without ST segment elevation in other leads, was deemed to represent posterior wall MI and was included in the ST elevation MI group.

Patients were treated according to current standard guidelines for ACS and underwent coronary angiography at the discretion of the attending cardiologist. The patients were contacted 2 months after the index event to follow up on morbidity and mortality data. On the basis of a resting 12-lead ECG obtained 60 days after the index event, the patients were categorized as being with or without pathologic Q waves and with and without fragmented QRS. The ECG recordings taken were similar to routine 12-lead ECG recordings but used low/high pass filters. A paper speed of 25 mm per second and a voltage of 1 mm per meter was used. The definition of fragmented QRS used in this study was based on the definition proposed by Das et al,[6] ie, the presence of an additional R wave (R') or notching in the nadir of the S wave, or the presence of more than one R' in two contiguous leads, corresponding to a major coronary artery territory on the resting 12-lead ECG. ECG interpretations was made by consensus between two cardiologists.

All patients were followed up for at least 6 months, during which monthly contact by telephone or office visits was made as necessary, and any interventional therapy and/or occurrence of study endpoints (readmission, revascularization, death)

were recorded. At the end of this period, the patient's clinical status, ECG, and echocardiogram were evaluated repeatedly over the study period. The primary endpoint of the study was mortality rate in patients presenting with ACS with and without fragmented QRS. Secondary endpoints included recurrence of ACS, any changes in left ventricular ejection fraction, and need for revascularization during a 6-month follow-up period.

Statistical analysis

Continuous variables were reported as the mean ± standard deviation and categorical variables as frequencies and percentages. Comparisons of continuous variables were based on two-sample Student's *t*-tests, and comparisons of proportions were based on Chi-square and Fisher's exact tests. A P value < 0.05 was considered to be statistically significant. Multivariate analysis was also used to control for the confounding effect of factors related to the severity of the condition.

The institutional review boards of Tabriz University of Medical Sciences approved the study protocol, and written informed consent was obtained from all patients after full discussion of the study process with the patients and their families. This study was performed as a thesis project and was registered at the Cardiovascular Research Center of Tabriz University of Medical Sciences (87/3-6/7).

Results

The mean age of the patients was 57.7 ± 12.8 years, with 84 (84%) being male and 16 (16%) female. The primary diagnosis was unstable angina in 17 (17%), non-ST elevation MI in 11 (11%), anterior or inferior ST elevation MI in 66 (66%), and postero-inferior MI in 6 (6%). Fragmented QRS was present in 30 (30%) patients during their first admission. Seventeen fragmented QRS complexes (57%) were located in the anterior leads and 13 (43%) in the inferior leads. Table 1 compares factors possibly contributing to development of fragmented QRS between the two groups. Baseline left ventricular function and severity of coronary artery disease were not significantly different between the two groups, and the need for revascularization during the index event was also similar. Data for patients with and without fragmented QRS at presentation are shown in Table 2.

Eighty-four patients (84%) attended the 2-month follow-up visit. At this time, 44 (52.4%) had fragmented QRS and 40 (47.6%) did not. A second analysis was then done to re-evaluate the role of potential causes of fragmented QRS, and showed that none of the potential risk factors

Table 1 Possible contributory factors in developing fragmented QRS

	Patients (n = 100)	With fQRS 30 (30%)	Without fQRS 70 (70%)	P-value
Hypertension	36 (36%)	11 (36.6%)	25 (35.7%)	0.52
Diabetes	17 (17%)	5 (16.7%)	12 (17.1%)	0.5
Smoking	47 (47%)	10 (33.3%)	37 (52.8%)	0.10
Hyperlipidemia	28 (28%)	10 (33.3%)	18 (25.7%)	0.34
Family history of CAD	15 (15%)	4 (13.3%)	11 (15.7%)	0.58
Thrombolytic therapy	37 (37%)	12 (60%)	25 (54.3%)	0.44
Elevated CPK	65 (65%)	20 (83.3%)	45 (77.6%)	0.39
Elevated cardiac troponin I	61 (61%)	16 (72.7%)	45 (72.7%)	0.60

Abbreviations: CAD, coronary artery disease; fQRS, fragmented QRS; CPK, creatine phosphokinase.

(hypertension, $P = 0.59$; diabetes, $P = 0.25$; smoking, $P = 0.41$; hyperlipidemia, $P = 0.20$; positive family history of coronary artery disease, $P = 0.10$) or prescribed medications (beta blockers, $P = 0.43$; calcium channel blockers, $P = 0.50$; angiotensin-converting enzyme inhibitors, $P = 0.30$; streptokinase, $P = 0.44$) had a significant association with the development of fragmented QRS. There was no difference in the rate of readmission, need for coronary angiography ($P = 0.53$), percutaneous coronary intervention ($P = 0.44$), or coronary artery bypass grafting ($P = 0.65$) between patients with and without fragmented QRS during this 2-month follow-up period.

Thirty patients had fragmented QRS at the time of first admission, and this number increased to 44 at 2-month follow-up and further to 53 at 6-month follow-up.

Similar follow-up was undertaken at 6 months. Of the 90 (90%) patients who completed their 6 months of follow-up, fragmented QRS was present in 53 (58.9%).

Table 2 Data of patients with and without fragmented QRS at the time of presentation

	Patients (n = 100)	With fQRS 30 (30%)	Without fQRS 70 (70%)	P-value
LVEF	41.2	41.2	42.2	0.73
Elective CAG	70 (70%)	23 (76.6%)	47 (67.1%)	0.2
CAG findings				
1. vessel disease	27 (39.7%)	7 (31.8%)	20 (43.5%)	0.4
2. vessel disease	22 (32.4%)	8 (36.4%)	14 (30.4%)	
3. vessel disease	19 (27.9%)	7 (31.8%)	12 (26.1%)	
LV dysfunction	51 (51%)	12 (44.4%)	39 (44.8%)	0.58
PCI	57 (57%)	16 (53.3%)	41 (59%)	0.44
CABG	18 (18%)	8 (26.6%)	10 (14.2%)	0.42

Abbreviations: CABG, coronary artery bypass grafting; CAG, coronary angiography; LV, left ventricular; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; fQRS, fragmented QRS.

The readmission rate ($P = 0.37$) and need for percutaneous coronary intervention or coronary artery bypass grafting ($P = 0.64$) were not different between the groups with and without fragmented QRS. At the end of month 6, mean left ventricular ejection fraction was 45.6% ± 12.9% in those with fragmented QRS and 54.3% ± 9.9% in those without (Table 2), and this difference were statistically significant ($P = 0.001$). Twenty-two (51.2%) patients who had fragmented QRS at 2 months had left ventricular dysfunction at 6 months, and 12 (30.8%) patients without fragmented QRS at 2 months had left ventricular dysfunction at 6 months ($P = 0.04$). Four (9%) patients in the group with fragmented QRS and one (2.7%) in the group without fragmented QRS died during this period, and the difference was statistically significant ($P = 0.032$). Three of four (75%) deaths in the fragmented QRS group were the result of sudden cardiac death. Multivariate analysis showed results consistent with bivariate analysis with respect to detection of values that were statistically significant.

Discussion

The prognosis of MI in both the short term and the long term has greatly improved over the past two decades as a result of the introduction of effective measures to decrease infarct size and treat residual ischemia. However, in a considerable number of patients, even without recurrent MI, the clinical course is that of progressive heart failure, with an adverse outcome.[14–17] Several clinical parameters have been shown to be associated with progression of heart failure and cardiac death, including older age, prior MI, and diabetes. Increased fragmentation of the QRS complex on a 12-lead ECG has been shown to predict cardiac events, including arrhythmia, heart failure, and death in patients with coronary artery disease.[9,10] We evaluated the role of various risk factors of coronary artery disease and different medications on development of fragmented QRS and found that none had a predictive role. Further, the likelihood of fragmented QRS did not change in patients who received thrombolysis. This issue has not been addressed in previous studies.

The mechanism of QRS complex fragmentation seen on the surface 12-lead ECG has been explained as inhomogeneous activation of the ventricles because of myocardial scarring and/or ischemia.[5] Earlier research has defined notching of the QRS wave after an MI as peri-infarction conduction block, which can also be defined as fragmented QRS.[13] The potential mechanism of fragmentation is supported by autopsy findings in patients with MI and left ventricular aneurysm confirming the presence of significant myocardial necrosis, with "islands" of viable myocardial tissue interspersed in fibrous tissue.[1,8,18,19]

The regions of chronically ischemic myocardium show slow activation as a result of partially depolarized and depressed velocity of the action potential upstroke, and the ischemic myocardium is probably responsible for inhomogeneous activation of the left ventricle.

In our study, inhospital mortality was not different between those with and without fragmented QRS. However, as in other studies,[9–11,20–22] out-of-hospital mortality during follow-up was significantly higher in patients with fragmented QRS ($P = 0.032$). Except for one case, this mortality was sudden in patients with fragmented QRS. This may indicate an arrhythmic substrate presenting on the surface ECG as fragmented QRS. Interestingly, Pietrasik et al[10] showed that the presence of persistent Q waves on the ECG in patients with Q wave MI during the stable post-infarction period (2 months after MI, on average) was associated with a more favorable prognosis than in patients with resolved Q waves. In those with resolved Q waves, fragmentation of the QRS complex, identified independently of the presence of Q waves, was associated with an increased risk of cardiac events. This risk in patients who had resolved Q waves and did not have QRS complex fragmentation was similar to that in patients with persistent Q waves. This finding, together with the sudden nature of cardiac death in most of our patients, indicates that early mortality in patients with fragmented QRS is mostly arrhythmic, whereas in the longer term, heart failure becomes an important mechanism because of remodeling and formation of scar tissue. Korhonen et al[21] showed a higher rate of sudden cardiac death (40%) in their cohort of patients. They also showed that patients who died of heart failure had a higher fragmentation index than those who succumbed to sudden cardiac death.

In present study, 30 patients had fragmented QRS at the time of first admission, which increased to 44 patients at the 2-month follow-up and to 53 at the 6-month follow-up. To determine the time course of appearance of fragmented QRS in patients with coronary artery disease, Das et al studied the serial ECGs of 896 patients with ACS who underwent cardiac catheterization.[20] Serial ECGs were obtained every 6–8 hours during the first 24 hours of diagnosis of MI and during the subsequent 24 hours. Fragmented QRS developed within 48 hours of presentation in 51% of patients who had MI as compared with only 3.7% of patients who had unstable angina. Also, in a recent analysis, they showed that approximately half of their patients with ACS and non-ST elevation MI developed fragmented QRS within 48 hours of presentation.[23] To the authors' knowledge, ours is the only study which has evaluated the possible appearance of

fragmented QRS over longer-term follow-up, and we have shown that some patients may develop fragmented QRS as late as 2 months after the index event. New appearance of fragmented QRS on follow-up ECG was more prevalent in those with Q waves at primary admission. These findings mandate histopathological studies to address the possibility of new necrosis or apoptosis in long-term follow-up of patients with an acute ischemic insult.

There was no significant difference in ejection fraction between patients with and without fragmented QRS on first admission and at 2-month follow-up in the present study. However, at 6-month follow-up, the left ventricular ejection fraction in patients with fragmented QRS was significantly lower than that in those without fragmented QRS, and those with fragmented QRS at the 2-month follow-up had a higher risk of developing left ventricular dysfunction at the 6-month follow-up. This difference in left ventricular function has also been observed in other studies, where gross left ventricular dilation and decreased ejection fraction were found to be faithfully reflected by fragmented QRS on the ECG.[4,5,24] The increase in the number of patients with left ventricular dysfunction without recurrent MI as demonstrated in our study may be a clue to continued remodeling, even in patients without Q wave infarction, which could lead to final development of left ventricular dilatation and failure as well as higher mortality in patients with fragmented QRS.

In our study, the rate of readmission due to heart failure or recurrent ischemic events was not different between those with or without fragmented QRS. This could be explained in part by the low number of readmissions in our cohort. In the study reported by Das et al,[25] patients with coronary artery disease who received an implantable cardioverter defibrillator for primary prevention of sudden cardiac death showed a higher rate of arrhythmic events. Further, Pietrasik et al[10] showed that among patients with history of Q wave MI, fragmented QRS predicted a more than two-fold higher risk of recurrent cardiac events (cardiac death, nonfatal MI) compared with those without fragmented QRS and persistent Q waves. It seems that the short follow-up period in this study was the main cause of this discrepancy.

In our study, the rate of revascularization during the follow-up period was not different between the groups with and without fragmented QRS, and this is most likely related to the higher rate of revascularization (72%) during the index event and the lower number of untreated patients in the follow-up period. Considering the higher rate of recurrent ischemic events and nonfatal MI reported in patients with fragmented QRS,[10] a higher rate of revascularization in these

patients is expected. The most recent study retrieved was by Brenyo et al,[26] who found that fragmented QRS complexes located inferiorly could predict sudden cardiac death/ implantable cardioverter defibrillator shock with a hazard ratio of 1.46. It could also predict sudden cardiac death with a hazard ratio of 2.05. The consistency between our findings and previous research is indicative of the prognostic value of the fragmented QRS complex.

There are some limitations to this study, the main one being the limited duration of follow-up. Although the impact of development of fragmented QRS following ACS is evident even at 6 months after the index event, further follow-up may clarify the potential subgroups that are at particularly high risk. Further, the study was performed at a single center with a relatively small sample size. Finally, patients with ECG evidence of bundle branch block were not enrolled; these patients constitute an important minority of patients with ACS, and there are emerging data suggesting that fragmented QRS is found on their ECGs, which could be a subject for further research.

Conclusion

This study suggests that fragmented QRS on presentation is not predictive of subsequent events, but that fragmented QRS present 6 months later could be predictive of the outcome. Both mortality and left ventricular ejection fraction was lower when fragmented QRS was present. Adding this parameter to the usual clinical and paraclinical determinants of risk in patients with ACS may improve the predictive value of scoring systems.

Disclosure

The authors report no conflicts of interest in this work.

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