ORIGINAL ARTICLE

Fragmented QRS on Admission Electrocardiography Predicts Long-Term Mortality in Patients with Non–ST-Segment Elevation Myocardial Infarction

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Background: Early diagnosis and identification of high-risk non-ST elevation myocardial infarction (NSTEMI) is an important issue. Fragmented QRS (fQRS) complexes are defined as various RSR' patterns on 12-lead resting electrocardiography (ECG). Previous studies revealed that fQRS is related with increased ventricular arrhythmias and cardiovascular mortality. The relation between fQRS and mortality in acute coronary syndromes, mitral valve disease severity and structural heart disease has been shown in different studies. The aim of this study was to investigate relation between fQRS and long-term cardiovascular mortality in NSTEMI patients.

Methods: Patients who admitted to our emergency unit and diagnosed NSTEMI between 2012 and 2013, 433 patients were included prospectively. fQRS complexes determined in 85 patients. Patients were divided into two groups according to fQRS existence. All patients evaluated for their clinical, laboratory, electrocardiographic, and echocardiographic characteristics. Angiographic features of 315 patients who underwent coronary angiography was also recorded. In-hospital, 30-day and 12-month mortality was compared between these groups.

Results: Demographic characteristics and cardiovascular risk factors were similar in both groups except hyperlipidemia. GRACE risk score was higher in patients with fQRS and positively correlated with existence of fQRS. In hospital and 30-days mortality were similar but late mortality was higher in fQRS group. Predictors of late mortality were found to be age, heart rate, male sex in addition to fQRS.

CONCLUSION: We found a relation between fQRS and late mortality. Fragmented QRS may be seen as a cautionary signal for extensive myocardial damage and thereby increased long-term mortality for patients with NSTEMI.

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non-ST elevation myocardial infarction; fragmented QRS; mortality

Coronary artery disease (CAD) is an important cause of morbidity and mortality all over the world. Acute coronary syndrome (ACS) which accounts for an important part of CAD, may be presented as unstable angina pectoris, non-ST elevation myocardial infarction, ST elevation myocardial infarction. Although in hospital early term mortality is higher in STEMI patients, long-term mortality is similar with NSTEMI patients.[1] Early risk stratification and guideline directed medical therapy in according to early intervention is important in these patients to reduce cardiovascular morbidity and mortality.[2] Risk scores, like GRACE or TIMI, are being used for this purpose.

Twelve-lead electrocardiography (ECG) is a very useful tool both for risk stratification and diagnosis in patients with NSTEMI. Dynamic ST segment deviation is an remarkable ECG finding which has

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been validated in the GRACE score was shown to have a prognostic value.[2] Fragmented QRS (fQRS) is another ECG finding that has been shown to have prognostic value in patients with ACS.[3–7] fQRS complexes are defined as various RSR′ patterns with or without Q waves on a 12-lead resting ECG. Various RSR′ patterns include an additional R wave (R′) or notching in the nadir of the S wave, or the presence of >1 R′ (fragmentation) in two contiguous leads, corresponding to a major coronary artery territory.[8]

Previous studies reported the prognostic value of fQRS in very limited patient cohort and was evaluated ECG in 48 hours. As in GRACE risk score, ECG changes on admission shows better prognostic value for early risk stratification and guidance of early invasive strategy. Our purpose was to determine prevalence of fQRS on 12-lead ECG on admission in patients with NSTEMI and to the investigate the relation with long-term mortality.

METHODS

Study Population and Design

Between January 2012 and January 2013, 433 patients (67% men, mean age 62.3 ± 12.8 years) who were hospitalized with NSTEMI were included in the study included prospectively. fQRS complexes determined in 85 (19.6%) patients and 348 (80.4%) patients without fQRS were accepted as control group. Diagnostic definition of NSTEMI were made according to the guidelines.[9] Local ethical committee has approved the study.

Patients with complete or incomplete bundle branch block, bradycardia, major comorbidity such as pulmonary or renal failure, history of pacemaker implantation, as well as those receiving cardiac glycosides were excluded from the study. All patients were examined by an experienced cardiologist immediately after hospitalization. Information obtained pertaining demographic characteristics, history of CAD including previous myocardial infarction and revascularization, family history, the presence of diabetes mellitus (DM), hypertension (HT), smoking and body mass index (BMI) were recorded. All patients were followed up for at least 12 months, during which monthly contact by telephone or office visits was made as necessary, and cardiovascular mortality were recorded. Patients were evaluated and treated according to the guidelines.[9]

ECG Analysis

All ECG analysis were derived from the first ECG recorded in the emergency unit. The ECG recordings taken were similar to routine 12-lead ECG recordings but used low/high pass filters. A paper speed of 50 mm per second and a voltage of 0.5 mm per meter was used. ECG interpretations was made by consensus between two cardiologists. Any disagreement was adjudicated by a third reviewer. Fragmented QRS was defined by the presence of various RSR′ patterns with or without a Q wave and included an additional R wave (R′), notching of the R wave, notching of the downstroke or upstroke of the S wave, or the presence of >1 R′ in two contiguous leads corresponding to a major coronary artery territory. fQRS was defined to be present if found in ≥2 contiguous anterior leads (V_1–V_5), lateral leads (I, aVL, V_6), or inferior leads (II, III, aVF).[8] QRS durations were also measured from surface ECGs.

Coronary Angiography

Three hundred fifteen (72.7%) patients underwent a coronary angiography by the femoral approach using the standard Seldinger's technique. Iopromide as a contrast agent (Ultravist-370, Bayer Schering Pharma, Germany) and a 6F diagnostic catheter were used in all. Diameter stenosis ≥70% with quantitative angiography was accepted as significant.

Statistical Analysis

All data analyzed using IBM SPSS 22.0 (IBM, Armonk, NY, USA). Descriptive statistics is presented as mean ± SD for continuous variables and as numbers and percentages for categorical variables. Continuous variables were analyzed using Student's *t*-test. Repeated measures variance analysis and Bonferroni tests were used for normally distributed groups. Multivariate analysis performed using backward logistic regression analysis. The results were considered significant, when the P value was less than 0.05.

Table 1. Demographic and Clinical Characteristics of Patients

	fQRS (+) n = 85	fQRS (−) n = 348	P Value
Background, demographic, and clinical characteristics			
Age(years)(mean±SD)	63.2 ± 12.9	62.1 ± 12.8	0.640
Female	26 (30.6%)	117 (33%)	0.7
Male	59 (69.4%)	231 (66.4%)	
Hypertension	67 (78.8%)	243 (69.8%)	0.109
Diabetes mellitus	30 (35.3%)	126 (36.2%)	0.90
Hyperlipidemia	31 (36.5%)	82 (23.6%)	0.019
Smoking	27 (31.8%)	86 (24.7%)	0.215
Family history	22 (25.9%)	89 (25.6%)	1.00
Chronic renal disease	12 (14.1%)	33 (9.5%)	0.234
Peripheral artery disease	7 (8.2%)	11 (3.2%)	0.061
CAD history	51 (60%)	152 (43.7%)	0.008
ASA	42 (49.4%)	131 (37.6%)	0.049
ACEI	21 (24.7%)	67 (19.3%)	0.293
BB	21 (24.7%)	70 (20.1%)	0.34
Clinical characteristics on admission			
SBP (mmHg) (mean±SD)	134.3±24.0	136.2±23.0	0.947
DBP (mmHg) (mean±SD)	74.6±16.0	74.7±13.6	0.957
Heart rate (bpm) (mean±SD)	80.8 ± 14.4	78.2 ± 16.3	0.957
GFR (mL/min/1.73 m^2)	70.4 ± 24.7	75.8 ± 25.6	0.08
LVEF (%) (mean±SD)	45.1 ± 13.1	50.5 ± 11.7	0.002
GRACE risk score	132.8 ± 39.3	122.5 ± 35.4	0.019
Electrocardiographic characteristics on admission			
Normal sinus rhythm	76 (89.4%)	321 (92.2%)	0.385
Atrial fibrillation	9 (10.6%)	27 (7.8%)	
ST depression ≥5 mm	40 (47.1%)	95 (27.4%)	0.001
ST depression <5 mm	18 (21.2%)	72 (20.7%)	1.00
LBBB	3 (3.5%)	9 (2.6%)	0.711
QRS duration (ms)	103.0±20.7	95.1±18.3	0.001
Laboratory measurements			
Troponin-I	2.93 ± 7.01	2.71 ± 4.56	0.776
hs-CRP	2.38 ± 3.68	3.32 ± 11.1	0.556
HbA1c	6.81 ± 1.61	6.59 ± 1.61	0.346
Coronary angiography characteristics			
Coronary angiography	56 (65.9%)	259 (82.2%)	0.135
Diseased vessel count	1.64 ± 1.22	1.41 ± 1.15	0.179
Normal coronary artery	1 (1.8%)	18 (7.0%)	0.215
LMCA	3 (5.4%)	8 (3.1%)	0.421
LAD	32 (57.1%)	123 (47.7%)	0.238
CXA	34 (60.7%)	109 (42.2%)	0.017
RCA	37 (66.1%)	122 (47.3%)	0.012
Cardiovascular mortality			
In-hospital mortality	2 (2.4%)	7 (2.0%)	0.692
30-days mortality	2 (2.4%)	9 (2.6%)	1.00
Mortality 12 months	12 (15.2%)	17 (5.4%)	0.006

ACEI = angiotensin converting enzyme inhibitor; ASA = asetylsalisylic asid; BB = beta-blocker, CAD = coronary artery disease; CXA = circumflex artery; GFR = glomerular filtration rate; DBP = diastolic blood pressure; hs-CRP = high sensitive C-reactive protein; HbA1c = hemoglobin A1c; LAD = left anterior descending artery; LBBB = left bundle branch block; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; RCA = right coronary artery; SBP = systolic blood pressure.

RESULTS

A total of 433 patients (mean age 62.3 ± 12.8 years, 290 [67%] male) were included in the study. Eighty-five patients (19.6%) had fQRS in two or more contiguous leads in the surface ECG. All patients divided into two groups according to having fQRS on admission ECG. There were no statistically significant differences in age and sex distribution between two groups. Demographic and clinical characteristics were shown in Table 1. There were no statistical significant difference in

cardiovascular risk factors except hyperlipidemia (36.5% vs. 23.6%, P = 0.019). Coronary artery disease and peripheral artery disease history was significantly higher in fQRS(+) group.

Admission parameters such as blood pressure and heart rate were similar in both groups. Levels of troponin, hs-CRP, and HbA1c on admission were also similar in both groups. Calculated GRACE risk score in both groups were significantly different between these groups (132.8 ± 39.3 vs. 122.5 ± 35.4, P = 0.019). GRACE risk score was positively correlated with fQRS (r = 0.086, P = 0.03). Severe ST segment depression (≥5) mm were seen significantly higher in fQRS(+) group (47.1% vs. 27.4%, P < 0.01). All patients underwent transthoracic echocardiographic evaluation during hospitalization period and lower left ventricular ejection fraction was found in fQRS(+) group (45.1% vs. 50.5%, P = 0.002).

Of 433 patients, 65.9% of fQRS(+) groups and 74.4% of fQRS(−) group, totally 315 patients underwent coronary angiography during hospitalization. Circumflex artery and right coronary artery lesion were significantly higher in fQRS(+) patients, but left anterior descending and left main lesions were similar in both groups. There were no statistically significant differences in terms of in-hospital mortality and mortality in 30 days. However, long-term mortality rate (12 months) was significantly higher in fQRS(+) patients (15.2% vs. 5.4%, $P = 0{,}006$).

Univariate and multivariate analyses were made for predictors of long term mortality. Age, male sex, heart rate, QRS duration, and fQRS were found to associated with long-term mortality in the univariate analysis. Multivariate analysis was also showed that these parameters except QRS duration were predictors of long term mortality (Table 2).

DISCUSSION

Non-ST elevation myocardial infarction is a heterogeneous population contrary to patients with ST-elevation myocardial infarction and risk stratification on admission carries a greater importance for guidance of early invasive strategy. GRACE score is most commonly accepted for early risk stratification of these patients. GRACE risk score includes ST segment deviation in admission ECG as a parameter. Our study revealed that, fQRS in 12-lead ECG on admission is an independent predictor of long-term mortality. Our study also showed that advanced age, male sex, and heart rate at the presentation were other predictors of long-term mortality in these patients. Long-term mortality rate was 17% in patients with fQRS and 12% in patients without fQRS. These mortality rates were similar to the previous studies with NSTEMI patients.[11,15] fQRS was evaluated in few studies that was made by limited number of patients. Bekler et al. only included 149 patients and Guo et al. included 179 patients with acute coronary syndrome.[4,7] We believe that our study population reveals more powerful data respect to these studies due to including only patients with NSTEMI and number of patients. Pathophysiology of fQRS in the surface ECG is not totally understood. Generally, it has been accepted that fQRS formed secondary to heterogeneous electrical activity due to ischemia, scar, and/or fibrous tissue.[10–13] fQRS is shown to be related with myocardial fibrosis, scar, aneurysm, and systolic dysfunction.[14,15] However, acute ischemia may also cause fQRS and reveals dynamic changes. Kocaman et al.[16] reported that fQRS may exhibit changes following primary percutaneous coronary intervention in ST elevation myocardial infarction patients. In addition, these authors also reported that surface ECG revealing fQRS could predict success of the reperfusion therapy.

In theory, the relation between fQRS and cardiovascular mortality may be due to increased risk of ventricular arrhythmias, sudden cardiac death, and worsening of left ventricular systolic function secondary to myocardial scarring. Twelve-lead ECG on admission revealing fQRS could be related to acute ischemia or previous myocardial fibrosis and/or scarring. Previous reports showed that fQRS was also found to be a marker of a prior myocardial infarction, demonstrated by regional perfusion abnormalities with scintigraphic evaluation, which has a substantially higher sensitivity and negative predictive value than the Q wave.[17] Certainly, previously affected myocardial tissue has the risk of deterioration during acute ischemic attack. As a result, as the affected left ventricular myocardial tissue increases, the risk of sudden cardiovascular death rises.[18] Both in our study and in the study by Bekler et al. left ventricular ejection fraction was considerably lower in those who have fQRS in surface ECG performed at the time of patient admission. In addition, according to our data, history of coronary

Table 2. Univariate and Multivariate Analyses for Long-Term Cardiovascular Mortality

	HR (95% CI)	P	HR (95% CI)	P
Age	1.07 (1.020–1.125)	0.006	1.07(1.038–1.118)	<0.01
Male sex	4.27 (1.194–15.305)	0.026	3.03(1.072–8.606)	0.037
Heart rate	1.03 (1.006–1.059)	0.016	1.029(1.004–1.053)	0.020
QRS duration	1.016 (1.004–1.029)	0.012	1.01(1.084–6.458)	0.280
fQRS	4.00 (1.428–11.211)	0.008	2.64(0.026–0.150)	0.033

artery disease was significantly higher in fQRS group.

In addition, the risk of ventricular arrhythmia also increases in the presence of fQRS. In an analysis carried out in subgroup of MADIT II study, it was determined that fQRS especially developing at inferior region and when together with LBBB, is associated with sudden cardiac death, appropriate ICD defibrillation and increased total mortality, and it was stated that ICD implanted patients showed high risk.[19] In another study, Sha et al. reported that fQRS was associated with ventricular arrhythmia and total mortality in patients who had dilated cardiomyopathy.[20] Similarly, Das et al. found that fQRS was related to sudden cardiac death.[21] In addition, fQRS was found to be associated with spontaneous ventricular fibrillation in patients with Brugada syndrome.[22] Because there is high risk of ventricular arrhythmia due to fQRS especially in patients who have left ventricular systolic dysfunction, it has been suggested that mechanisms other than myocardial scar could be contributing to this condition. However, on the contrary to these findings, in one study by Cheema et al., presence of fQRS was not found to be associated with total mortality or arrhythmic mortality, in ICD implanted patients who had ischemic or nonischemic left ventricular systolic function.[23] Studies in support of this result that was found in that study are very limited.

Özcan et al. reported that fQRS was associated with functional capacity in patients who had heart failure.[24] In patients with heart failure, as the New York Heart Association (NYHA) class increases, the risk of cardiovascular mortality also increase.[18] In patients who have fQRS on admission, functional capacity might show a worse deterioration in the long term; this might be an important factor for the increase in mortality in long term.

Another possible theory that is that fQRS in surface ECG on admission might be associated with the severity and extent of acute ischemia. There is no data directly in support of this theory in our study; however, ST segment depression at or above 5 mm was significantly higher in fQRS group. This data might be an indirect sign showing increased severity of ischemia.

In our study 12-lead surface ECG revealing fQRS on admission was correlate higher risk of long-term mortality. These patients may benefit from early invasive strategy and secondary preventive treatment. Larger cohort studies needed to examine this relation and fQRS as a prognostic parameter addition to GRACE risk score.

Limitations

Our study is limited for detailed follow-up of patients regarding left ventricular ejection fraction and other major cardiovascular risk factors. Changes in clinical follow-up may effect long-term cardiovascular mortality.

Conclusion

Presence of fQRS on admission in patients with NSTEMI is independent predictor of late cardiovascular mortality in addition to advanced age, male sex, and increased heart rate. It should raise our awareness in addition to GRACE risk score in NSTEMI patients.

REFERENCES

1. Terkelsen CJ, Lassen JF, Nørgaard BL, et al. Mortality rates in patients with ST-elevationvs. Non-ST-elevation acute myocardial infarction: Observations from an unselected cohort. Eur Heart J 2005;26:18–26.
2. Ezra A., et al. AHA/ACC Guideline for the management of patients with non–ST-elevation acute coronary syndromes. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Circulation 2014;130:e344–e426.
3. Akgul O, Uyarel H, Pusuroglu H, et al. Predictive value of a fragmented QRS complex in patients undergoing primary angioplasty for ST elevation myocardial infarction. Ann Noninvasive Electrocardiol 2015;20:263–272.

4. Bekler A, Gazi E, Erbağ G, et al. Relationship between presence of fragmented QRS on 12-lead electrocardiogram on admission and long-term mortality in patients with non-ST elevated myocardial infarction. Turk Kardiyol Dern Ars 2014;42:726–732.
5. Das MK, Michael MA, Suradi H, et al. Usefulness of fragmented QRS on a 12-lead electrocardiogram in acute coronary syndrome for predicting mortality. Am J Cardiol 2009;104:1631–1637.
6. Akbarzadeh F, Pourafkari L, Ghaffari S, et al. Predictive value of the fragmented QRS complex in 6-month mortality and morbidity following acute coronary syndrome. Int J Gen Med 2013;6:399–404.
7. Guo R, Zhang J, Li Y, et al. Prognostic significance of fragmented QRS in patients with non-ST elevation myocardial infarction: results of a 1-year, single-center follow-up. Herz 2012;37:789–795.
8. Das MK, Khan B, Jacob S, et al. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation 2006;113:2495–2501.
9. Wright RS, et al. ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;57:e215–e367.
10. Flowers NC, Horan LG, Thomas JR, et al. The anatomic basis for high-frequency components in the electrocardiogram. Circulation 1969;39:531–539.
11. Lesh MD, Spear JF, Simson MB. A computer model of the electrogram: What causes fractionation? J Electrocardiol 1988;21:S69–S73.
12. Friedman PL, Fenoglio JJ, Wit AL. Time course for reversal of electrophysiological and ultrastructural abnormalities in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. Circ Res 1975;36:127–144.
13. Wiener I, Mindich B, Pitchon R. Fragmented endocardial electrical activity in patients with ventricular tachycardia: a new guide to surgical therapy. Am Heart J 1984;107:86–90.
14. Homsi M, Alsayed L, Das MK, et al. Fragmented QRS complexes on a 12-lead ECG is a marker of greater myocardial scarring related to coronary artery disease by magnetic resonance imaging. J Am Coll Cardiol 2008;51:A31.
15. Reddy CV, Cheriparambill K, Saul B, et al. Fragmented left sided QRS in absence of bundle branch block: Sign of left ventricular aneurysm. Ann Noninvasive Electrocardiol 2006;11(2):132–138.
16. Kocaman SA, Çetin M, Kırış T, et al. The importance of fragmented QRS complexes in prediction of myocardial infarction and reperfusion parameters in patients undergoing primary percutaneous coronary intervention. Turk Kardiyol Dern Ars 2012;40(3):213–222.
17. Das MK, Khan B, Jacob S, et al. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation 2006;113:2495–2501.
18. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006;27:65–75.
19. Brenyo A, Pietrasik G, Barsheshet A, et al. QRS fragmentation and the risk of sudden cardiac death in MADIT II. J Cardiovasc Electrophysiol 2012;23:1343–1348.
20. Sha J, Zhang S, Tang M, et al. Fragmented QRS is associated with all-cause mortality and ventricular arrhythmias in patient with idiopathic dilated cardiomyopathy. Ann Noninvasive Electrocardiol 2011;16:270–275.
21. Das MK, Zipes DP. Fragmented QRS: A predictor of mortality and sudden cardiac death. Heart Rhythm 2009;6(3 Suppl):S8–S14.
22. Morita H, Kusano KF, Miura D, et al. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. Circulation 2008;118:1697–1704.
23. Cheema A, Khalid A, Wimmer A, et al. Fragmented QRS and mortality risk in patients with left ventricular dysfunction. Circulation: Arrhythmia and Electrophysiology 2010;3:339–344
24. Ozcan S, Cakmak HA, Ikitimur B, et al. The prognostic significance of narrow fragmented QRS on admission electrocardiogram in patients hospitalized for decompensated systolic heart failure. Clin Cardiol 2013;36:560.