Fragmented QRS Is Associated with All-Cause Mortality and Ventricular Arrhythmias in Patient with Idiopathic Dilated Cardiomyopathy

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Background: Several studies have showed that fragmented QRS complexes (f-QRS, defined as different RSR' patterns) on a routine 12-lead electrocardiogram were associated with increased mortality and arrhythmic events in patients with coronary artery disease, but relatively little data were available regarding idiopathic dilated cardiomyopathy (IDCM).

Objective: The purpose of this study was to evaluate the relationship between fragmentation of QRS and the combined end point of all-cause mortality and ventricular arrhythmias in patients with IDCM.

Methods: One hundred twenty-eight patients with IDCM and left ventricular dysfunction (ejection fraction, $EF \leq 40\%$) were analyzed, respectively. According to QRS duration and the existence of f-QRS on 12-lead electrocardiograph (ECG), the study populations were divided into three groups: (1) the f-QRS group (QRS < 120 ms and with fragmented QRS, $n = 51$), (2) the wide QRS (wQRS) group (QRS ≥ 120 ms, $n = 48$), and (3) the nonfragmented QRS (non-fQRS) group (QRS < 120 ms and without f-QRS, $n = 29$).

Results: During a mean follow-up of 14 ± 5 months, 25 (19.5%) patients had deaths and ventricular arrhythmic events. The combined end point of all-cause mortality and ventricular tachyarrhythmias was significantly higher in the f-QRS and wQRS groups than the non-fQRS group (23.5%, 25%, and 3.4%, respectively; $P < 0.05$ for both). Event-free was significantly decreased in the f-QRS group versus the non-fQRS group ($P = 0.02$). Univariate regression analysis revealed that f-QRS was a stronger predictor of mortality and arrhythmic events in IDCM patients.

Conclusion: f-QRS on 12-lead ECG has a high predictive value for the combined end point of all-cause mortality and ventricular tachyarrhythmias in IDCM patients with left ventricular dysfunction.

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fragmented QRS; idiopathic dilated cardiomyopathy; mortality; ventricular arrhythmia

Risk stratification of sudden cardiac death (SCD) is to identify subjects who are at high risk and eventually to reduce the incidence of sudden death in clinical. Several studies have described non-invasive tests (repolarization and depolarization abnormality) for serious cardiac events mostly in structural heart disease patients such as coronary artery disease (CAD), cardiomyopathy, and heart failure. However, some tests predicting adverse outcome in ischemic cardiomyopathy have a low predictive value for an arrhythmic event or death in nonischemic dilated cardiomyopathy

(NIDCM).¹ Recently, the existence of fragmented QRS complexes (f-QRS) on a routine 12-lead electrocardiogram as another marker of depolarization abnormality was reported.^{2–4} f-QRS are defined as different RSR' patterns with or without Q wave, including an additional R wave, notched S wave, or > 1 R' wave in two contiguous leads, corresponding to a major coronary artery territory.⁵ Although scholars found that f-QRS were associated with increased mortality and arrhythmic events in CAD patients,^{6–8} relatively little data are available regarding idiopathic dilated cardiomyopathy (IDCM,

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a disease of unknown cause that results in an enlarged heart that does not pump properly). f-QRS have also been defined as a predictor of arrhythmic events in patients with cardiomyopathy who received an implantable cardioverter-defibrillator (ICD) for primary or secondary prevention of SCD.⁹ Therefore, it is hypothesized that f-QRS in IDCM patients with left ventricular dysfunction are associated with death or life-threatening ventricular arrhythmias. The aim of the present study is to estimate the relationship between f-QRS and mortality and arrhythmic events in patients with IDCM. The results of this study can help us to identify whether f-QRS would be effective in risk-stratifying patients eligible for ICD therapy in IDCM patients.

METHODS

Study Populations

This retrospective study enrolled 128 patients who were diagnosed as IDCM with left ventricular dysfunction (ejection fraction, EF $\leq$ 40%) at our hospital from January 1, 2009 to December 31, 2009. The clinical diagnosis of IDCM was based on the criteria of the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies. Exclusion criteria included patients with heart failure due to CAD, secondary cardiomyopathy (hypertensive, alcoholic, or perinatal), valvular or congenital heart disease, or patients with orthopic cardiac transplantation during follow-up. Patients with paced rhythm at baseline were also excluded from this study.

Data Collection and ECG Analysis

Standard 12-lead ECGs and baseline characteristics of all patients were obtained from medical records. All cases underwent echocardiography or cardiac magnetic resonance imaging to assess left ventricular function estimated by EF. Two independent readers who blinded to the outcome data analyzed ECGs. We defined the presence of f-QRS in 12-lead ECG according to the previous study.⁵⁻⁹ f-QRS were defined by the presence of an additional R wave (R') or notching of the R wave or the S wave, or the presence of >1 R' in two contiguous leads corresponding to a major lead set (anterior V₁-V₅; inferoposterior II, III, aVF; or lateral I, aVL, V₆) in patients with narrow QRS (QRS $<$ 120 ms). QRS duration was determined by the

longest QRS in any lead. We divided the study patients into three groups: (1) the f-QRS group included patients who presented f-QRS; (2) the wide QRS (wQRS) group consisted of patients with any QRS morphology and QRS duration $\geq$ 120 ms, including bundle branch block and intraventricular conduction delays; and (3) the nonfragmented QRS (non-fQRS) group included patients with QRS duration $<$ 120 ms and without QRS fragmentation.

Follow-Up and Study End Points

All patients or their relatives were contacted by phone during follow-up. Ventricular tachyarrhythmias (ventricular tachycardia [VT] or ventricular fibrillation [VF]) were obtained from medical records or ICD interrogations. The end points of this study were all-cause mortality and ventricular arrhythmias, including appropriate ICD therapy (antitachycardia pacing or ICD shock) for ventricular arrhythmias.

Statistical Analysis

Continuous variables were presented as mean $\pm$ standard deviation values and compared using *t*-test. Comparison of categorical variables was performed with chi-square or Fisher's exact test and expressed as frequency and percentages. Kaplan-Meier estimator was generated to estimate survival curves and log-rank test was used to compare survival probability among the f-QRS, wQRS, and non-fQRS groups. Cox proportional hazard model was used to model the association between the study end point (all-cause mortality and ventricular arrhythmias) to a relevant variable(s) for univariate analyses. For all tests, *P* $<$ 0.05 was considered significant. All analysis was performed using SPSS17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

This study recruited a total of 128 patients who fulfilled the inclusion criteria. The study populations included 51 (39.8%) patients with f-QRS (group f-QRS), 48 (37.5%) patients with QRS duration $\geq$ 120 ms (group wQRS), and 29 (22.7%) patients with QRS duration $<$ 120 ms and without QRS fragmentation (group non-fQRS). Baseline demographics of the study patients are delineated in Table 1. The mean age of study cases was 54 $\pm$ 14 (range 19-83) years and 68.5% were male. ICDs were implanted in 10 (7.8%) patients for primary or

Table 1. Clinical Characteristics for Study Patients of the Three Groups

	All Cases (n = 128)	f-QRS (n = 51)	wQRS (n = 48)	Non-fQRS (n = 29)	P-Value	
					f-QRS vs non-fQRS	wQRS vs non-fQRS
Age (years)	53.6 ± 13.9	50.2 ± 15.2	57 ± 12	53.3 ± 13.1	0.347	0.177
Male	87 (68%)	36 (70.6%)	33 (68.8%)	18 (62.1.0%)	0.434	0.548
SVT/VF	12 (9.4%)	5 (9.8%)	7 (14.6%)	0 (0%)	0.153	0.041
ICD	10 (7.8%)	3 (5.9%)	7 (14.6%)	0 (0%)	0.550	0.041
QRS duration (ms)	116 ± 31	98 ± 13	150 ± 17	89 ± 12	0.004	<0.001
LVEF (%)	30 ± 6	29 ± 6	28 ± 5	33 ± 7	0.013	0.001
LVEDD (mm)	68.2 ± 8.1	68.8 ± 7.9	69.4 ± 9.0	65.2 ± 6.5	0.039	0.018
Diabetes mellitus	24 (18.8%)	10 (19.6%)	8 (16.7%)	6 (20.7%)	0.907	0.657
Renal dysfunction	7 (5.5%)	2 (3.9%)	3 (6.3%)	2 (6.9%)	0.957	1.0
Atrial fibrillation	33 (25.8%)	12 (23.5%)	13 (27.1%)	8 (27.6%)	0.687	0.962
ACEI/ARB	103 (80.5%)	38 (74.5%)	40 (83.3%)	25 (86.2%)	0.345	0.990
BB	124 (96.9%)	50 (98%)	45 (93.8%)	29 (100%)	1.0	0.286
Amiodarone	11 (8.9%)	6 (11.8%)	5 (10.4%)	0 (0%)	0.082	0.150
Death or VT/VF	25 (19.5%)	12 (23.5%)	12 (25.0%)	1 (3.4%)	0.043	0.033
Death	12 (9.4%)	5 (9.8%)	6 (12.5%)	1 (3.4%)	0.551	0.353
VT/VF	13 (10.1%)	7 (13.7%)	6 (12.5%)	0 (0%)	0.045	0.078

Values are mean ± standard error (SE) or n (%). ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotension II receptor blocker; BB = beta-blocker; f-QRS = fragmented QRS; ICD = implantable cardioverter-defibrillator; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; non-fQRS = nonfragmented QRS; SVT = sustained ventricular tachycardia; VF = ventricular fibrillation; wQRS = wide QRS.

secondary prevention of SCD. To compare with the non-fQRS group, clinical characteristics of cases for the f-QRS and wQRS groups were significantly different in QRS duration, left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), and sustained VT or VF at baseline (only for the wQRS group). LVEF was significantly lower in the f-QRS group than the non-fQRS group ($29\% \pm 6\%$ vs $33\% \pm 7\%$, $P = 0.013$). LVEDD in the f-QRS and the wQRS groups were 68.8 ± 7.9 mm and 69.4 ± 9.0 mm, respectively, which was significantly larger than in the non-fQRS group ($P < 0.05$ for both). Twelve (9.4%) patients had sustained VT or VF at baseline, while most of them (58.3%) were in the wQRS group ($P = 0.041$, compared with the non-fQRS group).

All-Cause Mortality and Ventricular Arrhythmic Events

A total of 25 (19.5%) patients had deaths and ventricular arrhythmic events (12 deaths and 13 VT/VF events) during a mean follow-up of 14 ± 5 (range 2–23) months. The combined end point of all-cause mortality and ventricular tachyarrhythmias was significantly higher in the f-QRS group than the non-fQRS group (23.5% vs 3.4%, $P = 0.043$). Seven (13.7%) patients received at least one

appropriate ICD therapy, external cardioversion, or ablation for a ventricular arrhythmic event in the f-QRS group, whereas no patient had a ventricular arrhythmic event in the non-fQRS group ($P = 0.045$). However, the incidence rate of all-cause deaths was not significantly different in patients with f-QRS versus patients with non-fQRS (9.8% vs 3.4%, $P = 0.551$). During follow-up, seven patients in the wQRS group implanted with cardiac resynchronization therapy (CRT). Although there is also significant difference in the combined end point between the wQRS group and the non-fQRS group (25% vs 3.4%, $P = 0.033$), it did not reach statistical significance in the analysis of mortality or ventricular tachyarrhythmias.

There were 11 deaths and four ventricular arrhythmia events in patients without ICD implantation ($n = 118$). Among this cohort, eight patients died during hospital admission for worsening heart failure and one had sudden death, while the causes of death were not known in the other two patients. The all-cause mortality rates were not significantly different among f-QRS (10.4%), wQRS (12.2%), and non-fQRS (3.4%) groups.

Kaplan-Meier survival analysis revealed that survival probability significantly decreased in the f-QRS and wQRS groups when compared with the non-fQRS group ($P = 0.02$ and $P = 0.039$,

Figure 1. Kaplan-Meier analysis for the combined end point of all-cause mortality and ventricular tachyarrhythmia in patients with fragmented QRS (the f-QRS group), wide QRS (the wQRS group), and nonfragmented QRS (the non-fQRS group).

respectively; Fig. 1). However, there was no significantly different in event-free between the f-QRS and wQRS groups ($P = 0.364$). Cox proportional hazard regression analysis revealed that f-QRS ($P = 0.015$, OR 7.90, 95% CI 1.20–62.12) and sustained VT or VF ($P < 0.001$, OR 9.77, 95% CI 3.81–25.03) at baseline were stronger univariate predictors of mortality and arrhythmic events in IDCM patients, whereas age, LVEF, LVEDD, QRS duration, and medicines were not predictors for the combined end point (Table 2).

DISCUSSION

This study revealed that f-QRS on a 12-lead ECG and sustained VT or VF predict a poor prognosis in patients with IDCM. In the present study, the incidence of all-cause mortality and ventricular tachyarrhythmias in patients with f-QRS increased significantly compared to without f-QRS patients (23.5% vs 3.4%, $P = 0.043$) during follow-up of 14 ± 5 months. Statistical analysis showed that the non-fQRS group had a high survival probability for the combined end point of mortality and

arrhythmic events ($P < 0.05$). The study showed that f-QRS predicted ventricular tachyarrhythmias but not all-cause mortality. That may be because arrhythmic deaths were prevented by the ICD therapy. Studies have revealed that the abnormality of

Table 2. Univariate Cox Proportional Hazards Analysis for Prediction of All-Cause Mortality and Ventricular Arrhythmic Events

Factors	Univariate Analysis	
	P-Value	OR (95% CI)
f-QRS	0.015	7.90 (1.20–62.12)
wQRS	0.35	2.76 (0.33–23.25)
SVT/VF	<0.001	9.77 (3.81–25.03)
Age	0.545	1.009 (0.980–1.040)
QRS duration	0.286	1.007 (0.994–1.029)
LVEF $\leq 40\%$	0.523	1.131 (0.997–67.019)
LVEDD	0.360	1.023 (0.974–1.074)
Amiodarone	0.854	1.121 (0.333–3.777)

Values are mean $\pm$ SE or n (%). f-QRS = fragmented QRS; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic dimension; non-fQRS = nonfragmented QRS; SVT = sustained ventricular tachycardia; VF = ventricular fibrillation; wQRS = wide QRS.

myocardium repolarization microvolt T-wave alternans (MTWA) and depolarization signal-averaged ECG (SAECG) may be available for the selection of appropriate candidates for ICD implantation. However, these invasive tests have high negative predictive values but low positive predictive values. f-QRS on 12-lead electrocardiogram are novel another marker of depolarization abnormality. f-QRS represent conduction delay caused by myocardial scar and is associated with increased mortality and arrhythmic events in patients with CAD. However, f-QRS are not specific for CAD and are also encountered in other myocardial diseases such as cardiomyopathy and congenital heart disease. Additionally, it has been demonstrated that f-QRS as a predictor of increased mortality and arrhythmic events in patients with ischemic cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy, and Brugada syndrome.

It is still unclear about the mechanism of f-QRS on the routine 12-lead ECG. Suggested mechanism of fragmentation QRS complex has been interpreted by inhomogeneous activation of the ventricles because of myocardial scar and/or ischemia. Disease states affect the amount, distribution, and pattern of scar. In patients with nonischemic cardiomyopathy, scars are patchy and midmyocardial or subepicardial. Therefore, different morphologies of f-QRS are caused by shifting of the QRS vector during depolarization in and around the areas of scarred or ischemic myocardium, depending on their extent and location in the ventricles.^{5,10–13} Studied showed¹⁴ that the combined end point of ICD therapy and mortality was significantly higher in the f-QRS group as compared to the non-fQRS group in patients with NIDCM who received an ICD for primary and secondary prophylaxis. Our findings are in accordance with the observation made in this report. But the conclusions are not always consistent. In a prospective, multisite cohort of primary prevention patients with left ventricular dysfunction representing both ischemic and nonischemic etiology, the presence of f-QRS on ECG was not associated with a higher risk of either all-cause or arrhythmic mortality.¹⁵ Therefore, the utility of f-QRS in risk stratification of SCD needs to be explored further, especially in nonischemic cardiomyopathy and heart failure. The predictive value of f-QRS (depolarization abnormality) for SCD may be enhanced

further by combining a marker of repolarization abnormality such as MTWA.

However, there was no predictive value of wQRS and LVEF for mortality and ventricular arrhythmias in this study. One possible cause of these is that QRS duration and left ventricular function likely improved in patients implanted with CRT.

Study Limitations

There are several limitations in our study. First, it was a retrospective study and there was probably a significant referral bias. Secondly, the study end point included appropriate ICD therapy, which may not always reflect lifesaving therapy in IDCM patients. Moreover, ICD may be arrhythmogenic, thus some arrhythmic events recorded in ICD group might be artificial events. In addition, there were fewer the end point events, so it could be lack of significantly predictive power in the analysis of mortality or ventricular tachyarrhythmias.

CONCLUSION

f-QRS on standard 12-lead ECG have an evidently predictive value for the combined end point of all-cause mortality and ventricular tachyarrhythmias in IDCM patients with left ventricular dysfunction.

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