ORIGINAL ARTICLE

Significance of Fragmented QRS Complexes for Identifying Left Ventricular Hypertrophy in Patients with Hypertension

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Background: Fragmented QRS complexes (fQRS) were associated with left ventricular mass (LVM) in hypertensive patients. Our study aimed to investigate the association between fQRS and left ventricular hypertrophy (LVH) in hypertensive patients.

Methods: Two hundred thirty-six hypertensive patients were divided into fQRS group and non-fQRS group. fQRS were defined as the presence of an additional R wave, notching in the R or S wave, or the presence of >1 R′ in two contiguous leads. Echocardiography was used to detect LVH.

Results: Patients with fQRS had higher levels of LVM than patients without fQRS (181.55 ± 65.64 g vs. 149.21 ± 35.08 g, $P < 0.001$). Receiver operating characteristic curves showed areas under the curve was 0.62 for fQRS (95% CI 0.54–0.69, $P = 0.003$). In univariate analyses, the presence of fQRS on ECG was positively associated with LVM. Multiple regression analyses found fQRS was associated with LVM, independently.

Conclusion: fQRS is a common electrocardiographic phenomenon in patients with hypertension. Although the diagnostic value for LVH is limited, the presence of fQRS on ECG is associated with a higher risk for worse LVH.

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fragmented QRS; hypertension; left ventricular hypertrophy; left ventricular mass

Fragmented QRS complexes (fQRS) are novel electrocardiographic signals, which include various RSR′ patterns with different morphologies of the QRS complexes on resting 12-lead electrocardiography (ECG). Various RSR′ patterns include an additional R wave (R′) or notching of the R wave or S wave, or the presence of >1 R′ in two contiguous leads, corresponding to the abnormal cardiac depolarization.[1] Previous studies have shown that fQRS might be a predictor of poor clinical outcomes in patients with coronary artery disease (CAD), dilated cardiomyopathy, hypertrophic cardiomyopathy, or structure heart disease.[2–5]

Hypertension is an important risk factor for cardiovascular disease and has become a major global burden on public health.[6] In 2002, one-sixth of all Chinese adults were found to be hypertensive.[7] Hypertension could lead to target organ damage, such as renal damage, cardiac damage, and vascular damage. Left ventricular hypertrophy (LVH) is a common cardiac damage and one of the most important risk factors of worse cardiovascular prognosis in patients with hypertension. Pathological changes present in patients with hypertensive LVH include an increase in the size of cardiomyocyte, alteration in the extracellular matrix, and cardiac fibrosis.[8]

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The pathological features would lead to abnormal electric conduction among cardiomyocytes, which may be presented as fQRS on surface ECG. A previous study about the prognostic value of fQRS in patients with acute myocardial infarction found that hypertension was associated with fQRS by multivariate logistic regression analysis.[9] Another small size study also found that hypertensive patients with fQRS had higher index of left ventricular mass (LVM) than patients without fQRS.[10]

In view of the possible relationship between fQRS and hypertension, the goal of the study was to investigate the association between fQRS and LVH in hypertensive patients. For this purpose, we analyzed the results of ECG and echocardiography in patients with hypertension.

METHODS

Study Population

From August 2012 to December 2013, we conducted a retrospective study on hypertensive patients with negative results of coronary angiography (CAG) at affiliated People's Hospital of Jiangsu University. The study protocol was approved by the affiliated People's Hospital of Jiangsu University's Ethics Committee. Hypertension was defined as a blood pressure ≥140/90 mmHg or the use of antihypertension medications. Exclusion criteria included patients with CAG proved CAD, structure heart disease, systolic heart failure, chronic renal dysfunction, history of pacemaker, or any abnormal characteristic on the ECG (included atrial fibrillation, abnormal Q wave, bundle branch block, Wolff–Parkinson–White syndrome and so on). All patients were evaluated by medical history, clinical presentation, examination recording, and clinical biochemistry.

ECG Analysis

An electronically recorded 12-lead ECG at rest (filter range, 0.15–100 Hz; AC filter, 60 Hz, 25 mm/s, and 10 mm/mV) was obtained within the first 24 hours after admission. fQRS complexes were defined as the presence of an additional R wave (R′), notching in the R or S wave, or the presence of >1 R′ in two contiguous leads in patients with QRS duration ≤120 ms. However, patients with a typical bundle-brunch block pattern or incomplete right bundle-branch block pattern were excluded.[1] The electrocardiogram was analyzed by two independent readers blinded to the echocardiogram and clinical findings.

Echocardiography Assessment

All patients underwent two-dimensional transthoracic echocardiography. The echocardiographer was blinded to the clinical data. Measurements included left atrium diameter (LAD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular end diastolic/systolic dimension (LVEDD/LVESD). LVM was calculated as $0.8 \times (1.04 \times [\mathrm{IVST} + \mathrm{LVEDD} + \mathrm{LVPWT}^3 - \mathrm{LVEDD}^3] + 0.6\ \mathrm{g})$,[11] and was used to assess the severity of LVH. In addition, we also evaluated the systolic function by left ventricular ejection fraction (LVEF) and the diastolic function by the ratio of peak of early diastolic transmitral flow to peak of early diastolic annular velocity (E/E′ ratio).

Statistical Analysis

Descriptive data for continuous variables were presented as mean ± standard deviation. Categorical data were summarized using frequency counts and percentages. For continuous variables, normal distribution was evaluated with Kolmolgorov-Smirnov test. The continuous variables were compared using the Student's t test (if homogeneity of variances was assumed) or the Mann-Whitney U test (if homogeneity of variances was not met). For categorical clinical variables, differences between groups were evaluated with the chi-square or Fisher's exact test when appropriate. A P value of ≤0.05 was taken as significance. Furthermore, receiver operating characteristic (ROC) curve was performed to investigate the value of fQRS in differentiating LVH in hypertensive patients. In addition, Spearman correction coefficients were used to evaluate correlations between LVM and other variables. Subsequently, analysis was undertaken through multiple linear regressions to investigate a set of independent variables predictors of LVM. All analyses were conducted with SPSS for Windows 13.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Comparison of Baseline Characteristics between the Two Groups

Characteristics	fQRS Group (n = 86, 36.4%)	Non-fQRS Group (n = 150, 63.6%)	P Value
Age (years)	62.35 ± 12.44	60.05 ± 9.90	0.17
Male gender, n (%)	54 (62.8)	84 (56.0)	0.31
Diabetes mellitus, n (%)	8 (9.3)	37 (23.1)	0.007
Smoking, n (%)	33 (38.4)	71 (47.3)	0.18
TC (mmol/L)	4.02 ± 0.74	4.30 ± 0.98	0.07
LDL (mmol/L)	2.15 ± 0.59	2.29 ± 0.75	0.12
Creatinine (umol/L)	82.34 ± 19.03	73.44 ± 14.47	<0.001
Length of hypertension (y)	9.67 ± 5.98	7.87 ± 7.66	0.002
Classification of hypertension			0.27
Class 1, n (%)	7 (8.1)	10 (6.7)	
Class 2, n (%)	27 (31.4)	63 (42.0)	
Class 3, n (%)	52 (60.5)	77 (51.3)	
Medications for hypertension			
ACEI/ARB, n (%)	40 (46.5)	52 (34.7)	0.073
CCB, n (%)	50 (58.1)	39 (26.0)	<0.001
Beta-blockers, n (%)	18 (20.9)	12 (8.0)	0.004
Diuretics, n (%)	28 (32.6)	29 (19.3)	0.022
Others, n (%)	14 (16.3)	34 (22.7)	0.24
Patients with controlled BP, n (%)	49 (57)	87 (58)	0.88

fQRS, fragmented QRS; TC, total cholesterol; LDL, low density lipoprotein; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BP, blood pressure.

RESULTS

Demographics and Clinical Data

A final cohort of 236 patients (138 males, mean age 61 years) was analyzed. The ECG findings showed that fQRS were presented 36.4% in the patients enrolled. In the patients with fQRS, there were 60 patients with fQRS in the inferior leads, and 26 patients with fQRS in the anterior leads. The baseline characteristics of the patients were shown in Table 1. The patients in the fQRS group had longer history of hypertension (9.67 ± 5.98 years vs. 7.87 ± 7.66 years, $P < 0.001$), higher proportion of treatment with beta-blockers (20.9% vs. 8.0%, $P = 0.004$) and diuretics (32.6% vs. 19.3%, $P = 0.022$), higher levels of serum creatinine (82.34 ± 19.03 umol/L vs. 73.44 ± 14.47 umol/L, $P < 0.001$), but lower proportion of diabetes (9.3% vs. 23.1%, $P = 0.007$) than patients in the non-fQRS group. No significant differences were observed in age, male proportion, history of smoking, classification of hypertension, other antihypertension medications, and prevalence of blood pressure control between the two groups.

Echocardiography Results

Patients in the fQRS group had higher levels of IVST (11.38 ± 2.08 mm vs. 10.50 ± 1.67 mm, $P = 0.002$) and LVM (181.55 ± 65.64 g vs. 149.21 ± 35.08 g, $P < 0.001$) than patients in the non-fQRS group, but the difference of LVPWT between the two group was not significant (8.93 ± 1.27 mm vs. 8.68 ± 0.89 mm, $P = 0.063$). The patients in the fQRS group also had larger LVEDD (48.33 ± 6.60 mm vs. 45.46 ± 3.47 mm, $P = 0.015$), LVESD (32.23 ± 7.75 mm vs. 29.67 ± 5.77 mm, $P = 0.005$), and LAD (35.35 ± 6.10 mm vs. 32.51 ± 5.47 mm, $P < 0.001$) than patients in the non-fQRS group.

We also evaluated the systolic and diastolic cardiac function by the echocardiography. The results showed that patients in the fQRS group had worse systolic and diastolic cardiac function than patients in the non-fQRS (LVEF 62.95 ± 10.68 vs. 66.38 ± 5.47, $P = 0.006$; fractional shortening 35.44 ± 4.74 vs. 36.98 ± 1.96, $P = 0.014$; E/E′ 10.21 ± 1.62 vs. 9.39 ± 1.30, $P < 0.001$, Table 2).

The Diagnostic Value of fQRS for LVH

We defined LVH as IVST or/and LVPWT ≥ 12 mm. There was higher proportion of patients with LVH in the fQRS group under this definition (43.5% vs. 30.0%, $P < 0.001$, Table 2). The presence of fQRS on ECG had high specificity (72%) for identifying LVH in patients with hypertension, but low sensitivity (51%). The positive and negative predictive values of fQRS for LVH were

Table 2. Comparison of the Echocardiographic Measurements between the Two Groups

Measurements	fQRS Group (n = 86, 36.4%)	Non-fQRS Group (n = 150, 63.6%)	P Value
IVST (mm)	11.38 ± 2.08	10.50 ± 1.67	0.002
LVPWT (mm)	8.93 ± 1.27	8.68 ± 0.89	0.063
LVEDD (mm)	48.33 ± 6.60	45.46 ± 3.47	0.015
LVESD (mm)	32.23 ± 7.75	29.67 ± 5.77	0.005
LAD (mm)	35.35 ± 6.10	32.51 ± 5.47	<0.001
FS (%)	35.44 ± 4.74	36.98 ± 1.96	0.014
LVEF (%)	62.95 ± 10.68	66.38 ± 5.47	0.006
E/E' ratio	10.21 ± 1.62	9.39 ± 1.30	<0.001
LVM (g)	181.55 ± 65.64	149.21 ± 35.08	<0.001
LVH n (%)	46 (43.5)	45 (30.0)	<0.001

fQRS, fragmented QRS; IVST, interventricular septal thickness; LVPWT, left ventricular posterior wall thickness; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; LAD, left atrium diameter; FS, fractional shortening; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVH, left ventricular hypertrophy; E/E' ratio, the ratio of peak of early diastolic transmitral flow to peak of early diastolic annular velocity.

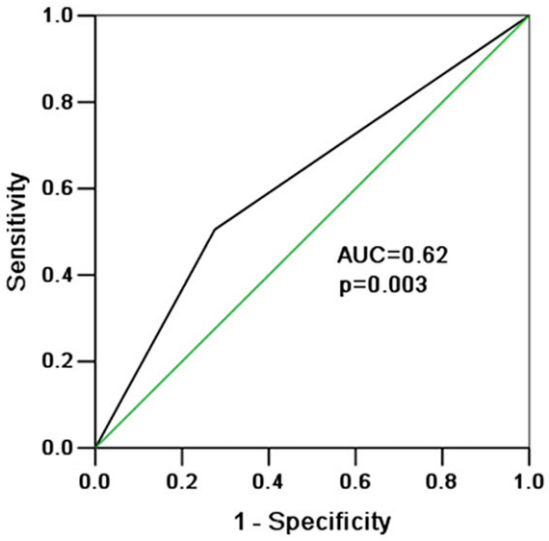

Figure 1. ROC curve was conducted to evaluate the diagnostic value of fQRS for LVH. The area under the curve (AUC) was 0.62 (95% CI 0.54–0.69, P = 0.003).

Table 3. Correction between Left Ventricular Mass and Other Variables

Parameter	R	P Value
fQRS	0.31	< 0.001
Male gender	−0.22	< 0.001
Age	0.03	0.33
Length of hypertension	0.18	0.002
Classification of hypertension	0.11	0.05
Treatment with ACEI/ARB	−0.07	0.14
Treatment with beta-blockers	0.04	0.29
Treatment with CCB	0.14	0.014
Treatment with diuretics	0.15	0.009
Treatment with other drugs	−0.06	0.17
Blood pressure control	−0.24	< 0.001
Smoking	0.10	0.07
Diabetes mellitus	0.02	0.40
Creatinine	0.33	< 0.001
Total cholesterol	−0.19	0.002
Low density lipoprotein	−0.12	0.04

fQRS, fragmented QRS; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

53% and 70%, respectively. Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of fQRS for LVH. The area under the curve was 0.62 (95% CI 0.54–0.69, P = 0.003, Fig. 1).

Association between fQRS and the Severity of LVH

LVM was used to assess the severity of LVH in hypertensive patients. Patients with fQRS on ECG had higher levels of LVM than patients without fQRS. To further investigate the association between fQRS and the severity of LVH, Spearman correction coefficients and multiple linear regressions were used. In univariate analyses, the presence of fQRS on ECG was positively associated with LVM (r = 31, P < 0.001, Table 3). Multiple regression analyses revealed that presence of fQRS on ECG was associated with LVM independently (Table 4).

DISCUSSION

This study demonstrated that fQRS was a common electrocardiographic phenomenon in patients

Table 4. Multivariable Linear Regression Analyses

Variables	Beta Coefficients	95% CI	P Value
fQRS	0.22	10.75 to 35.80	< 0.001
Creatinine	0.25	0.39 to 1.11	< 0.001
Blood pressure control	−0.20	−32.30 to −8.56	0.001
Length of hypertension	0.17	0.37 to 2.01	0.005

fRQS, fragmented QRS; CI, confidence interval.

with hypertension. Patients with fQRS had higher risks of LVH, systolic, and diastolic heart dysfunction. ROC curve showed that fQRS had value in distinguishing patients with LVH. Although the diagnostic value was limited, multiple linear regression analysis found that presence of fRQS on ECG was associated with LVM independently, which was used to assess the severity of LVH.

fQRS was described as a marker of myocardial scar in patients with CAD. The presence of fQRS might be related to the electrophysiological features of viable myocardial tissue islands in the myocardial scar. The islands of chronically ischemic myocardium displayed slow conduction, which would be responsible for inhomogeneous activation of the left ventricular. This altered the depolarization of ventricular, which was probably represented fragmentation in the QRS complex on the ECG.[1] However, some other studies found that fQRS was also related to acute coronary syndrome, Brugada syndrome, dilated cardiomyopathy, hypertrophy cardiomyopathy, and left ventricular noncompaction cardiomyopathy. And the formation of fQRS might be related by inhomogeneous activation of ventricles and myocardial conduction delay because of myocardial scar, ischemia, fibrosis, or abnormal iron channels.[3,4,12–14]

The formation of fQRS in patients with hypertension might be related to the LVH. An exaggerated accumulation of collagen type I and III fibers within the myocardial interstitium and surrounding intramural coronary arteries and arterioles have been described in hypertensive patients with LVH.[15] Microvascular disease and endothelial dysfunction were also apparent in hypertensive heart disease. In addition, increased arterial stiffness and the concomitant fall in central diastolic blood pressure were characteristics of macrovascular remodeling in patients with long-standing hypertension.[16] The falling of central diastolic blood pressure would decrease coronary perfusion and contribute to myocardial ischemia. The fibrosis and myocardial ischemia might promote inhomogeneous activation of ventricles, and lead to the formation of fQRS on ECG.

In addition, hypertension-related myocardial remodeling was also accompanied by cell-to-cell gap junction alterations. It has been shown that the expression of connexin 43 was decreased in spontaneous hypertensive rats with LVH.[17] Another animal study found enhanced neoformation of side-to-side type and internalization of end-to-end type of gap junctions prevailed in the myocardium of rats with hypertension.[18] The remodeling of gap junction in hypertensive hearts might also promote inhomogeneous activation of ventricles and the formation of fQRS.

Similar to other ECG criteria for diagnosing LVH[19], the fQRS also had some limitations for detection of LVH, one of which was the low sensitivity. In our study, the presence of fQRS on ECG had a poor sensitivity of 51% for detection of LVH. This may be related to the complicated mechanisms of LVH in hypertensive patients. In addition to the fibrosis and myocardial ischemia, the pathological changes present in patients with LVH also include the increase in the size of cardiomyocyte and other changes. The formation of fQRS might be related to the alteration in the extracellular matrix and cardiac fibrosis, and just was the tip of the iceberg. However, univariate analyses showed that the presence of fQRS on ECG was associated with LVM positively, and multiple linear regression analyses found that the fQRS was associated with LVM independently. All these results indicated that fQRS was associated with a significantly higher risk for worse LVH. This may be more important to hypertensive patients. LVH is a marker of cardiovascular risk, and the risk increases with the increasing of severity of LVH.[20] Therefore, the presence of fQRS on ECG may be associated with high risk of cardiovascular events in patients with hypertension.

In addition, our study also found that patients with fQRS had higher risk of left ventricular systolic and diastolic dysfunction, which was

similar to previous study.[21] This might be related to the higher degree of myocardial fibrosis and myocardial ischemia in the fQRS group.

Study Limitations

There are several limitations of the present study. The relatively small sample size might influence the relationship between fQRS and hypertension. In addition, this is a retrospective study and has some disadvantages comparing to prospective study. Furthermore, the exact mechanism of fQRS in patients with hypertension is unknown at present. The clinical significance of fQRS in patients with hypertension needs further prospective studies.

CONCLUSION

The present study suggests that fQRS is a common electrocardiographic phenomenon in patients with hypertension. Although the presence of fQRS on ECG has limited diagnostic value for detection of LVH, fQRS is associated with a significantly higher risk for worse LVH.

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