ORIGINAL ARTICLE

Fragmented QRS Complexes Are Associated with Increased Left Ventricular Mass in Patients with Essential Hypertension

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Background: Left ventricular hypertrophy (LVH) is an independent predictor of poor prognosis in patients with hypertension. In hypertensive hypertrophy, the pathophysiological mechanism is the accumulation of collagen in the myocardium. Fragmented QRS (fQRS) complexes are associated with myocardial fibrosis.

Methods: The study population included 90 patients with hypertension and a normal coronary angiogram. The fQRS was defined as the presence of an additional R wave (R'), notching of the R or S wave, or the presence of fragmentation in two contiguous leads corresponding to a major coronary artery. Echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography.

Results: Forty-five patients who had fQRS and were suitable for the study criteria were compared with 45 age- and gender-matched patients who did not have fQRS according to demographic data and echocardiographic findings. The left ventricular (LV) mass index (g/m^2) was significantly higher ($P < 0.001$) in the group with fQRS. The wall thickness, diameter, volume, and ejection fraction (EF) were higher in this group ($P < 0.001$). Concentric and eccentric hypertrophy were also higher in this group ($P < 0.001$). In the logistic regression analysis, fQRS on ECG was an indicator of LVH in hypertensive patients ($B = 0.064$; $P < 0.001$; odds ratio = 1.066; 95% confidence interval = 1.041–1.092).

Conclusion: The LV mass index of the hypertensive patients who had fQRS on their ECGs was significantly higher than that of the patients who did not, and fQRS on ECG was an important indicator of LVH in hypertensive patients.

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Hypertension is one of the most common diseases in the world and the major cause of cardiac arrhythmias, left ventricular hypertrophy (LVH), coronary artery disease, stroke, renal failure, and both low ejection-fraction (EF) (systolic) and preserved EF (diastolic) heart failure. Aortic aneurisms and endothelial dysfunction are also among the major vascular complications of hypertension.^{1,2} LVH has been reported as an independent predictor of

morbid events and poor prognosis in patients with hypertension.³ In hypertensive hypertrophy, the major pathophysiological mechanisms are fibrosis of myocytes and the accumulation of type I and III collagen in the myocardium.^{4–6} In patients with hypertension, LVH develops as a response to chronic pressure load and elevated wall stress. Myocardial adaptation takes places to restore the wall stress to normal levels, but the adaptation

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in hypertension is not uniform and is quite complicated. No change occurs in the LV geometry in some hypertensive patients, whereas others seem to show concentric remodeling (an increase in the relative wall thickness but no increased LV mass), eccentric hypertrophy (a normal relative wall thickness but an increased LV mass), or concentric hypertrophy (increased relative wall thickness and LV mass).⁷⁻¹¹

Fragmented QRS (fQRS) complexes are defined as changes in QRS morphology with different RSR' patterns. It has been reported that myocardial scarring and ischemia cause slow and inhomogeneous ventricular activation, which results in fragmentation on the ECG.¹² Cardiac magnetic resonance imaging (CMR) and myocardial single-photon emission tomography (SPECT) studies have shown that fQRS on ECG signifies myocardial fibrosis.¹³⁻¹⁶

The aim of this study was to investigate the relationship between fQRS on ECG and the LV mass in hypertensive patients. We hypothesized that the fQRS on the ECG would be related with an increased LV mass in patients with hypertension.

METHODS

Patients

The study group was prospectively selected from patients who underwent elective coronary angiography at our center. Hypertensive patients who had normal coronary arteries were included in this study. The following exclusion criteria were applied:

- (1) Coronary artery disease, coronary ectasia coronary slow flow, coronary anomalies.
- (2) Diabetes mellitus.
- (3) Cardiomyopathy, myocarditis, pericarditis.
- (4) Moderate or severe valve disease.
- (5) Another systemic illness (such as connective tissue disease, renal failure).
- (6) Typical left bundle block or right bundle block on the ECG (QRS duration >120 ms) and incomplete right bundle block (QRS duration <120 ms and RSR' patterns in V₁₋₂ precordial leads).

Diagnostic Criteria of Hypertension

Hypertension was defined according to the Adult Treatment Panel III (ATP-III)¹⁷ criteria (blood pressure $\geq 130/85$ mmHg or the use of antihypertensive drugs)

ECG Criteria for fQRS

The resting baseline 12-lead ECG (filter range, 0.05–150 Hz; AC filter, 60 Hz, 25 mm/s, 10 mm/mv) was analyzed by two independent cardiologists blinded to the study. The fQRS was defined as the presence of an additional R wave (R'), notching of the R or S wave, or the presence of fragmentation (more than one R') in two contiguous leads corresponding to a major coronary artery. There was 99% concordance for ECG signs of fQRS.

Echocardiography

Prior to further echocardiographic examination, the patients' height, weight, systolic and diastolic blood pressure, and heart rate were measured after a period of at least 10 minutes rest. The echocardiographic examination was performed with a 2.5 MHz probe using the Vivid I system (GE Medical Systems, Andover, MA, USA). All the images were recorded on one system. At the end of the study, the recorded images were examined by two experienced cardiologists blinded to the study. On the recorded images, at least three consecutive measurements were made, and their mean was calculated. All the measurements were performed at the end of expiration.

In the parasternal short-axis images, the LV end-diastolic diameter, LV end-systolic diameter, EF, and fractional shortening measured by the Teichholz method¹⁸ were obtained. The relative wall thickness was calculated as twice the posterior wall in diastole, divided by the LV internal diastolic diameter. A value of more than 42% was accepted as indicating an increase.¹⁹ Using the formula defined by Devereux et al.,²⁰ the LVMI was measured on the parasternal short-axis images according to the guidelines of the American Society of Echocardiography.²¹

Statistical Analyses

The statistical software package SPSS for Windows 18.0 (SPSS Inc. Chicago, IL, USA) was

used for the statistical analysis. Normal distributed continuous data are expressed as the mean $\pm$ standard deviation (SD); nonnormal distributed continuous variables are presented as the median (IQR). Categorical data are expressed as numbers with percentages. The student's *t*-test was used for the normally distributed continuous variables, and the Mann-Whitney *U* test was used for the non-normally distributed continuous variables. The categorical data were compared using the chi-square test. The interobserver and intraobserver variability was calculated for the first 5 patients with Pearson's correlation test using the data generated by the two cardiologists (HK and KC) for the interobserver variability and those generated by one cardiologist (HK) for the intraobserver variability. To define factors that affected the presence of fQRS on the ECG independently, the presence of fQRS on the ECG (fQRS [+] and fQRS [-]) was accepted as a dichotomous dependent variable, and logistic regression analysis was performed to search for independent variables. A *p* value less than 0.05 was accepted as statistically significant.

RESULTS

The 45 hypertensive patients who had fQRS on their ECGs and were suitable for the study criteria were compared with 45 age- and gender-matched hypertensive patients who did not have fQRS on their ECGs according to the demographic data and the echocardiographic findings. The results are given in Tables 1–3. Both groups were similar in terms of risk factors for coronary artery disease and cardiovascular drug use. Although the average duration of hypertension was longer in the patient group with fQRS on their ECGs, the difference was not significant ($P = 0.163$). The LVMI (g/m^2) was significantly higher ($P < 0.001$) in the group with fQRS on their ECGs. The wall thickness, diameter, volume, and EF of the LV were also higher in this group ($P < 0.001$). Concentric and eccentric hypertrophy (elevated LV mass) were higher in the group with fQRS on their ECGs, whereas normal geometry and concentric remodeling (LV mass was within normal limits) was higher in the group without fQRS on their ECGs ($P < 0.001$). The presence of fQRS on the ECG was an important indicator of LVH according to the logistic regression analyses ($B = 0.064$, $P < 0.001$, odds

ratio = 1.066, 95% confidence interval = 1.041–1.092). The parasternal short-axis views and 12-derivation ECGs of two patients without and with fQRS on their ECGs are given in Figures 1 and 2, respectively.

DISCUSSION

The main finding in the present study was that the LV mass index of the hypertensive patients who had fQRS on their ECGs was significantly higher than the LV mass index of those who did not. The LV geometry in the form of eccentric or concentric hypertrophy (LV mass index elevated) was also significantly higher in the patients with fQRS on their ECGs compared to the patients without fQRS on their ECGs (75.5 and 22.3%, respectively). The patient group who did not have fQRS on their ECGs more commonly showed normal LV geometry or concentric remodeling. In addition, the presence of fQRS on the ECGs of the hypertensive patients was an independent predictor of an increased LV mass.

The determination of the real prevalence of LVH in a hypertensive population is because of quite different diagnostic criteria and the use of different apparatus for diagnosis. The prevalence of LVH determined with ECG in the patients with hypertension was 6%–17%,²² but a higher prevalence was observed using echocardiography. The prevalence of LVH in a hypertensive population was reported to be 20%–60% in different studies using echocardiography.²³ In the present study, the presence of fQRS on the ECGs had a positive predictive value of 0.75 for revealing LVH.

A body of evidence has pointed to the presence of two key pathological processes affecting the myocardial structure in hypertensive LVH: myocyte hypertrophy and progressive fibrous tissue accumulation in the cardiac interstitium.^{24–26} In patients with hypertensive hypertrophy, homogeneous myocardial tissue becomes heterogeneous. Both postmortem and endomyocardial biopsy studies showed that collagen volume fractions increase in patients with hypertensive hypertrophy compared to normal subjects.^{27–29} Given this body of evidence, it can be considered that the presence of fQRS on ECG might reveal myocardial fibrosis, and hence LVH, in patients with hypertension. In an experimental study, Gardner et al.³⁰ clearly showed that the presence of fQRS on ECG was

Table 1. Demographic Findings in the Two Groups

Variable\Group	fQRS (-)	fQRS(+)	P
Age, year (mean $\pm$ SD)	53.3 $\pm$ 5.65	51.51 $\pm$ 6	0.153
Women, n (%)	31 (68.9)	23 (51.1)	0.087
Smoking, n (%)	6 (13.3)	11 (24.4)	0.181
HL, n (%)	17 (37.8)	16 (35.6)	0.828
HT duration, year (mean $\pm$ SD)	8.64 $\pm$ 2.23	9.31 $\pm$ 2.27	0.153
BSA, kg/m ²	1.7 $\pm$ 0.12	1.76 $\pm$ 0.1	0.048
ACE-ARB, n (%)	24 (53.3)	26 (57.8)	0.673
BB, n (%)	18 (40)	8 (17.8)	0.021
CCB, n (%)	6 (13.3)	7 (15.8)	0.766
STATIN, n (%)	9 (20)	14 (31.1)	0.230

SD = standard deviation; HL = hyperlipidemia; HT = hypertension; BSA = body surface area; ACE-ARB = angiotensin converting enzyme inhibitor-angiotensin receptor blockers; BB = beta-blocker; CCB = calcium canal blockers.

Table 2. Echocardiographic Findings in the Two Groups

Variable\Group	fQRS (-)	fQRS (+)	P
IVS, cm (mean $\pm$ SD)	0.87 $\pm$ 0.15	1.03 $\pm$ 0.1	<0.001
PD, cm (mean $\pm$ SD)	0.9 $\pm$ 0.16	1.07 $\pm$ 0.1	<0.001
EDD, cm (mean $\pm$ SD)	4.75 $\pm$ 0.35	5.48 $\pm$ 0.48	<0.001
ESD, cm (mean $\pm$ SD)	2.8 $\pm$ 0.27	3.4 $\pm$ 0.4	<0.001
EDV, ml (mean $\pm$ SD)	106.5 $\pm$ 19	150.9 $\pm$ 28.4	<0.001
ESV, ml (mean $\pm$ SD)	31.1 $\pm$ 8.8	48.8 $\pm$ 15.5	<0.001
SV, ml (mean $\pm$ SD)	75 $\pm$ 14.8	101 $\pm$ 17.2	<0.001
EF, (%) (mean $\pm$ SD)	70.3 $\pm$ 4.2	67.9 $\pm$ 4.7	0.033
FS, (%) (mean $\pm$ SD)	39.9 $\pm$ 3.4	38.4 $\pm$ 3.5	0.04
LVMI, gr/m ² (mean $\pm$ SD)	87.8 $\pm$ 26.2	133.7 $\pm$ 21.4	<0.001
RWT (mean $\pm$ SD)	0.38 $\pm$ 0.06	0.39 $\pm$ 0.04	0.107

SD = standard deviation; IVS = interventricular septum; PD = posterior wall; EDD = end-diastolic diameter; ESD = end-systolic diameter; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction; FS = fractional shortening; LVMI = left ventricular mass index; RWT = relative wall thickness.

Table 3. Left Ventricular Geometric Findings in the Two Groups

Variable\Group	fQRS(-)	fQRS (+)	P
Normal, n (%)	26 (57.8)	4 (8.9)	<0.001
Concentric remodeling, n (%)	9 (20)	7 (15.6)	
Concentric hypertrophy, n (%)	3 (6.7)	11 (24.4)	
Eccentric hypertrophy, n (%)	7 (15.6)	23 (51.1)	

associated with myocardial fibrosis. In this study, the presence of fQRS complexes was apparent by the existence of depolarization waves, which produced zigzags because of myocardial fibrosis. In controlled studies using CMR and SPECT, the presence of fQRS on ECG was reported to indicate myocardial fibrosis in different patient groups.¹³⁻¹⁶ The appearance of the fQRS complexes on the ECG of hypertensive patients could be due to the alteration of the depolarization vectors by interstitial fibrosis.

The prevalence and the degree of interstitial fibrosis progressively increase in hypertensive

patients and are related to the duration of hypertension.²⁸ In the present study, although not statistically significant, the duration of hypertension in the patients who had fQRS on their ECGs was longer than in the patients without fQRS on their ECGs. In addition, the end-systolic diameter was statistically higher and the EF was lower in the patient group with fQRS on their ECGs compared to the group without fQRS on their ECGs. Fractional shortening was lower in the patient group with fQRS on their ECGs. These findings suggest that interstitial fibrosis was more common and severe in the patient group with

Figure 1. Twelve-Lead ECG (upper panel) and parasternal short-axis echocardiographic view (bottom panel) of a patient without fQRS on ECG.

fQRS on their ECGs because reactive interstitial fibrosis seen in hypertension has been shown to result in the impairment of LV contractile function.³¹ Furthermore, a negative correlation

has been determined between the LVEF and the collagen volume fraction, which is an indicator of the prevalence and the severity of interstitial fibrosis in hypertensive patients.³²

Figure 2. Twelve-Lead ECG (upper panel) and parasternal short-axis echocardiographic view (bottom panel) of a patient with fQRS on ECG. There are fQRS complexes in Lead II-III-aVF-V₆ (arrowheads).

LV adaptation to hypertension is quite complicated. Four different groups were determined in the hypertensive patients in terms of relative wall thickness and ventricular mass index: (1) a normal

group (both the relative wall thickness and the LV mass were within normal limits); (2) a concentric remodeling group (the LV mass was normal, but the relative wall thickness was elevated); (3) a

concentric hypertrophy group (both the relative wall thickness and the LV mass were elevated); (4) an eccentric hypertrophy group (the LV mass was elevated, but the relative wall thickness was normal).³³ The frequency of fQRS on the ECG was statistically higher in the group with LVH (eccentric and concentric hypertrophy) compared to the group without LVH (normal and concentric remodeling). According to multivariate logistic regression analysis, the presence of fQRS on the ECG was an important indicator of LVH ($B = 0.064$, $P < 0.001$, odds ratio = 1.066, 95% confidence interval = 1.041–1.092)

LV geometry in the form of eccentric or concentric hypertrophy was higher in the patient group who had an elevated LV mass with fQRS on their ECGs. In addition, the frequency of normal or concentric remodeling of the LV geometry was significantly higher in the patient group without fQRS on their ECGs than the group with fQRS on their ECGs.

CONCLUSION

The presence of fQRS on the ECG was an important indicator of LVH in hypertensive patients. We conclude that the fQRS on the ECG could be the result of the interstitial fibrosis observed in these patients.

REFERENCES

1. Frohlich ED, Apstein C, Chobanian AV, et al. The heart in hypertension. *N Engl J Med* 1992;327:998–1008.
2. Leonetti G, Cuspidi C. Heart and vascular changes in hypertension. *J Hypertens* 1995;13(Suppl 2):S29–S34.
3. Ducharme A, Swedberg K, Pfeffer MA, et al. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J* 2006;152:86–92.
4. Jalil JE, Doering CV, Janicki JS, et al. Fibrillar collagen and myocardial stiffness in the intact hypertrophied rat left ventricle. *Circ Res* 1989;64:1041–1050.
5. Diez J, Lopez B, Gozales A, et al. Clinical aspects of hypertensive myocardial fibrosis. *Curr Opin Cardiol* 2001;16:328–335.
6. Gonzales A, Lopez B, Diez J. Fibrosis in hypertensive heart disease role of the angiotensin-aldosterone system. *Med Clin N Am* 2004;88:93–97.
7. Abi-Samra F, Fouad FM, Tarazi RC. Determinants of left ventricular hypertrophy and function in hypertensive patients: An echocardiographic study. *Am J Med* 1983;75(Suppl 3A):26–33.
8. Devereux RB, Savage DD, Sachs1, et al. Relation of hemodynamic load to left ventricular hypertrophy and performance in hypertension. *Am J Cardiol* 1983;51:171–176.
9. Campus S, Malavasi A, Ganau A. Systolic function of the hypertrophied left ventricle. *J Clin Hypertens* 1987;3:79–87.
10. de Simone G, DiLorenzo L, Costantinue G, et al. Supernormal contractility in primary hypertension without left ventricular hypertrophy. *Hypertension* 1988;11:457–463.
11. de Simone G, DiLorenzo L, Costantinue G, et al. Hemodynamic hypertrophied left ventricular patterns in systemic hypertension. *Am J Cardiol* 1987;60:1317–1321.
12. Flowers NC, Horan LG, Thomas JR, et al. The anatomic basis for high-frequency components in the electrocardiogram. *Circulation* 1969;39:531–539.
13. Basaran Y, Tigen K, Karaahmet T, et al. Fragmented QRS complexes are associated with cardiac fibrosis and significant intraventricular systolic dyssynchrony in nonischemic dilated cardiomyopathy patients with a narrow QRS interval. *Echocardiography* 2011;28:62–68.
14. Mahenthiran J, Khan BR, Sawada SG, et al. Fragmented QRS complexes not typical of a bundle branch block: a marker of greater myocardial perfusion tomography abnormalities in coronary artery disease. *J Nucl Cardiol* 2007;14(3):347–353.
15. 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.
16. Homsy M, Alsayed L, Safadi B, et al. Fragmented QRS complexes on 12-lead ECG: A marker of cardiac sarcoidosis as detected by gadolinium cardiac magnetic resonance imaging. *Ann Noninvasive Electrocardiol* 2009;14:319–326.
17. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497.
18. Feigenbaum H. Echocardiographic Evaluation of Cardiac Chamber. In: Feigenbaum H (ed.): *Echocardiography*. 5th ed. Baltimore: Williams Wilkins, 1994, pp. 134–180.
19. Savage DD, Garrison RJ, Kannel WB, et al. The spectrum of left ventricular hypertrophy in a general population sample: The Framingham Study. *Circulation* 1987;75:26–33.
20. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 1986;57:450–458.
21. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358–367.
22. Levy D, Labib SB, Anderson KM, et al. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. *Circulation* 1990;81:815–820.
23. Levy D, Anderson KM, Savage DD, et al. Echocardiographically detected left ventricular hypertrophy: Prevalence and risk factors. The Framingham Heart Study. *Ann Intern Med* 1988;108:7–13.
24. Diez J, Lopez B, Gonzales A, et al. Clinical aspects of hypertensive myocardial fibrosis. *Curr Opin Cardiol* 2001;16:328–335.
25. Gonzalez A, Lopez B, Diez J. Fibrosis in hypertensive heart disease role of the angiotensin-aldosterone system. *Med Clin N Am* 2004;88:83–97.

26. Rossi MA. Connective tissue skeleton in the normal left ventricle and in hypertensive left ventricular hypertrophy and chronic chagasic myocarditis. *Med Sci Monit* 2001;7:820-832.
27. Olivetti G, Melissari M, Balbi T, et al. Myocyte cellular hypertrophy is responsible for ventricular remodelling in the hypertrophic heart of middle aged individuals in the absence of heart failure. *Cardiovasc Res* 1994;28:1199-1208.
28. Rossi MA. Pathologic fibrosis and connective tissue matrix in left ventricular hypertrophy due to chronic arterial hypertension in humans. *J Hypertens* 1998;16:1031-1041.
29. Ciulla MM, Paliotti R, Hess DB, et al. Echocardiographic patterns of myocardial fibrosis in hypertensive patients: Endomyocardial biopsy versus ultrasonic tissue characterization. *J Am Soc Echocardiogr* 1997;10:657-664.
30. Gardner PI, Ursell PC, Fenoglio JJ Jr, et al. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. *Circulation* 1985;72:596-611.
31. Averill DB, Ferrario CM, Tarazi RC, et al. Cardiac performance in rats with renal hypertension. *Circ Res* 1976;38:280-288.
32. McLennan JM, Dargie HJ. Ventricular arrhythmias in hypertensive left ventricular hypertrophy. Relation to coronary artery disease, left ventricular dysfunction, and myocardial fibrosis. *Am J Hypertens* 1990;3:735-740.
33. Ganau A, Devereux RB, Roman MJ, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol* 1992;19:1550-1558.