Association of fragmented QRS complexes on ECG with left ventricular diastolic function in hypertensive patients

Hipertansiyonlu hastalarda fragmente QRS komplekslerinin sol ventrikül diyastolik fonksiyonu ile ilişkisi

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ABSTRACT

Objectives: Diastolic dysfunction occurs as a result of interstitial fibrosis in hypertensive patients. Fragmented QRS (fQRS) on ECG signifies myocardial fibrosis in various clinical situations. We investigated whether fQRS on ECG is related to diastolic dysfunction in patients with hypertension.

Study design: The study population included 72 hypertensive patients with normal coronary angiogram. Fragmented QRS was defined as the presence of an additional R wave (R'), notching of the R or S wave or fragmentation in two contiguous leads corresponding to a major coronary artery. Echocardiography was performed to all patients to detect diastolic dysfunction. Diastolic dysfunction was regarded as non-severe if patients had normal diastolic function or grade 1 diastolic dysfunction or severe if they had grade ≥2 diastolic dysfunction.

Results: Thirty-two patients had fQRS on ECGs (fQRS [+] group) and there were 40 patients who did not have fQRS on their ECGs (fQRS [-] group). The two groups were similar in terms of baseline characteristics. In patients with fQRS on the ECG, severe diastolic dysfunction was more prevalent (59.4% *vs.* 7.5%, p<0.001). The duration of hypertension was longer in patients with fQRS on the ECG (p<0.001). The presence of fQRS on the ECG was an indicator for severe diastolic dysfunction (B=1.954; odds ratio=7; 95% confidence interval=1.4-35.4; p=0.018).

Conclusion: The presence of fQRS complexes on ECG predicts more severe diastolic dysfunction in patients with hypertension.

ÖZET

Amaç: Hipertansiyonlu hastalarda diyastolik fonksiyon bozukluğu interstisiyel fibrozun bir sonucudur. EKG'de fragmente QRS (fQRS) farklı klinik durumlarda miyokart fibrozunu gösterir. Bu çalışmada, hipertensiyonlu hastalarda fQRS'nin ciddi diyastolik fonksiyon bozukluğuyla ilişkisi olup olmadığı araştırıldı.

Çalışma planı: Çalışmaya koroner anjiyografisi normal olan 72 hipertansiyonlu hasta alındı. Fragmente QRS, majör koroner arterin beslediği alanda en az iki ardışık derivasyonda ek bir R dalgasının varlığı (R'), R veya S dalgasının çentiklenmesi ya da fragmentasyonu olarak tarif edildi. Diyastolik fonksiyon bozukluğunu belirlemek için tüm hastalara ekokardiyografi yapıldı. Normal diyastolik işlevler veya evre 1 diyastolik işlev bozukluğu ağır olmayan, evre 2 veya üstü diyastolik işlev bozukluğu ise ağır diyastolik işlev bozukluğu olarak kabul edildi.

Bulgular: Hastaların 32'sinde EKG'de fQRS mevcut iken (fQRS [+] grup), 40 hastada yoktu (fQRS [–] grup). Her iki grup bazal özellikler bakımından benzerdi. fQRS (+) grupta ciddi diyastolik fonksiyon bozukluğu daha fazla bulundu (%59.4 ve %7.5, p<0.001). Hipertansiyonun süresi fQRS (+) grupta daha uzun idi (p<0.001). EKG'de fQRS'nin varlığının ciddi diyastolik fonksiyon bozukluğunun bir belirteci olduğu bulundu (B=1.954; odds oranı=7; %95 güven aralığı=1.4-35.4; p=0.018).

Sonuç: Hipertansiyonlu hastalarda EKG'de fQRS komplekslerinin varlığı ciddi diyastolik fonksiyon bozukluğu için bir belirteçtir.

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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 systolic and diastolic heart failure. About half of hypertensive patients with heart failure symptoms have diastolic heart failure, a severe condition.[1] Causes of left ventricular (LV) diastolic dysfunction are impaired ventricular relaxation and decreased compliance in patients with hypertension. Although the pathophysiological mechanism of LV diastolic dysfunction in hypertensive patients is multifactorial, interstitial fibrosis and accumulation of type I and III collagen in the myocardium play a significant role.[2] These alterations in hypertensive hearts account for the development of LV diastolic dysfunction.[3] On the other hand, it has been reported that degree of myocardial fibrosis is the most significant factor related to diastolic dysfunction in patient with hypertension.[4]

Fragmented QRS (fQRS) complexes are defined as changes in QRS morphology with different RSR' patterns. Cardiac magnetic resonance imaging (CMR) and myocardial single-photon emission tomography (SPECT) studies have shown that presence of fQRS on ECG signifies myocardial fibrosis.[5,6] The presence of fQRS complexes on 12-lead ECG has been found to be associated with all-cause mortality and recurrent cardiac events.[7] Recently, Brenyo et al.[8] reported that the presence of fQRS complexes on ECG were an independent predictor for sudden cardiac death in a patient with idiopathic dilated cardiomyopathy.

The aim of this study was to investigate the relationship between fQRS complexes on ECG and LV diastolic function in hypertensive patients. We hypothesized that fQRS on ECGs would be related to severe diastolic abnormalities in patients with hypertension.

PATIENTS AND METHODS

Patients

Patients who underwent coronary angiography in our center between January 2011 and December 2012 were evaluated in this prospective case control study. Hypertensive patients who had normal coronary arteries were included in this study. Indications for coronary angiography were typical symptoms, positive exercise testing or myocardial perfusion imaging in the study group. Patients with coronary artery disease, coronary anomalies, diabetes mellitus, other systemic illnesses (such as connective tissue disease or renal failure), cardiomyopathy, moderate or severe valve disease, atrial fibrillation, typical left bundle block or right bundle block on the ECG (QRS duration >120 ms), incomplete right bundle block (QRS duration <120 ms and RSR' patterns in V1-2 precordial leads), or poor quality imaging preventing analysis were excluded. Patients who were unable to perform Valsalva maneuver were also excluded. Secondary forms of hypertension were not included in this study.

Abbreviations:

A	*Mitral late wave*
CMR	*Cardiac magnetic resonance*
E	*Mitral early wave*
EDT	*E deceleration time*
fQRS	*Fragmented QRS*
LV	*Left ventricular*
LVM	*LV mass*
SPECT	*Single-photon emission tomography*

Diagnostic criteria of hypertension

Hypertension was defined according to the Adult Treatment Panel III (ATP-III)[9] criteria (blood pressure ≥130/85 mmHg or the use of antihypertensive drugs).

ECG criteria for fQRS

The resting baseline 12-lead ECG (filter range, 0.05 to 150 Hz; AC filter, 60 Hz; 25 mm/s; 10 mm/mV) was analyzed by two independent cardiologists blinded to the study. 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.[10] Examples of 12-derivation ECG of two patients with and without fQRS in ECG are given in Fig. 1 and Fig. 2 respectively.

Echocardiographic examination

Prior to 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 using the Vivid I system (GE Medical Systems, Andover, MA, USA). All the images were recorded on this system. At the end of the study, the recorded images were examined by two experienced cardiologists blinded to the study. On the recorded images, an average of 2 consecutive measurements was taken at the end of expiration. All the echocardiographic measurements were taken according to the guidelines of the American Society of Echocardiography.[11]

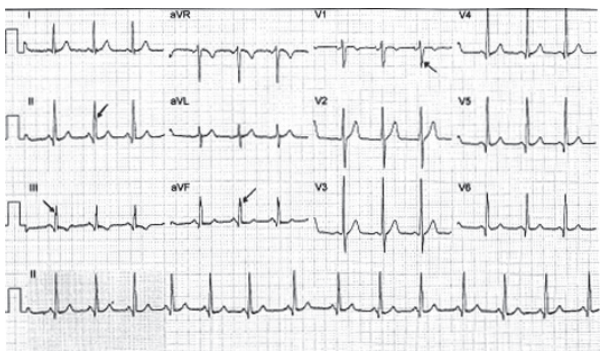

Figure 1. 12-lead ECG from a hypertensive patient with Grade 2 diastolic dysfunction showing fragmented QRS complexes in leads II, III, aVF, and V1 (arrow heads).

M-mode measurements and calculations

Left ventricular volumes were estimated from end-diastolic and end-systolic dimensions by using the Teichholz formula[12] on the parasternal short-axis images. Using the formula defined by Devereux et al.,[13] the LV mass (LVM) was calculated and indexed for body surface area. Increased LVM index was defined as LVM index ≥95 g/m^2 for female and LVM index ≥115 g/m^2 for male patients.[14]

Doppler measurements and calculations

Transmitral early (E) and late (A) velocities and their ratio (E/A) and the E deceleration time (EDT) were measured in the apical four-chamber view.

Myocardial velocities measurements and calculations

The myocardial velocities were measured at lateral and septal annulus levels on the apical four-chamber images. Among the mitral annular tissue Doppler parameters, peak diastolic early (e'), and late (a') velocities were measured. The pulmonary capillary wedge pressure was calculated using the E/e' ratio as defined by Nagueh et al.[15]

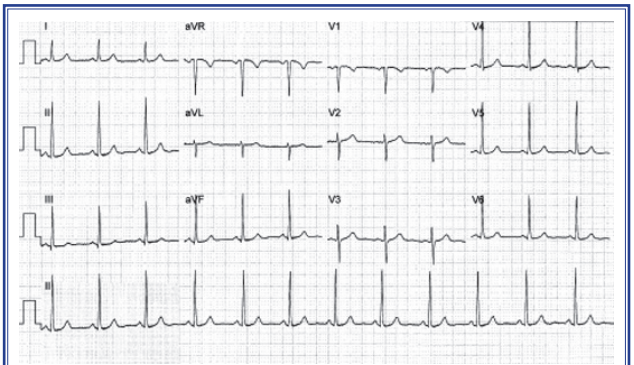

Figure 2. 12-lead ECG from a hypertensive patient with Grade 1 diastolic dysfunction showing no fragmented fQRS on the ECG.

Grading diastolic function

Grading of diastolic function was carried out according to Redfield et al.:[16]

1. Normal diastolic function: Subjects who had all of the following Doppler findings were classified as having normal diastolic function: *i)* mitral E/A rate higher than 0.75 and lower than 1.5 and EDT higher than 140 msn, *ii)* change in E/A rate higher than 50% during peak Valsalva maneuver, and *iii)* E/e' rate lower than 9.

2. Grade 1 (impaired relaxation type) diastolic dysfunction: Patients with at least two of the following Doppler criteria were considered as having Grade 1 (impaired relaxation) diastolic dysfunction: *i)* mitral E/A rate lower than 0.75 and EDT higher than 140 msn, *ii)* change in E/A rate lower than 50% during the peak Valsalva maneuver, and *iii)* E/e' rate lower than 9.

3. Grade 2 (pseudo-normal type) diastolic dysfunction: Patients with at least two of the following Doppler criteria were considered as having Grade 2 (pseudo-normal) diastolic dysfunction: *i)* mitral E/A rate higher than 0.75 and lower than 1.5 and EDT higher than 140 msn, *ii)* change in E/A rate higher than 50% during the peak Valsalva maneuver, and *iii)* E/e' rate between 9 and 12.

4. Grade 3 (restrictive type) diastolic dysfunction: Patients with at least two of the following Doppler criteria were considered as having Grade 3 (restrictive) diastolic dysfunction: *i)* mitral E/A higher than 1.5 and EDT lower than 140 msn, *ii)* change in E/A rate higher than 50% (reversible Grade 3) or less than 50% (irreversible Grade 3) during the peak Valsalva maneuver, and *iii)* E/e' rate more than 12.

5. Unclassified patients: Patients who had only one of the above-mentioned Doppler criteria were considered unclassified and excluded from the study.

Diastolic function was regarded as non-severe if patients had normal diastolic function or grade 1 diastolic dysfunction, and severe if they had grade ≥2 diastolic dysfunction.

Statistical analyses

SPSS for Windows 18.0 (SPSS Inc. Chicago, Illinois, USA), a statistical package program, was used for statistical analysis. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. Normally distributed, continuous data are expressed as mean±standard deviation (SD). Categorical data are expressed as numbers with percentages. We used the Student's t-test for normally distributed continuous variables. Categorical data were compared using the Chi-square or Fisher's exact test, where applicable. Severe diastolic dysfunction was used as a dichotomous dependent variable, and multivariate logistic regression analysis was performed to identify independent variables. A p-value of <0.05 was considered statistically significant.

Informed consent was received from all patients. The study protocol was approved by the institutional ethics committee.

RESULTS

347 of the 2.082 consecutive patients who underwent a coronary angiography at our institution from January 2011 to December 2012 had normal coronary arteries. Seventy two patients were suitable for the study according to the above criteria. Thirty-two patients had fQRS on their ECGs (fQRS [+] group), 40 patients did not have fQRS on their ECGs (fQRS [–] group). Both groups were compared in terms of demographic data, echocardiographic findings, and cardiovascular drug use. The results are given in Tables 1-3. The groups were similar in terms of risk factors for coronary artery disease and cardiovascular drug use.

Whereas Grade 2 diastolic dysfunction (pseudonormal type) was present in 3 patients (7.5%) without fQRS on their ECGs, it was present in 19 patients (59.4%) with fQRS on their ECGs. In patients with fQRS on their ECGs, Grade 2 diastolic dysfunction was statistically more prevalent (p<0.001). None of the patients had Grade 3 (restrictive) diastolic dysfunction. The average duration of hypertension (year) was longer in the patient group with fQRS on their ECGs than in those without fQRS (15.72±4.3 versus 11.85±3.9), and the difference between the groups was significant (p=0.002). The LVM index (g/m^2) was significantly higher in the patients with fQRS on their ECGs (131.6±14.9 *vs.* 95.7±13.3, p<0.001).

We classified those with normal diastolic function and Grade 1 diastolic dysfunction as patients with non-severe diastolic dysfunction, and those with Grade 2 diastolic dysfunction as patients with severe diastolic dysfunction. To define factors that affected diastolic function, classified diastolic function (non-

Table 1. Demographic findings in the fQRS (–) and fQRS (+) groups

Variable\Group	fQRS (–) (n=40)			fQRS (+) (n=32)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			54.18±7.9			55±5.5	0.620
Male	11	27.5		11	34.4		0.529
Smoking	6	15		8	25		0.287
Hyperlipidemia	7	17.5		10	31.3		0.172
Hypertension duration (year)			11.85±3.9			15.72±4.3	**<0.001**
Body mass index (kg/ m^2)			26.93±2.2			27.24±1.7	0.513
Body surface area (m^2)			1.72±0.1			1.76±0.1	0.108
ACE-ARB	19	47.5		21	65.6		0.124
Beta blocker	14	35		12	37.5		0.826
Calcium canal blocker	6	15		10	31.3		0.099
STATIN	6	15		5	15.6		0.942
Increased LVM index	11	27.5		31	96.9		**<0.001**

fQRS: Fragmented QRS; SD: Standard deviation; ACE-ARB: Angiotensin converting enzyme inhibitor-Angiotensin receptor blocker; LVM: Left ventricular mass.

Table 2. Echocardiographic findings in the fQRS (–) and fQRS (+) groups

Variable\Group	fQRS (–) (n=40)	fQRS (+) (n=32)	*p*
	Mean±SD	Mean±SD	
Mitral early wave (cm/s)	59.8±12.98	74.66±12.74	**<0.001**
Mitral late wave (cm/s)	90.98±12.7	80.13±11	**<0.001**
Mitral early wave/ Mitral late wave	0.66±0.13	0.946±018	**<0.001**
E wave deceleration time (ms)	234.6±27.6	195.75±23.08	**<0.001**
e' (lateral), (cm/s)	9.2±1.3	8.4±1.2	**0.006**
e' (septal), (cm/s)	7.38±1.93	6.53±1.74	0.056
E/e' (average)	7.29±1.41	9.74±1.96	**<0.001**
Left ventricular mass index (g/m^2)	95.7±13.3	131.6±14.9	**<0.001**

fQRS: Fragmented QRS, SD: Standard deviation, e': Tissue Doppler mitral annular early wave.

Table 3. Left ventricular diastolic function findings in the fQRS (–) and fQRS (+) groups

Variable/Group	fQRS (–) (n=40)		fQRS (+) (n=32)		p
	n	%	n	%	
Normal	5	12.5	0	0	**0.061***
Grade 1 diastolic dysfunction	32	80	13	40.6	**<0.001**
Grade 2 diastolic dysfunction	3	7.5	19	59.4	**<0.001**

*: Fisher's exact test. fQRS: Fragmented QRS.

Table 4. Univariate analyses results of patients in the severe and non-severe diastolic dysfunction groups

Variable/Group	Severe DD	Non-severe DD	p	OR	95% CI
fQRS n (%)	20 (60.6)	12 (30.8)	0.013	3.45	1.3-9.2
HT duration, year (mean±SD)	12.67±4.14	14.64±4.59	0.063	1.1	0.99-1.24
Age, year (mean±SD)	56.03±4.40	53.28±6.34	0.044	1.096	1.002-1.199

severe *vs.* severe) was accepted as a dichotomous dependent variable, and multivariate logistic regression analysis was performed to search for independent variables. In the multivariate logistic regression analysis, age, hypertension duration, and fQRS on ECG were independent variables. Univariate analyses results of the patients in the severe and non-severe diastolic dysfunction groups are given in Table 4. Multivariate logistic regression analysis revealed that fQRS was an indicator of patients in the severe diastolic dysfunction (B=1.954; odds ratio=7; 95% confidence interval=1.4-35.4; p=0.018). Examples of 12-derivation ECG of two patients with and without fQRS in ECG are given in Figure 1 and 2 respectively.

DISCUSSION

The main finding of the present study is that LV diastolic dysfunction is more severe in hypertensive patients with fQRS on their ECGs compared to those without fQRS. Additionally, the presence of fQRS on ECG is shown to be an indicator of severe (Grade 2) diastolic dysfunction.

The risk of heart failure is higher in hypertensive

patients than normal individuals.[17] Left ventricular diastolic dysfunction is a common finding in hypertensive patients[18] and the major cause of heart failure in these patients. The mechanisms by which diastolic dysfunction develops in hypertensive patients are multifactorial. A substantial body of evidence suggests that myocardial fibrosis and collagen deposition play an important role, and experimental and clinical studies have shown that myocardial fibrosis is critically involved in development of diastolic dysfunction. In biopsy-proven studies, it was shown that myocardial collagen volume fraction frequently increased in hypertensive patients.[19,20] Moreover, one study revealed that antihypertensive treatment was related to regression of myocardial fibrosis.[21] In their study, Matsubara et al.[2] found that increased myocardial collagen concentration was associated with diastolic dysfunction in rats with unilateral renal ischemia. In another experimental study, Conrad et al.[22] reported that in spontaneous hypertensive rats, myocardial fibrosis accounted for the development of diastolic dysfunction and eventual diastolic heart failure by increasing myocardial stiffness. In other experimental studies on hypertensive rats, these findings were confirmed.[23-25] These experimental findings have also been supported by clinical studies in patients with hypertension. Treatment with lisinopril, an angiotensin converting enzyme inhibitor was associated with decreasing the concentration of myocardial collagen and improvement in diastolic function parameters in hypertensive patients.[26] In addition, it was demonstrated that collagen volume fraction assessed by endomyocardial biopsy was related to parameters showing diastolic functions in patients with essential hypertension and treatment with losartan (an angiotensin receptor blocker) was associated with improvement of diastolic functions.[27] Thus, it appears that myocardial fibrosis is one of the main causes of impaired diastolic function in hypertensive patients.

Although endomyocardial biopsy is the gold standard method in the diagnosis of myocardial fibrosis, it may cause major complications. CMR and SPECT are the most commonly used and accurate noninvasive methods for the detection of myocardial fibrosis. Using these two methods, the presence of fQRS on ECG was shown to indicate myocardial fibrosis in studies of patients with idiopathic dilated cardiomyopathy,[28] coronary artery disease,[5] and collagen tissue disease.[6] Furthermore, an experimental study has shown that fQRS complexes are associated with interstitial myocardial fibrosis.[29] In the study,[29] researchers speculated that the reason of fQRS on ECG were produced zigzags of depolarization waves. The appearance of fQRS complexes on the ECGs of hypertensive patients may be associated with this mechanism.

In the present study, advanced diastolic dysfunction in patients with fQRS can be explained by more diffuse and serious myocardial fibrosis. The significantly higher LVMI observed in patients with fQRS provides additional evidence for more advanced myocardial fibrosis in these patients. The significantly longer duration of hypertension in patients with fQRS also points to more diffuse and serious myocardial fibrosis. Rossi[30] reported that myocardial collagen volume fraction, a measure of tissue collagen level, increased progressively in hypertensive patients, and the severity of myocardial fibrosis increased with the increase in severity of hypertensive heart disease. It seems plausible to suggest that prolonged disease duration increases the severity of myocardial fibrosis, and consequently leads to further deterioration of LV diastolic function in patients with fQRS on their ECGs.

Limitations

Several limitations should be considered. The first limitation of the study is the small sample size because our study consists of selected cases. The absence of a qualitative measure of myocardial scarring, such as myocardial SPECT and cardiac magnetic resonance imaging, is another limitation. Further studies with larger numbers and a qualitative measure of myocardial scarring are needed to confirm these findings.

The most important finding of this study is that diastolic dysfunction is more severe in patients with fQRS on their ECGs than in those without fQRS. In addition, the presence of fQRS on the ECG is established as an independent risk factor for advanced diastolic dysfunction. Finally, it may be speculated that more severe diastolic abnormalities in hypertensive patients with fQRS can be explained by more diffuse and serious myocardial fibrosis in these patients.

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Key words: Echocardiography; electrocardiography; heart failure, diastolic; hypertension; ventricular dysfunction, left.

Anahtar sözcükler: Ekokardiyografi; elektrokardiyografi; kalp yetersizliği, diyastolik; hipertansiyon; ventrikül disfonksiyonu, sol.