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Fragmented QRS May Be Associated with Subclinical Left Ventricular Dysfunction in Patients with Hypertension

Muzaffer Kahyaoğlu[1], Çetin Geçmen[2], Mehmet Çelik[2], Yusuf Yılmaz[3], Emrah Bayam[2], Ender Özgün Çakmak[2], Özkan Candan[4], İbrahim Akın İzgi[5], Cevat Kırma[2]

[1] Department of Cardiology, Abdulkadir Yuksel State Hospital, Gaziantep, Turkey
[2] Department of Cardiology, Kartal Koşuyolu High Specialization Training and Research Hospital, Istanbul, Turkey
[3] Department of Cardiology, Goztepe Training and Research Hospital, Istanbul, Turkey
[4] Department of Cardiology, Faculty of Medicine, University of Usak, Usak, Turkey
[5] Department of Cardiology, Faculty of Medicine, University of Abant Izzet Baysal, Bolu, Turkey

ABSTRACT

Introduction: In hypertensive patients, the early detection of subclinical left ventricular dysfunction could prevent or delay patients from heart failure by aggressive risk factor control and rigorous medical management. Fragmented QRS (fQRS) is a marker of myocardial fibrosis, and myocardial fibrosis causes left ventricular dysfunction in hypertensive patients. In this study, we aimed to assess the association between the presence of fQRS and LV function at hypertensive patients using the speckle tracking echocardiography method.

Patients and Methods: The study included a total of 95 hypertensive patients. Detailed anamnesis, physical examination, laboratory tests, 12-lead electrocardiography, and conventional echocardiography were administered to all patients. The participating patients were divided into two groups as fQRS (+) (n= 33) and fQRS (-) (n= 62).

Results: Compared to the fQRS (-) group, the fQRS (+) group had older age, the average duration of hypertension was longer, and had a higher hemoglobin level. In the fQRS (+) group, interventricular septum thickness, posterior wall thickness, left ventricular mass index, relative wall thickness, deceleration time, and E/Em were significantly higher while left ventricular global longitudinal strain values were lower compared to fQRS (-) group. In the multiple linear regression analysis, fQRS and duration of hypertension were identified as independent predictors of LV-GLS.

Conclusion: In this study, we demonstrated that subclinical left ventricular dysfunction developing secondary to myocardial fibrosis could be predicted by fQRS, a simple marker in 12-lead electrocardiography..

Key Words: Fragmented QRS; hypertension; left ventricular dysfunction; speckle tracking echocardiography.

Fragmente QRS, Hipertansiyonlu Hastalarda Subklinik Sol Ventrikül Disfonksiyonu ile İlişkili Olabilir

ÖZ

Giriş: Hipertansif hastalarda, subklinik sol ventrikül disfonksiyonunun erken tespiti, agresif risk faktörü kontrolü ve tıbbi tedavi ile hastaların kalp yetmezliğini önleyebilir veya geciktirebilir. Fragmente QRS (fQRS), miyokardiyal fibrozisin bir belirtecidir ve miyokardiyal fibrozis, hipertansif hastalarda sol ventrikül disfonksiyonuna neden olur. Bu çalışmada, hipertansif hastalarda fQRS varlığı ile sol ventrikül fonksiyonu arasındaki ilişkiyi benek takip ekokardiyografi yöntemi ile değerlendirmek amaçlanmıştır.

Hastalar ve Yöntem: Çalışmaya toplam 95 hipertansif hasta dahil edilmiştir. Tüm hastalara ayrıntılı anamnez, fizik muayene ve laboratuvar testleri yapılmış, 12 derivasyonlu elektrokardiyografi çekilmiş ve konvansiyonel ekokardiyografi yapılmıştır. Katılan hastalar fQRS (+) (n= 33) ve fQRS (-) (n= 62) olarak iki gruba ayrılmıştır.

Bulgular: fQRS (-) grubuyla karşılaştırıldığında, fQRS (+) grubu daha yaşlı, ortalama hipertansiyon süresi daha uzun ve daha yüksek hemoglobin düzeyine sahip bulunmuştur. fQRS (+) grubunda interventriküler septum kalınlığı, arka duvar kalınlığı, sol ventriküler kitle indeksi, rölatif duvar kalınlığı, deselerasyon zamanı ve E/Em parametreleri anlamlı olarak yüksek iken, sol ventriküler global longitudinal strain değerleri fQRS (-) grubuna göre anlamlı olarak daha düşük tespit edilmiştir. Çoklu doğrusal regresyon analizi sonucunda, fQRS varlığı ve hipertansiyon süresi, sol ventriküler global longitudinal strain için bağımsız prediktörler olarak tanımlanmıştır.

Sonuç: Bu çalışmada, miyokardiyal fibrozise sekonder gelişen subklinik sol ventrikül disfonksiyonunun, 12 derivasyonlu elektrokardiyografide basit bir belirteç olan fQRS ile tahmin edilebileceğini göstermiştir.

Anahtar Kelimeler: Fragmente QRS; hipertansiyon; sol ventriküler disfonksiyon; benek takip ekokardiyografi.

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Correspondence

Muzaffer Kahyaoğlu

E-mail: mkahyaoglu09@hotmail.com
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INTRODUCTION

Essential hypertension is a serious public health problem which is one of the leading causes of mortality and morbidity worldwide[1]. Hypertension is associated with a significant increase in the risk of adverse cardiovascular and renal outcomes such as left ventricular hypertrophy, heart failure, ischemic and hemorrhagic stroke, ischemic heart disease, or chronic kidney disease[1]. Hypertension creates a chronic pressure load on the heart, causing structural changes on the left ventricle (LV) and left atrium, which leads to impaired left ventricular systolic and diastolic functions. Longstanding pressure and volume overload cause left ventricular hypertrophy which plays a significant role in the pathophysiology of heart failure with both reduced and preserved ejection fraction (EF)[2]. Chronic pressure load due to hypertension also causes various abnormalities in electrocardiography (ECG). Previous studies have shown that fragmented QRS (fQRS) is a more common finding in hypertensive patients than normotensive patients, and it is associated with LV hypertrophy, increased epicardial adipose tissue, non-dipper status, diastolic dysfunction, and increased arterial stiffness[3-6]. Secondary to hypertension, myocardial fibrosis caused by myocardial hypertrophy and excessive collagen accumulation in interstitial tissue could be one crucial early mechanism in the transition from hypertension to heart failure[2]. Based on this information, we think that fQRS, which is shown as an indirect indicator of the myocardial fibrotic burden on ECG in hypertensive patients, may also be an indicator of left ventricular subclinical systolic dysfunction. In this study, we aimed to assess the association between the presence of fQRS and LV function at hypertensive patients using the speckle tracking echocardiography method.

PATIENTS and METHODS

This study was designed as a prospective single-center, non-randomized observational study. We recruited 95 cardiology outpatients with hypertension who meets the inclusion criteria, between January 2021 and March 2021. Hypertension is defined as office systolic blood pressure (SBP) values ≥ 140 mmHg, diastolic BP (DBP) values ≥ 90 mmHg, or the use of antihypertensive medicine[7]. Exclusion criteria were the presence of coronary artery disease, objective signs of myocardial ischemia detected with exercise test or single photon emission computerized tomography (SPECT), a moderate or severe valvular disease, secondary hypertension, heart failure, atrial fibrillation, chronic renal and liver disease, poor quality echocardiographic images, and the presence of left or right bundle branch block with QRS width > 120 ms. Detailed anamnesis, physical examination, laboratory tests, 12-lead ECG, and conventional echocardiography were administered to all patients. The patients were separated into two groups as those with and without fQRS complexes on ECG. The following characteristics were recorded for each participant: Age, gender, duration of hypertension, history of smoking, history of diabetes mellitus, body mass index, and blood measurements were taken of 12-hour fasting glucose, creatinine, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, total cholesterol, hemoglobin, white blood cell count and albumin. The study was approved by the local ethics committee, and all participants gave written and oral informed consent.

Electrocardiography

In this study, the presence of fQRS in all patients was analyzed with superficial 12-lead resting ECG (filter interval: 0.5-150 Hz; AC filter: 60 Hz; 25 mm/s, 10 mm/mV). 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') without a typical bundle-branch block in two contiguous leads corresponding to a major coronary artery[8]. All ECGs were evaluated by two cardiologists who did not know the patients' echocardiographic data and the study protocol. Figure 1 demonstrates an example of fQRS.

Echocardiography

Echocardiographic examinations were performed with an ultrasound platform (Epiq; Philips Healthcare, Andover, Massachusetts, USA) equipped with a 5-1 MHz transthoracic transducer (X5-1; Philips Healthcare). Offline analyses were performed by using the QLAB advanced quantification software version 7.1 (Philips, Amsterdam, The Netherlands). All echocardiographic examinations were performed by two cardiologists who were blinded to the clinical two-dimensional and Doppler measurements (including tissue Doppler measurements) and evaluated according to the guidelines of the American Society of Echocardiography[9]. All variables were measured 3 times, and an average of these measurements was used in the statistical analysis.

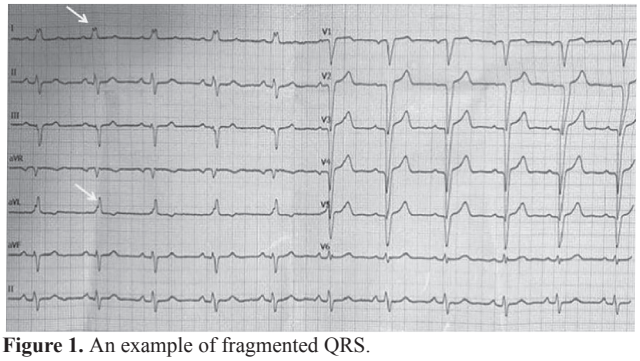

Figure 1. An example of fragmented QRS.

The interventricular septum (IVS) thickness, posterior wall (PW) thickness, left atrium, ascending aorta, and LV dimensions were measured in M-mode at end-diastole from the parasternal long-axis view according to the current guidelines[9]. LA maximum volume was obtained using a biplane area-length method at end-systole before mitral valve opening. LV ejection fraction (LVEF) was obtained by using Simpson's rule[10]. LV mass was calculated using the ASE formula and was indexed to body surface area[10]. Relative wall thickness (RWT) was calculated using the ASE formula: RWT = 2 x posterior wall thickness/left ventricular dimension in diastole[10].

Mitral inflow velocities were measured from the apical four-chamber view by placing the pulsed-wave Doppler sample volume to the leaflet tips. Mitral early diastolic velocity (E, cm/s), late diastolic velocity (A, cm/s), E/A ratio, and deceleration time (DT) were determined. Tissue Doppler imaging echocardiography was performed with a 3.5 to a 4.0-MHz transducer, adjusting the Doppler pulse repetition frequency until a Nyquist limit of 15-20 cm/s was reached, and using the minimal optimal gain. The monitor sweep speed was set at 50-100 mm/s to optimize the spectral display of myocardial velocities. Myocardial peak systolic (Sm, cm/s), early (Em, cm/s), late (Am, cm/s) diastolic velocities and isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT) were obtained by placing the tissue Doppler sample volume in the basal segments of lateral and septal walls of the LV. Also, the E/Em ratio was calculated.

For left ventricular speckle-tracking analysis, three cycles were recorded at the rate of 50 to 80 frames per second, and the mean values calculated for the strain analysis. The aortic valve opening and closing times were measured with the LV outflow Doppler profile and were integrated into the speckle-tracking strain profile to exclude the post systolic components. LV endocardial borders were automatically detected by the software in apical views with the help of three manually selected landmark points (lateral and septal mitral annulus and LV apex). Finally, automatic tracking of myocardial speckles was performed throughout the cardiac cycle. Manual correction of the border tracings was avoided as much as possible. Global longitudinal strains (GLS) were obtained for apical 4-chamber, 3-chamber, and 2-chamber views, including all LV myocardial segments (six segments per view). LV global longitudinal strain (LV-GLS) was calculated as the arithmetic mean of the three values.

Statistical Analysis

Statistical analyses were performed by using the IBM-SPSS 22.0 statistical software package (IBM, Armonk, NY). Continuous variables were expressed as mean ± SD, while categorical variables were presented as numbers and percentages. The Chi-squared and Fisher's exact tests were used for the comparison of categorical variables, while the Student's t-test and Mann-Whitney U tests were used to compare parametric and non-parametric continuous variables, respectively. The correlation of continuous variables was analyzed by Spearman's and Pearson's correlation analyses. Values of $p< 0.05$ were considered statistically significant. Finally, multiple linear regression analysis was applied to identify independent predictors of the severity of GLS.

RESULTS

A total of 95 patients were included in this study. The participating patients were divided into two groups based on the 12-lead ECG, thirty-three patients had fQRS on their ECGs [fQRS (+) group], 62 patients did not have fQRS on their ECGs [fQRS (-) group]. The clinical and demographic characteristics and laboratory findings of the patients were summarized in Table 1. Compared to fQRS (-) group, the fQRS (+) group had older age, the average duration of hypertension was longer, and had a higher hemoglobin level.

The echocardiographic parameters of the fQRS (+) and fQRS (-) groups are presented in Table 2. In fQRS (+) group, IVS (1.23 ± 0.17 vs. 1.11 ± 0.13; p= 0.001), PW (1.12 ± 0.13 vs. 1.02 ± 0.9; p< 0.001), left ventricular mass index (95.6 ± 17.5 vs. 83.7 ± 14.7; p= 0.001), RWT (0.51 ± 0.05 vs. 0.48 ± 0.05;

Table 1. Clinical characteristics and laboratory parameters of the study population

	fQRS (+) (n= 33)	fQRS (-) (n= 62)	p
Age (year)	58 ± 13.7	51.5 ± 11.2	0.015
Sex (female)	24 (72%)	39 (63%)	0.371
DM	14 (42%)	14 (23%)	0.038
Smoking history	6 (18%)	14 (22%)	0.433
HT duration (year)	11.5 ± 3.1	7.3 ± 2.2	< 0.001
BMI (kg/m^2)	29.4 ± 3.5	28.9 ± 3.5	0.530
Glucose (mg/dL)	110.5 ± 21.5	108.8 ± 20.1	0.741
GFR (mL/min/1.73 m^2)	88.1 ± 21.8	90.1 ± 19.3	0.676
LDL (mg/dL)	115 ± 29	116 ± 29	0.845
HDL (mg/dL)	51.1 ± 12.1	56.9 ± 14.7	0.130
TG (mg/dL)	153.2 ± 51	141.7 ± 47.8	0.383
Total cholesterol (mg/dL)	196.8 ± 39.9	197.9 ± 37.1	0.907
Hemoglobin (mg/dL)	13.9 ± 1.5	12.9 ± 1	0.001
WBC	8.5 ± 2.5	7.8 ± 2.1	0.243
Albumin (g/dL)	4.4 ± 0.3	4.3 ± 0.1	0.190

BMI: Body mass index, DM: Diabetes mellitus, GFR: Glomerular filtration rate, HDL: High density lipoprotein, HT: Hypertension, LDL: Low density lipoprotein, TG: Triglyceride, WBC: White blood cell count.

Table 2. Echocardiographic characteristics of patients in the fQRS (+) and fQRS (-) groups

	fQRS (+) (n= 33)	fQRS (-) (n= 62)	p
LVEDD (cm)	4.37 ± 0.42	4.26 ± 0.33	0.185
IVS (cm)	1.23 ± 0.17	1.11 ± 0.13	0.001
PW (cm)	1.12 ± 0.13	1.02 ± 0.9	< 0.001
Ascending aorta (cm)	3.5 ± 0.4	3.3 ± 0.3	0.127
LA (cm)	3.4 ± 0.4	3.3 ± 0.3	0.159
LVEF (%)	62.2 ± 2.1	63.1 ± 2.5	0.07
LVMI (g/m2)	95.6 ± 17.5	83.7 ± 14.7	0.001
RWT	0.51 ± 0.05	0.48 ± 0.05	0.001
E/A	0.81 ± 0.27	0.91 ± 0.22	0.052
DT (ms)	215.9 ± 47.2	189.4 ± 44.1	0.01
E/Em	9.8 ± 3.3	8.2 ± 1.8	0.004
IVRT (ms)	108.8 ± 20.4	102.8 ± 18.3	0.142
IVCT (ms)	85.7 ± 21.6	85.8 ± 20.1	0.991
LAVmax (mL)	46.7 ± 11.2	46.9 ± 9.1	0.914
LV-GLS (%)	-16.6 ± 2.4	-19.3 ± 2.4	< 0.001

A: Mitral inflow late diastolic velocity, DT: Deceleration time, E: Mitral inflow early diastolic velocity, Em: Ventricular tissue doppler early diastolic velocity, IVCT: Isovolumetric contraction time, IVRT: Isovolumetric relaxation time, IVS: Interventricular septum, LA: Left atrium, LAVmax: Maximal left atrial volume, LVEDD: Left ventricular end-diastolic diameter, LVEF: Left ventricular ejection fraction, LV-GLS: Left ventricular global longitudinal strain, LVMI: Left ventricular mass index, PW: Posterior wall, RWT: Relative wall thickness.

Table 3. Univariate analysis and independent predictors of LV-GLS in multiple linear regression analysis

	Univariate analysis		Multivariate analysis		
	r	p	β coefficient	95% CI	p
Age	0.021	**0.837**			
DM	-0.024	0.815			
HT duration	-0.414	< 0.001	-0.132	(-0.238) to (-0.025)	0.016
fQRS	-0.483	**< 0.001**	-2.057	**(-3.150) to (-0.964)**	**< 0.001**
LVEF	-0.219	**0.033**	0.112	(-0.092) to (0.315)	0.279
LVMI	0.003	**0.976**			
E/A	0.035	**0.734**			
DT	-0.169	**0.101**			
E/Em	-0.051	**0.626**			
LAV_{max}	-0.042	**0.686**			

A: Mitral inflow late diastolic velocity, DM: Diabetes mellitus, DT: Deceleration time, E: Mitral inflow early diastolic velocity, Em: Ventricular tissue doppler early diastolic velocity, LAVmax: Maximal left atrial volume, LVEF: Left ventricular ejection fraction, LV-GLS: Left ventricular global longitudinal strain, LVMI: Left ventricular mass index.

p= 0.001), DT (215.9 ± 47.2 vs. 189.4 ± 44.1; p= 0.01) and E/Em (9.8 ± 3.3 vs. 8.2 ± 1.8; p= 0.004) were significantly higher while LV-GLS (-16.6 ± 2.4 vs. -19.3 ± 2.4; p< 0.001), were lower compared to fQRS (-) group.

We performed univariate and multivariate analyses to identify independent predictors of GLS and in the multiple linear regression analysis, fQRS (β= -2.057, p< 0.001) and duration of hypertension (β= -0.132, p= 0.016) were identified as independent predictors of LV-GLS (Table 3).

DISCUSSION

In this study, we showed that fQRS and duration of hypertension had a predictive value for subclinical LV dysfunction detected with speckle tracking echocardiography in patients with hypertension.

Hypertension is one of the leading causes of cardiovascular mortality and morbidity and it is well known to be associated with deterioration in LV systolic and diastolic functions by the way that causing myocardial fibrosis[2,11,12]. The adaptive mechanisms for increased afterload, such as myocyte hypertrophy, myocardial fibrosis, endothelial dysfunction, could cause functional and structural left ventricular dysfunction[13]. Myocardial fibrosis plays a prominent role in left ventricular systolic dysfunction[2]. However, overt LV failure may not occur until the late stages. Furthermore, subendocardial fibers are more vulnerable to injury and the first to be affected by interstitial and perivascular fibrosis[14]. Thus, longitudinal fibers, which are predominantly located sub-endocardial, are more prone to fibrosis and hemodynamic alterations, so that primarily due to these subendocardial fibers being affected would probably result in a subtle decline in LV function that could not be detected by conventional echocardiographic techniques[14]. With speckle tracking echocardiography these subtle changes in myocardial deformation can be detected before the more extensive impairment of the LV, that is detectable by changes in conventional echocardiographic parameters. It is showed that decreased LV global longitudinal strain values obtained by speckle-tracking echocardiography were defined as subclinical LV dysfunction in many different pathologies such as diabetes mellitus, hypertrophic cardiomyopathy, hypertensive patients[15-17]. Similarly, in our study, LV GLS values were found to be lower, and the decrease in GLS values seems more pronounced, especially in the fQRS (+) group.

fQRS is a useful parameter that can be easily determined on the surface ECG, and it has been shown in previous studies that its frequency is increased in many cardiovascular and non-cardiovascular pathologies such as myocardial infarction, hypertrophic cardiomyopathy, chronic renal failure, cardiac

sarcoidosis, metabolic syndrome, diabetes mellitus, androgenic steroid users, acromegaly[15,18-24]. Its accuracy and clinical usefulness have been reported in these studies and it was emphasized that the presence of fQRS is a reliable sign of scar and fibrosis in the myocardium. Also, in many studies, It has been shown that fQRS is associated with increased arterial stiffness, complex ventricular arrhythmia, diastolic dysfunction, left ventricular hypertrophy and increased epicardial adipose tissue thickness in hypertensive patients[3,4,6,12,25]. In our study, we detected lower GLS values in hypertensive patients with fQRS. The pathogenesis of fQRS and myocardial dysfunction is similar. Increase fibrotic areas in the myocardium may delay and impair homogeneity of electrical stimuli conduction, so this situation appears as fQRS in ECG. Similarly, increased fibrotic tissue in the myocardium contributes to left ventricular dysfunction by disrupting the myocardial contraction mechanism. In other words, it would not be wrong to say that as myocardial fibrotic tissue increases, the frequency of fQRS increases in ECG, and at the same time, there is an increase in left ventricular systolic dysfunction. In our study, the significant association between the presence of fQRS and subclinical LV dysfunction may be related to these mechanisms.

Myocardial fibrosis was demonstrated with cardiac magnetic resonance imaging (CMR), SPECT, circulating biomarkers, and animal-based experimental studies in hypertension and many other diseases[8,26-28]. However, this condition of myocardial fibrosis, which consists of an increase in the size of myofibrils and an accumulation of collagen in the extracellular matrix, in an adaptive response to increased load in hypertensive patients may not be diffuse in every patient. In SPECT and CMR-based studies, it has been detected focal and regionally[8,26]. Therefore, it may not be possible to see overt left ventricular dysfunction in the early period since there is no diffuse fibrosis condition. And also, previous studies have shown that a decrease in LV longitudinal deformation parameters has been detected even in patients with mild to moderate hypertension or newly diagnosed[29]. So, even in uncomplicated hypertension, we may see left ventricular global longitudinal strain impairment as an early sign of this myocardial fibrosis. Therefore, detection of early subclinical cardiac dysfunction in patients with hypertension is essential that aggressive risk factor control and medical management of hypertension could prevent or delay heart failure. Detection of this risky group can be evaluated with fQRS. In previous MR-based studies, fQRS was shown as a reliable marker in detecting myocardial scar tissue in coronary and non-coronary artery diseases, and various studies have highlighted the potential importance of fQRS about subclinical LV dysfunction in different pathologies such as coronary artery disease, dilated cardiomyopathy, metabolic syndrome, anabolic steroid users, acromegaly[18-24,30-32]. Consistent with previous studies' findings, in our study, we detected that the use of fQRS is a predictive marker in identifying patients with subclinical LV systolic dysfunction.

The present study has several limitations. The primary limitation was that our study was non-randomized, has a cross-sectional design, and a single-center study with a relatively small number of patients. Second, even if coronary artery disease is tried to be ruled out by exercise test or SPECT, patients with possible subclinical coronary artery disease may have been included in this study, as coronary angiography is not used as a gold standard diagnostic method. Third, myocardial fibrosis was not be verified using imaging modalities such as CMR or SPECT. Fourth, our study population consists of selected hypertensive patients. Therefore, our results cannot be generalized to the general population. Lastly, the lack of prognostic information due to the absence of clinical follow-up was another limitation.

CONCLUSION

The result of our study demonstrated that fQRS was associated with subclinical LV dysfunction, which was assessed by speckle-tracking echocardiography in hypertensive patients. Myocardial fibrosis is one of the major myocardial structural alterations in patients with hypertension and may eventually lead to both overt or subclinical LV dysfunction. The assessment of fQRS by 12-lead ECG gives new insight into myocardial function in hypertension that might improve pathophysiologic understanding and identifying patients at high risk of LV systolic dysfunction. In daily practice, this inexpensive, easily accessible, and useful parameter may identify individuals who are required to follow closely and pursue more rigorous blood pressure control. All these findings strongly support the need for physicians to integrate in their daily practice the identification of fQRS when evaluating ECG in hypertensive patients.

Ethics Committee Approval: The approval for this study was obtained from Kartal Koşuyolu High Speciality Training and Research Hospital Ethics Committee (Decision no: 2021/1/435, Date: 12.01.2021).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - MK, ÇG; Analysis/Interpretation - MK, ÖC; Data Collection - MÇ, YY; Writing - MK, EB; Critical Revision - İİ, CK; Statistical Analysis - MK, ÇG; Overall Responsibility - MK, ÇG; Final Approval - All of authors.

Conflict of Interest: The authors have no conflicts of interest to declare.

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