

## Investigation of the frequency and relationship of fragmented QRS in patients with ischemic stroke

Fragmented QRS in patients with ischemic stroke

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### Abstract

**Aim:** Acute ischemic stroke is an important cause of morbidity and mortality. Fragmented QRS (fQRS) is a depolarization disorder, which may be easily detected in 12-lead superficial electrocardiography (ECG), which displays a conduction delay caused by myocardial fibrotic tissue. Although the association of fQRS with ischemic heart disease is well known, there is no clear information about its relationship with ischemic stroke. In the present study, we aimed to investigate the relationship between fQRS and ischemic stroke.

**Material and Methods:** Seventy consecutive patients with a diagnosis of ischemic stroke and 48 healthy individuals were included in this cross-sectional study. Baseline demographic and echocardiographic characteristics were recorded, and surface 12-lead standard ECGs were used.

**Results:** The mean age of the patients was 65.19±13.91 years, and 46.6% were male. The number of patients with fQRS in the ischemic stroke group was greater than in the control group ( $p = 0.009$ ). In multiple logistic regression analysis, left ventricular end-systolic diameter (LVESD) ( $p = 0.013$ , Odds ratio (OR) = 4.284, 95% Confidence interval (C.I.) = 1.366–13.432), and left atrium diameter ( $p = 0.020$ , OR = 3.985, 95% C.I. = 1.240–12.803) were found to be independent predictors of ischemic stroke.

**Discussion:** The current study was the first to focus on evaluating the relationship between fQRS and ischemic stroke. In light of these results, we can say that patients with fQRS, who had lower LVEF, greater LVESD, and larger left atrium represent a high-risk group for ischemic stroke. fQRS may be utilized in a follow-up of these patients and in any consideration of early anticoagulation treatment

### Keywords

Ischemic Stroke; Fragmented QRS; Echocardiography

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## Introduction

Acute ischemic stroke is an important cause of morbidity and mortality, and cardiovascular complications are common after an acute stroke [1,2]. Ischemic stroke accounts for approximately 85% of all stroke cases and can be classified into five main subtypes based on their etiopathogeneses: 1) small vessel occlusion (lacunar infarction), 2) large artery atherosclerosis (atherothrombotic), 3) cardio-embolism, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology [3]. In particular, patients with cardio-embolic stroke tend to have higher mortality, disability, and poor neurological outcomes compared to the other types of ischemic stroke. Previous studies have demonstrated that atrial fibrillation (AF) is the most common source of cardio-embolism due to the formation of left atrial thrombus [4]. However, there is no clear information about left ventricle-associated ischemic stroke except for left ventricular apical thrombus after myocardial infarction.

Several electrocardiographic (ECG) abnormalities have been reported in patients following acute cerebrovascular events including QT interval prolongation, ST-segment deviation, and T-wave changes [5]. Dysregulation of autonomic nervous system after acute cerebrovascular events can cause sympathetic activation leading to cardiac arrhythmia. Besides the effect of acute cerebrovascular events on ECG, some abnormal findings detected in ECG are also associated with acute cerebrovascular events. Fragmented QRS (fQRS) is a depolarization disorder that can be easily detected in 12-lead superficial ECG, which displays conduction delay caused by myocardial fibrotic tissue. Fibrotic tissue slows down the electrical conduction and causes notching in the QRS complex [6,7].

Although the association of fQRS with ischemic heart disease is well known, there is insufficient information about its relationship with ischemic stroke. In the present study, we aimed to investigate the relationship between fQRS and ischemic stroke.

## Material and Methods

### Study population

Seventy consecutive patients aged 18-80 years, who were hospitalized in Neurology and Neurosurgery clinics with a diagnosis of ischemic stroke between February 2018 and August 2019, and 48 healthy individuals were included in this cross-sectional study. Patients with a history of cranial surgery and/or cerebral endovascular intervention, hemorrhagic stroke, coronary endovascular intervention and/or open cardiac surgery in the previous 3 months, prior atrial arrhythmias (atrial fibrillation, atrial flutter, atrial tachycardia etc.), heart failure, cardiac pacemaker, bundle branch block, severe valvular disease, cardiomyopathy, pericardial disease, patients under 18 and over 80 years of age, and with poor ECG quality were excluded from the study. The study was approved by the local ethics committee. All patients signed an informed consent form. Demographic and echocardiographic evaluation of patients

Baseline demographic characteristics of the study population were recorded. Hypertension (HT) was defined by a previous diagnosis of HT or the presence of systolic blood pressure (SBP)  $\geq 140$  mm Hg or diastolic blood pressure (DBP)  $\geq 90$  mm Hg. Diabetes mellitus (DM) was defined as fasting plasma

glucose level  $\geq 126$  mg/dl or plasma glucose level  $\geq 200$  mg/dl 2 hours after the 75 mg oral glucose tolerance test or glycated hemoglobin  $\geq 6.5\%$  or patients using antidiabetic medications. Cigarette smoking was defined as smoking  $\geq 1$  packet of cigarettes per day.

All patients underwent 2-dimensional transthoracic echocardiography (HD11 XE Ultrasound system, Philips, Canada) equipped with a 1.5- 4.0 MHz transducer. Left ventricular ejection fraction (LVEF) was obtained using a modified Simpson's method as specified in the current American Society of Echocardiography guidelines for chamber quantification [8].

### ECG analysis

Surface 12-lead standard ECGs were recorded in each patient with a 25 mm/s paper speed at 10 mm/mV amplitude (Nihon Kohden Cardiofax M ECG-1350). fQRS was defined as the presence of an additional R wave (R'), a notch of a R or S wave, or the presence of fragmentation (more than one R') in two contiguous leads on ECGs [6, 9]. All ECG measurements were analyzed by two cardiologists who were blinded to all other data. The intraobserver and interobserver variations for all measurements were less than 5% and therefore nonsignificant.

### Statistical analysis

SPSS 26.0 (IBM Corp., Armonk, NY, USA) was used in the analysis of variables. Correspondence of univariate data to normal distribution was assessed using the Shapiro-Wilk Francia test, while the homogeneity of variance was evaluated by the Levene test. Independent Samples t- test was used in conjunction with Bootstrap results, while the Mann-Whitney U test was used with the Monte Carlo simulation technique in comparing two independent groups with each other according to the quantitative data. In the comparison of categorical variables with each other, the Pearson Chi-Square test was tested using Exact results, and the column proportions were compared with each other and expressed according to the Benjamini-Hochberg corrected p- value results. The Odds ratio was used with a 95% confidence interval to show how many times those with a risk factor were higher than those without. The sensitivity and specificity coefficients for the relationship between the classification separated by the cut-off value calculated according to the variables of the groups and the actual classification were investigated and expressed using the ROC (Receiver Operating Curve) curve analysis. In order to reveal the causality between the dependent variable and the independent variables in the form of a mathematical model, binary logistic regression analysis was tested with the backward method. Normally distributed continuous data were expressed as mean  $\pm$  standard deviation. Continuous variables that were not normally distributed were expressed as median (percentile 25/percentile 75), and categorical variables were shown as n (%) in tables. The variables were examined with a 95% confidence level. A p-value  $< 0.05$  was considered statistically significant.

## Results

Demographic and echocardiographic characteristics of the study population are presented in Table 1. The current study consisted of 70 patients with ischemic stroke and 48 patients without ischemic stroke (control group). The mean age of the

patients was 65.19±13.91 years, and 46.6% were male. Among all patients, 66.9% had HT, 33.9% had DM, and 37.3% were current smokers (Table 1). The patients with ischemic stroke had more comorbidities, including HT and DM than those without ischemic stroke (p = 0.048, and p = 0.048, respectively). The number of patients with fQRS in the ischemic stroke group was greater than in the control group (p = 0.009) (Table 1). There were not any significant differences between groups in respect of age, heart rate, and smoking (Table 1).

In the echocardiographic assessment; left atrium diameter and left ventricular end-systolic diameter (LVESD) were significantly higher in the ischemic stroke group than in the control group (p = 0.002, and p = 0.001, respectively). LVEF was also significantly lower in the ischemic stroke group than in the control group (p = 0.002) (Table 1).

After performing multiple logistic regression analysis, LVESD (p = 0.013, Odds ratio (OR) = 4.284, 95% Confidence interval (C.I.) = 1.366–13.432), tricuspid annular plane systolic excursion (TAPSE) (p = 0.016, OR = 1.362, 95% C.I. = 1.059–1.752), male gender (p = 0.017, OR = 3.292, 95% C.I. = 1.234–8.786), and left atrium diameter (p = 0.020, OR = 3.985, 95% C.I. = 1.240–12.803) were found to be independent predictors of ischemic stroke (Table 2).

In order to determine the ideal cut-off values to predict the presence of ischemic stroke, ROC analyses were performed. An LVESD value of > 31 had a 70% sensitivity and 64.6% specificity; an LVEF value of ≤ 60 had an 88.6% sensitivity and 37.5% specificity; and a left atrium diameter value of > 41 had a 41.4% sensitivity and 83.3% specificity in detecting the presence of ischemic stroke [AUC 0.687, (p < 0.001); AUC 0.667, (p = 0.001); and AUC 0.660, (p = 0.001), respectively] (Figures 1a, 1b, and 1c).

**Table 1.** Demographic and echocardiographic characteristics of study population

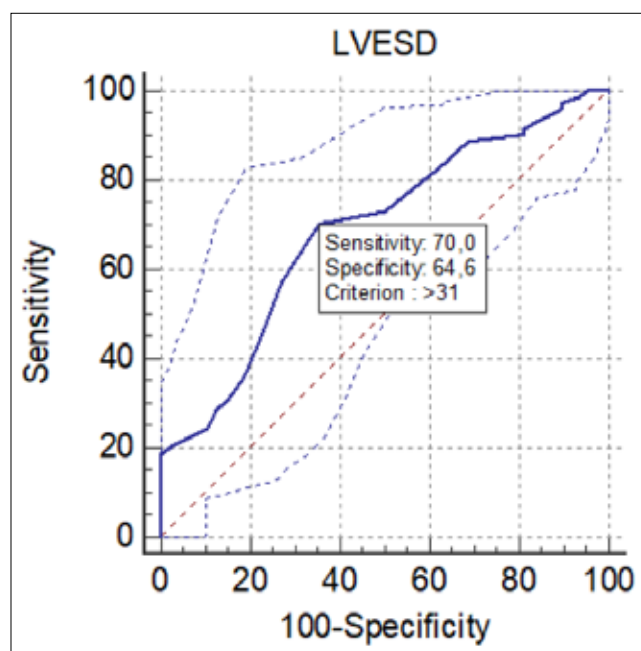
	Control group (n = 48)	Ischemic stroke group (n = 70)	p-value
Age	62.29 ± 15.34	67.17 ± 12.56	0.081 <sup>a</sup>
Male gender, n (%)	14 (29.2)	41 (58.6)	0.003 <sup>b</sup>
Heart rate (bpm)	73 (68/80)	72 (68/76)	0.325 <sup>c</sup>
Hypertension, n (%)	27 (56.3)	52 (74.3)	0.048 <sup>b</sup>
Smoking, n (%)	18 (37.5)	26 (37.1)	0.999 <sup>b</sup>
Diabetes Mellitus, n (%)	11 (22.9)	29 (41.4)	0.048 <sup>b</sup>
Presence of fQRS, n (%)	9 (18.8)	30 (42.9)	0.009 <sup>b</sup>
LVEF (%)	60 (57/62)	58.5 (52/60)	0.002 <sup>c</sup>
PWT (mm)	10 (9/11)	10 (9/11)	0.142 <sup>c</sup>
LVSWT (mm)	11 (10/12)	11 (10/12)	0.990 <sup>c</sup>
LVEDD (mm)	45 (43/48.5)	48 (45/50)	0.056 <sup>c</sup>
LVESD (mm)	30.5 (28/33)	33 (30/37)	0.001 <sup>c</sup>
Left atrium diameter (mm)	37.54 ± 5.28	41.20 ± 6.57	0.002 <sup>a</sup>
Right ventricle diameter (mm)	34.60 ± 3.51	34.17 ± 3.04	0.501 <sup>a</sup>
Right atrium diameter (mm)	35 (33.5/38)	35.5 (34/40)	0.271 <sup>c</sup>
SPAP (mmHg)	23.5 (21/27)	25 (22/30)	0.234 <sup>c</sup>
TAPSE (mm)	21 (20/22)	21 (20/22)	0.083 <sup>c</sup>

<sup>a</sup> Independent Samples t Test (Bootstrap), <sup>b</sup> Pearson Chi-Square test (Exact), <sup>c</sup> Mann Whitney U test (Monte Carlo)  
 fQRS: fragmented QRS, LVEF: left ventricular ejection fraction, PWT: posterior wall thickness, LVSWT: left ventricular septal wall thickness, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, SPAP: systolic pulmonary artery pressure, TAPSE: tricuspid annular plane systolic excursion

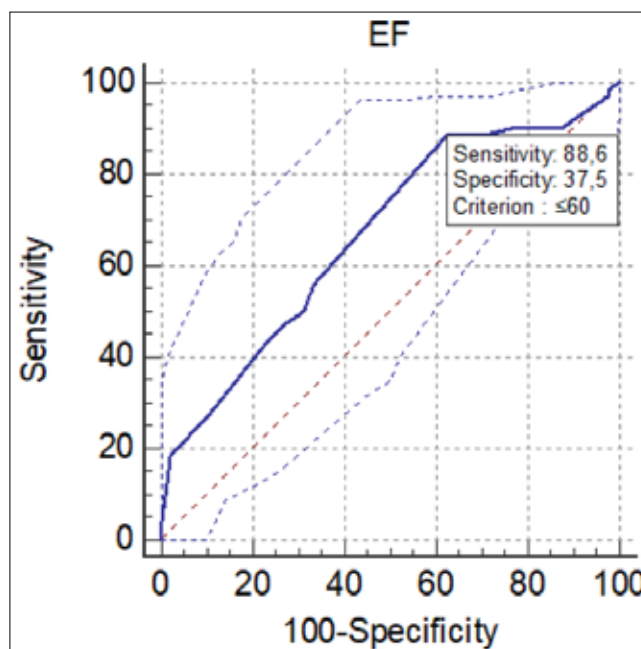
**Table 2.** The independent predictors of ischemic stroke in multiple logistic regression analysis

Variable	P	Odds Ratio (%95 C.I.)
Age	0.285	1.021 (0.983 – 1.060)
Male gender	0.017	3.292 (1.234 – 8.786)
Diabetes Mellitus	0.175	2.054 (0.726 – 5.810)
fQRS	0.115	2.263 (0.819 – 6.250)
Left atrium diameter	0.020	3.985 (1.240 – 12.803)
LVEDD	0.324	1.059 (0.945 – 1.187)
LVESD	0.013	4.284 (1.366 – 13.432)
LVEF	0.307	1.833 (0.573 – 5.868)
TAPSE	0.016	1.362 (1.059 – 1.752)

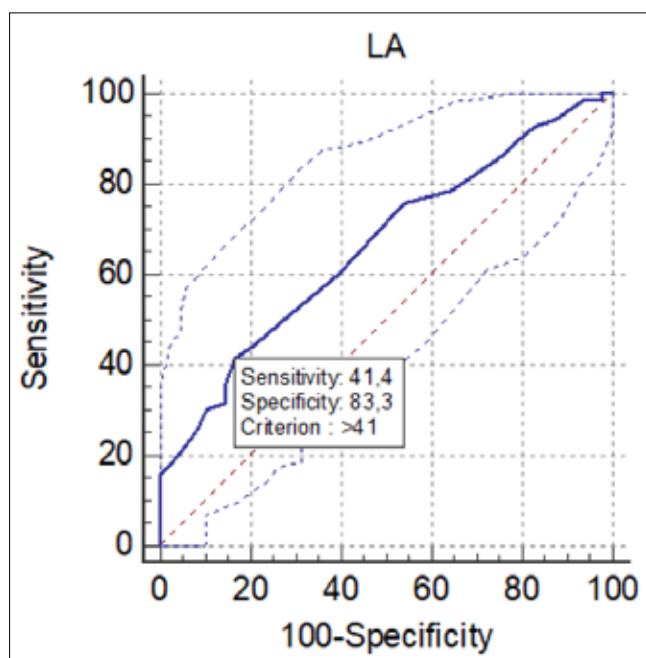
Multiple Logistic Regression (Method = Enter), C.I.: Confidence interval, fQRS: fragmented QRS, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LVEF: left ventricular ejection fraction, TAPSE: tricuspid annular plane systolic excursion



**Figure 1a.** ROC curve of LVESD



**Figure 1b.** ROC curve of LVEF



**Figure 1c.** ROC curve of LA

## Discussion

In the present study, we found that patients with ischemic stroke had greater LVESD and lower LVEF compared to those in the control group. In addition, the left atrium diameter was greater in patients with ischemic stroke. Although the frequency of fQRS was significantly higher in the ischemic stroke group compared to that in the control group ( $p = 0.009$ ), it did not reach statistical significance in predicting ischemic stroke as an independent predictor ( $p = 0.115$ ). To the best of our knowledge, the present study was the first to focus on evaluating the relationship between fQRS, reflecting abnormal ventricular depolarization and ischemic stroke.

Recent studies have demonstrated that the LVEF is strongly correlated with the formation of left atrial thrombus in patients with atrial fibrillation (AF) undergoing transesophageal echocardiography (TEE) examination. Rader et al. found that an LVEF  $<40\%$  was an independent predictor of left atrial thrombus in 524 patients with AF, who underwent TEE [10]. Ayirala et al. performed a study in patients with AF, who had undergone TEE examination for the presence of left atrial thrombus, and they showed that LVEF was an independent predictor of left atrial thrombus [11]. Cinar et al. aimed to determine independent predictors of left atrial thrombus in acute ischemic stroke patients without AF using TEE. They demonstrated that a low LVEF was an independent predictor of left atrial thrombus [12]. Consistent with these studies, it was shown in our study that without AF, lower LVEF is associated with ischemic stroke. An LVEF  $<60\%$  and an LVESD  $> 31$  mm were found to be independent predictors of ischemic stroke. A left atrium diameter ( $>41$  mm) was also found to be an independent predictor in our study in terms of its leading to left atrial thrombus and causing ischemic stroke.

Although the presence of fQRS on ECG seems to also be associated with non-cardiac conditions and cardiac diseases other than coronary artery disease (CAD) [13,14]; its importance

and prognostic value have been well demonstrated in patients with CAD and acute myocardial infarction (AMI) [15,16]. The importance of fQRS was first described in patients with CAD, and as a sign of inhomogeneous ventricular conduction, the presence of fQRS on ECG indicates myocardial fibrosis and scar tissue in these patients [17,18]. fQRS also seems to be associated with impaired cardiac structure, unfavorable left ventricular remodeling, increased risk of adverse events and more severe CAD in patients with AMI [19, 20]. Although the association of fQRS with cardiovascular disease is well known, fQRS has not been adequately investigated in patients with ischemic stroke. In the current study, we aimed to assess the relationship between fQRS and ischemic stroke. We found that the frequency of fQRS was significantly higher in the ischemic stroke group compared to that in the control group. More frequent detection of fQRS, which is an indicator of impaired cardiac structure in the ischemic stroke group, can be associated with an increased LVESD and a decreased LVEF. Impaired cardiac structure may have paved the way for the cardio-embolic source even in the absence of overt thrombus.

Given its association with left ventricular impairment and electromechanical dysfunction, fQRS may facilitate the anatomical-electrical substrate for thrombus formation and embolism. According to these inferences, fQRS, a simple ECG finding, may be utilized to identify high-risk ischemic stroke patients, in a follow-up of these patients and in any consideration of early anticoagulation treatment

## Limitations

The present study had several limitations. This study had a limited number of patients (118). Due to the cross-sectional design of our study, we were unable to distinguish causality between fQRS and ischemic stroke clearly. More large-scale, multicenter studies with follow-up are needed to validate our findings.

## Conclusion

In conclusion, the current study was the first to focus on evaluating the relationship between fQRS and ischemic stroke. We consider that our findings may be useful in terms of clinical applicability. We can say that patients with fQRS, who had a lower LVEF, a greater LVESD, and a larger left atrium represent a high-risk group for ischemic stroke. fQRS may be utilized in a follow-up of these patients and in any consideration of early anticoagulation treatment.

## Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

## Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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## Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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