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General Cardiology

Association between Fragmented QRS and Left Ventricular Systolic Function in Patients with Erectile Dysfunction

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Purpose: The aim of this study was to investigate the association between fragmented QRS and left ventricular (LV) systolic function in patients with erectile dysfunction (ED).

Methods: A total of 106 patients with ED and without a history of coronary artery disease (CAD) were compared with 54 age- and gender-matched healthy controls. LV systolic function was evaluated using speckle tracking echocardiography via global longitudinal strain (GLS) and global circumferential strain (GCS). The patients with ED were compared with healthy controls. The study group was further subdivided into fQRS (+) and fQRS (-) groups and compared with each other.

Results: The frequency of fQRS was significantly higher in the patients with ED ($p = 0.01$). The frequency of fQRS was higher in the patients with mild and moderate ED, and significantly higher in those with severe ED ($p < 0.001$). LV-GLS (%) was 17.46 ± 1.37 and 20.05 ± 1.42 in the fQRS (+) and fQRS (-) groups, respectively ($p \leq 0.001$). LV-GCS (%) was 17.33 ± 0.81 and 18.55 ± 0.92 in the fQRS (+) and fQRS (-) groups, respectively ($p \leq 0.001$). fQRS and age were independent predictors of LV-GLS.

Conclusions: The frequency of fQRS was higher in the patients with ED even in the absence of overt CAD. In the patients with ED, the fQRS (+) group had significantly lower values of LV-GLS and LV-GCS. These results indicate that presence of fQRS is associated with subclinical LV dysfunction in patients with ED.

Key Words: Erectile dysfunction • Fragmented QRS

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to have or maintain an erection for sexual activity. Coronary artery disease (CAD) and ED share many common risk factors such as diabetes mellitus (DM), hypertension (HT), dyslipidemia, obesity, smoking and metabolic syndrome. These risk factors can lead to endothelial cell damage and functional impairment secondary to an increase in oxidative stress.

Endothelial cell dysfunction causes a decrease in nitric oxide production which plays an important role in the mechanism of erection. Hence, as ED can be considered to be a type of endothelial dysfunction, the hypothesis that the risk factors that increase oxidative stress may also play a role in the pathogenesis of ED is widely accepted. In both CAD and ED, it has been shown that deterioration of nitric oxide pathways cause vasodilatation in the short term and vascular abnormalities in the long term.[1] Moreover, it is well known that CAD itself is an important risk factor for the development of ED.[2] Consequently, the similarities in the etiopathogenesis of

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ED and CAD suggest that ED may be a predictor of CAD, as supported by previous studies.

It has been shown that the presence of fragmented QRS on electrocardiograms (ECGs) can be used as predictor of CAD. Previous nuclear and magnetic resonance imaging studies have revealed that the presence of fQRS on ECGs is associated with myocardial perfusion impairment and development of scar tissue.[3,4] Furthermore, it is well known that the presence of fQRS is a predictor of increased cardiovascular mortality.[5,6]

In this study, we investigated the frequency of fQRS in patients with ED. The association between fQRS and severity of ED was also evaluated. The effects of the presence of fQRS on left ventricular (LV) systolic function were evaluated using speckle tracking echocardiography. The aim of the study was to detect the patients with increased cardiovascular risk before manifesting overt CAD.

METHODS

Study population

A total of 106 patients who were diagnosed with ED at the urology outpatient clinic were compared with 54 age- and gender-matched healthy controls. The patients with LV regional wall motion abnormalities, LV ejection fraction < 55%, left bundle branch block (LBBB), atrial fibrillation, history of coronary revascularization (percutaneous coronary intervention and coronary bypass grafting), advanced heart valve disease and history of heart valve surgery, pacemaker and implantable cardioverter defibrillator devices, polyneuropathy due to surgical trauma (radical retropubic prostatectomy, cystectomi vs) and neurological diseases, poor echocardiographic images and positive cardiovascular stress test, and patients taking phosphodiesterase inhibitors and beta blockers were excluded from the study. Data including age, smoking, medications used and the presence of DM and HT were recorded in all of the subjects. All of the participants underwent a cardiovascular stress test using a modified Bruce protocol.

A 12-lead ECG was applied to all patients with a filter range of 0.5 Hz to 150 Hz (25 mm/s, 10 mm/mV). fQRS was defined as crenation in the R wave and S wave, the presence of an RSR' pattern or more than one R' wave in at least two consecutive derivations corresponding to areas supplied by the major coronary arteries.[7] The presence of fQRS was evaluated by two experienced cardiologists blinded to the subjects' clinical status. The study design was cross-sectional and non-randomized. Informed consent was obtained from all participants, and the study was approved by the local ethics committee.

ED was diagnosed according to the replies to 5 questions in the International Index of Erectile Function (IIEF-5). The subjects were categorized as not having ED when the total score was 22-25, mild ED when the total score was 17-21, mild-moderate ED when the total score was 12-16, moderate ED when the total score was 8-11, and severe ED when the total score was 1-7.[8] Considering the insufficient number of the patients with fQRS in the mild-moderate ED group, this patient population was evaluated in the moderate ED group.

Transthoracic echocardiography

Echocardiographic evaluations were performed using a commercially available echocardiography device (Philips, iE33, the Netherlands) in accordance with the recommendations of the American Echocardiography Society.[9] All of the participants were evaluated in a lateral decubitus position at rest by two experienced physicians. They were monitored via ECG throughout the imaging procedure. LV and left atrial (LA) diameters and LV wall thickness were measured in the parasternal long axis view. LV ejection fraction (LVEF) was calculated using Simpson's method in apical four- and two-chamber views.[9]

Speckle tracking echocardiography

Global longitudinal strain (GLS) was evaluated using standard two dimension gray-scale images obtained from apical two-, three- and four-chamber views, while global circumferential strain (GCS) was evaluated in the parasternal short axis views at the basal, mid and apical levels. The images were obtained during an end-expiratory breath-hold at a frame rate of 60 to 80 frames/s. All images were transferred to a workstation for further off-line analysis, which was performed using automated software. Analysis was performed using QLAB advanced quantification software version 7.1 (Philips, the Netherlands). Automated tracking of myocardial speckles was reviewed and manually adjusted as minimally as possible.

For each view, the LV endocardial border was manually traced in the end-systolic frame. The software then automatically divided the entire circumference of the left ventricle into six equal segments and generated myocardial strain curves by frame-by-frame tracking of the natural acoustic markers throughout the cardiac cycle. Longitudinal strain was derived from the apical two-, three-, and four-chamber views, whereas circumferential strain was calculated from the three short-axis views.[10] In order to perform optimal GLS and GCS analysis, 11 subjects with insufficient image quality were excluded from the study.

Statistical analysis

All statistical studies were carried out using SPSS version 20.0 for Windows. Continuous variables were expressed as mean ± SD, while categorical variables were expressed as percentages. An analysis of normality of the continuous variables was performed using the Kolmogorov-Smirnov test. The student's t-test was used to compare parametric continuous variables, and the Mann-Whitney U-test was used to compare non-parametric continuous variables. Associations between variables were tested using Spearman or Pearson correlation coefficients when appropriate. The chi-square test was used to compare categorical variables. Multiple linear regression analysis was used to identify independent predictors of the severity of GLS. All variables showing significance at < 0.05 in univariate analysis were included in the multivariate models. p values < 0.05 were considered to be statistically significant.

RESULTS

The clinical characteristics of the patient and control groups are given in Table 1. The IEFF-5 score was significantly lower in the ED group ($p < 0.001$), while the frequency of fQRS was significantly higher in the ED group ($p = 0.01$). The two groups were similar in terms of age, smoking status and presence of DM and HT.

The frequency of fQRS was lower in the mild and moderate ED groups, while it was significantly higher in the severe ED group ($p < 0.001$). In the ED subgroups, the mean ages were 63.28 ± 9.5 and 57.9 ± 7.8 years in the fQRS (+) and fQRS (-) groups, respectively ($p = 0.002$). The demographic characteristics and laboratory findings of the fQRS (+) and fQRS (-) groups are given in Table 2. When the fQRS distribution was assessed in the ED patient population, the frequency of fQRS in the patients with severe ED was significantly higher without any derivation (Table 3).

LV-GLS (%) was 17.46 ± 1.37 and 20.05 ± 1.42 in the fQRS (+) and fQRS (-) groups, respectively ($p \leq 0.001$). LV-GCS (%) was 17.33 ± 0.81 and 18.55 ± 0.92 in the fQRS (+) and fQRS (-) groups, respectively ($p \leq 0.001$). Other echocardiographic parameters are given in Table 4.

Table 1. Clinical characteristics and laboratory parameters of the study

Variable	Control group (n = 54)	ED group (n = 106)	p value
Age, years	63.2 ± 7.2	64 ± 6.1	0.685
Body mass index	22.2 ± 3.5	23 ± 4.6	0.748
IEFF-5 score	23 ± 3.5	9.2 ± 2.5	< 0.001
DM, n %	11 (20.3)	23 (21.6)	0.578
HT, n %	18 (33.3)	38 (35.8)	0.679
Smokers	10 (18.5)	19 (17.9)	0.705
fQRS, n %	6 (11.1)	39 (36.8)	0.010
QRS duration, ms	102.8 ± 14.8	104 ± 15.2	0.453
LDL-cholesterol (mg/dL)	114 ± 38	118 ± 32	0.354
HDL-cholesterol (mg/dL)	37 ± 6	39 ± 8	0.762
Triglyceride (mg/dL)	182 ± 38	195 ± 58	0.321
Creatinine (mg/dl)	1.0 ± 0.4	1.0 ± 0.3	0.525
Hemoglobin (g/dl)	14.3 ± 1.9	13.7 ± 2.1	0.185

DM, diabetes mellitus; ED, erectile dysfunction; fQRS, fragmented QRS; HDL, high-density lipoprotein; HT, hypertension; IIEF-5, International Index of Erectile Function; LDL, low-ensity lipoprotein.

Table 2. Clinical characteristics and laboratory parameters of the fQRS(+) fQRS(-) groups in the ED population

	fQRS(+) group (n = 39)	fQRS(-) group (n = 67)	p value
Age (year)	63.28 ± 9.5	57.9 ± 7.8	0.002
DM, n %	7 (17.9)	16 (23.9)	0.475
HT, n %	14 (35.9)	24 (35.8)	0.994
Smoking history, n %	11 (16.4)	8 (20.4)	0.596
LDL-cholesterol (mg/dL)	112 ± 38	118 ± 32	0.276
HDL-cholesterol (mg/dL)	39 ± 6	38 ± 7	0.772
Triglyceride (mg/dL)	187 ± 48	197 ± 62	0.313

DM, diabetes mellitus; fQRS, fragmented QRS; HDL, high-density lipoprotein; HT, hypertension; LDL, low-ensity lipoprotein.

Correlation analysis of fQRS, LV-GLS, LV-GCS and E/E' is given in Table 5. Multiple linear regression analysis showed that fQRS and age were independent predictors of LV-GLS (Table 6).

DISCUSSION

Our results revealed that the frequency of fQRS was higher in patients with ED even in the absence of overt CAD. Moreover, the frequency of fQRS was increased as the severity of ED increased. LV-GLS and LV-GCS values were significantly lower in the ED patients who had fQRS on ECG. These findings demonstrated that the presence of fQRS was associated with subclinical LV dysfunction in the patients with ED.

fQRS is an easily recognizable depolarization abnormality on surface ECG. It represents the conduction delay secondary to fibrotic tissue in the myocardium.[11] Fibrotic tissue causes prolongation of the distance that the electrical impulse has to cover, slows the rate of transmission, and results in inhomogeneous ventricular activation. This gives rise to the development of a crenation in the QRS complex on surface ECG. It has been shown that the fQRS detected on surface ECGs of subjects with overt or suspected CAD is associated with myocardial scar tissue. Furthermore, the presence of fQRS was more sensitive and had higher negative predictive value than the Q wave in detecting scar tissue.[7] fQRS has also been reported to be an independent predictor of arrhythmic events and mortality in patients with CAD.[11] Various biochemical, echocardiographic, and radiological methods have been described for the detection of myocardial fibrosis, however these are often expensive and difficult to apply. Studies with gadolinium-based cardiac magnetic resonance imaging have shown

Table 3. Distribution of fQRS in mild, moderate and severe ED groups

Frequency of fQRS (n = 39)	Mild ED	Moderate ED	Severe ED	p value
n = 39 (%)	3 (7.7)	3 (7.7)	33 (84.6)	< 0.001
Anterior, n (%)	1 (2.5)	1 (2.5)	10 (25.6)	< 0.001
Inferior, n (%)	2 (5.1)	2 (5.1)	18 (46.1)	< 0.001
Lateral, n (%)	1 (2.5)	1 (2.5)	6 (15.3)	< 0.001

ED, erectile dysfunction; fQRS, fragmented QRS.

Table 4. Echocardiographic parameters in fQRS(+) and fQRS(-) groups

	fQRS(+) group (n = 39)	fQRS(-) group (n = 67)	p value
LVEF (%)	59.5 ± 3.6	60.5 ± 4.7	0.271
LA (cm)	3.85 ± 0.3	3.96 ± 0.9	0.480
LVEDD (cm)	4.7 ± 0.3	4.5 ± 0.8	0.232
LVESD (cm)	3.2 ± 0.5	3.3 ± 0.4	0.208
PWD (cm)	1.08 ± 0.7	1.06 ± 0.5	0.146
IVSD (cm)	1.16 ± 0.9	1.12 ± 0.8	0.267
LVMI (g/m^2)	118 ± 29.5	115 ± 27.6	0.201
E (m/s)	0.64 ± 0.16	0.75 ± 0.20	0.033
A (m/s)	0.78 ± 0.12	0.72 ± 0.10	0.139
E/A	0.93 ± 0.22	1.14 ± 0.32	0.028
S (m/s)	0.09 ± 0.01	0.89 ± 0.01	0.895
E' (cm/s)	8.8 ± 2.7	11.2 ± 2.4	0.025
A' (cm/s)	9.4 ± 1.5	9.8 ± 2.7	0.384
E/E'	9.5 ± 2.4	7.4 ± 1.6	0.012
LV-GLS (%)	17.46 ± 1.37	20.05 ± 1.42	< 0.001
LV-GCS (%)	17.33 ± 0.81	18.55 ± 0.92	< 0.001

A, late diastolic filling; E, early diastolic filling; E', early diastolic velocity at basal mitral annulus; E/E', ratio of peak early diastolic velocity to early diastolic velocity at basal mitral annulus; IVSD, interventricular septum diameter; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LV-GCS, global circumferential strain; LV-GLS, left ventricular global longutidinal strain; PW, posterior wall diameter; S', early systolic velocity at basal mitral annulus.

Table 5. Correlation analysis of fQRS and LV-GLS, LV-GCS, E/E'

	fQRS		LV-strain	
	Correlation coefficient	p value	Correlation coefficient	p value
LV-GLS	0.47	< 0.001	-	-
LV-GCS	0.45	< 0.001		
fQRS	-	-	0.47	< 0.001
E/E'	0.19	0.028	-	-

fQRS, fragmented QRS; LV, left ventricular; GCS, global circumferential strain; GLS, global longutidinal strain.

Table 6. Independent predictors of LV-GLS in multiple linear regression analysis

	β coefficient	SE	95%CI	p value
Age (year)	-0.220	0.092	(-0.402)-(0.039)	0.015
fQRS	-2.420	0.449	(-3.307)-(-.533)	< 0.001
E/E'	-0.026	0.083	(-0.138)-(0.189)	0.758

fQRS, fragmented QRS.

that evaluating fQRS is useful for predicting myocardial scar areas.[12,13] Other studies have also found an association between fQRS and myocardial scar tissue as well as myocardial perfusion defects.[4,13] The benefits of fQRS over other scar detection methods include a low cost and the wide availability as a ECG parameter that does not require special equipment or training.

ED is known as an early predictor of coronary events, stroke and cardiovascular mortality in men even in the absence of overt CAD.[14] In our study, the higher frequency of fQRS in the patients with ED, and especially in those with known CAD, was not a surprising finding. However, the detection of more frequent fQRS in the patients without overt CAD and a positive exercise test was notable. Furthermore, the higher frequency of fQRS in the severe ED patients than that in the mild ED patients implies that these patients require more strict monitoring in terms of CAD.

ED and CAD share similar risk factors and pathophysiological mechanisms including endothelial dysfunction.[15] Previous studies have especially focused on the fact that ED is a precursor of CAD.[16] CAD usually manifests 2-5 years after the development of ED.[17] In addition to higher cardiovascular and all-cause mortality in men with ED, it has also been shown that ED can be the first sign of systemic vascular disease.[18,19]

ED is a common health problem that affects the quality of life, and it is usually accompanied by CAD. The IIEF-5 test has been shown to be a very useful method for identifying men with ED in clinical practice.[8] A previous study demonstrated that ED was observed in 57% of patients who underwent coronary bypass surgery, and in 64% of patients who had myocardial infarction.[20] While ED was once accepted to be a consequence of systemic disorders such as HT, DM, and other vascular diseases, it is now widely believed that ED is an early finding of premature atherosclerosis and hence systemic vascular diseases.[21] Previous studies have shown that LV systolic dysfunction is more prevalent in patients with ED compared to control groups.[22] It has also been shown that the presence of fQRS is associated with LV systolic and diastolic dysfunction.[23,24] These previous studies clearly demonstrate the association between ED and LV systolic dysfunction and the association between fQRS and LV systolic dysfunction. The strength of the current study was to verify these relationships in the same patient population. Our results demonstrated that the presence of fQRS affected LV systolic function in patients with ED. In light of these findings, we suggest that fQRS can be used to detect the individuals with increased cardiovascular risk. Additionally, the hypothesis that a more detailed assessment of cardiovascular disease is required in the presence of atherogenic ED in men over the age of 50 years seems to be confirmed by the results of our study.[25] Paying attention to the presence of fQRS on the ECGs of the patients with ED thus appears to be rational.

A recent study demonstrated that the presence of coronary microvascular endothelial dysfunction is an independent marker of ED in middle-aged men without CAD.[26] In that study, univariate analysis showed that the development of ED was associated with only DM and age among the traditional risk factors for atherosclerosis.[26] On the other hand, only microvascular endothelial dysfunction and increasing age predicted the development of ED in multivariate analysis. Thus, the results revealed that microcirculatory dysfunction may play an important role in the mechanism of ED.[26] In our study, the presence of fQRS and decreased GLS values in ED patients may have been due to microvascular endothelial dysfunction.

Study limitations

The limited number of patients, especially in the subgroup analysis can be considered to be a limitation. Although all of the patients underwent a cardiovascular exercise test, exclusion of silent CAD may not have been possible, because CAD can be detected via cardiac computed tomography in ED patients even if they have a normal exercise test.[27] The lack of quantitative evaluations of myocardial fibrosis is also a limitation. Another limitation is that the relationships between the grade of ED and GLS and IIEF-5 score could not be evaluated because of the limited number of patients.

CONCLUSIONS

The frequency of fQRS was higher in the patients with ED. The ED patients with fQRS had more subclinical LV deterioration compared to those without. We suggest that fQRS may be used to predict future cardiovascular events in patients with ED.

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