Presence of fragmented QRS and its correlation with myocardial performance index in patients with nephrotic syndrome

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Abstract

Objective: More cardiovascular events are seen in nephrotic syndrome (NS) patients than in the normal population. Fragmented QRS (fQRS) includes various RSR' patterns with different morphologies of the QRS complexes with or without the Q wave on a resting 12-lead ECG. A relationship between the presence of fQRS and myocardial function impairment has been shown in several studies. The purpose of this study was to evaluate the presence of fQRS in this patient group and the relationship with myocardial functions.

Methods: Thirty-four NS patients were included in the cross-sectional study. Demographic data were recorded, and electrocardiograms (ECGs) were analyzed for the presence of fQRS following investigation of biochemical parameters and 24-h protein excretion. In addition to classic echocardiographic parameters, the myocardial performance (Tei index) was calculated as an indicator of cardiac function. For comparison of group's data Student's t-test and Mann-Whitney U test were used. Multiple linear regression analysis was performed for parameters affecting presence of fQRS.

Results: We identified fQRS in half of our patients group. Patients with fQRS had significantly greater proteinuria level and Tei index than those without ($p<0.05$ and $p<0.001$, respectively). Tei index was also affected presence of fQRS ($p<0.05$, $\beta=0.45$, $R^2=0.32$) and positively correlated with proteinuria levels ($p<0.05$ $r=0.366$).

Conclusion: We demonstrated, for the first time in the literature, that the determination of fQRS in patients with NS in surface ECG, an easily accessible technique, can be used as a parameter in the prediction of myocardial functions. *(Anadolu Kardiyol Derg 2014; 14: 450-5)*

Key words: fragmented QRS complex, fQRS, nephrotic syndrome, Tei index, myocardial performance index

Introduction

The prevalence of chronic kidney disease (CKD) has increased steadily. Mortality and morbidity are seen more frequently in CKD compared to in healthy individuals. Cardiovascular events are the most frequent cause of mortality and morbidity in this patient group (1, 2). In addition to classic risk factors, such as hypertension (HT), dyslipidemia, diabetes mellitus (DM), age and gender, certain specific risk factors also contribute to the development of cardiovascular events in this patient group. These specific risk factors include proteinuria, inflammation and hyperhomocysteinemia.

Nephrotic syndrome (NS) is a condition characterized by severe proteinuria, hypoalbuminemia and dyslipidemia (3). More cardiovascular events are also seen in NS patients than in the normal population. The main reasons for these increased cardiovascular events are thought to be inflammation cascade activation secondary to proteinuria and malnutrition (4-6). However, there are few studies in the literature analyzing the reasons for the increased incidence of cardiovascular events and cardiac functions in this patient group.

Fragmented QRS (fQRS) includes various RSR' patterns with different morphologies of the QRS complexes with or without the Q wave on a resting 12-lead ECG. Various RSR' patterns include an additional R wave (R') or notching in the nadir of the S wave, or the presence of >1 R' (fragmentation) in 2 contiguous leads, corresponding to a major coronary artery territory (7). Studies to date have shown that presence of fQRS is associated with a rise in cardiovascular event incidence and cardiovascular mortality and morbidity. This association is thought to stem from myocardial scarring, ventricular arrhythmia and structural cardiac defects (7-11). There are no previous studies evaluating the

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relationship between presence of fQRS and myocardial functions in NS patients.

Classically, some echocardiographic parameters such as ejection fraction, peak systolic mitral annular velocity and rate of early and late mitral inflow velocities have been used to analyze systolic and diastolic myocardial functions. However, in some conditions these indices do not accurately reflect myocardial functions. The myocardial performance (Tei) index was first developed by Tei et al. (12) to evaluate combined myocardial systolic and diastolic function. Several studies have shown that the Tei index is a more reliable parameter in the evaluation of systolic and diastolic function than classic echocardiographic indices (13).

The purpose of this study was to assess the presence of fQRS in patients with NS. We also intended to evaluate the parameters affecting the presence of fQRS and the relationship between fQRS and myocardial functions.

Methods

Study design

The current study has a cross-sectional observational design. The study was conducted in the nephrology clinic at the Karadeniz Technical University School of Medicine. The study was approved by Karadeniz Technical University Ethical Committee.

Study population

Nephrotic syndrome patients who agreed to participate in the study and under monitoring at the adult nephrology clinic were included in the study. Patients with a history of malignity, findings of active infection or inflammation, significant organic heart disease, known coronary artery disease (history of coronary bypass graft, previous myocardial infarction, angina pectoris, percutaneous coronary intervention) non-ischemic dilated cardiomyopathy, bundle-branch block (left bundle-branch block, incomplete or complete right bundle-branch block) or intraventricular conduction delay (duration of QRS >120 ms) on ECG, as well as patients with permanent pacemakers, were excluded from the study.

Baseline clinical examinations

Patients' demographic data, including age, gender, body mass index (BMI), blood pressure, medicine used, history of diabetes mellitus (DM) and hypertension (HT), cigarette use, nephrotic syndrome (NS) etiology and duration of NS monitoring were recorded.

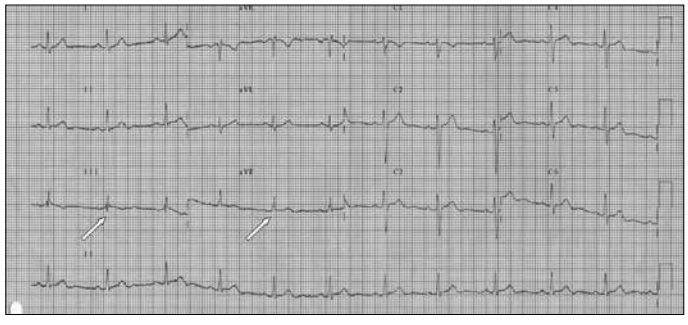

Figure 1. Examples of fragmented QRS

Study protocol

Thirty-four NS patients were included in this study. Patients' demographic data were recorded. Blood specimens were collected for biochemical tests. Twelve-lead surface resting ECGs (filter range 0.5 Hz to 150 Hz, alternative current filter 60 Hz, 25 mm/s, 10 mm/mV) were taken from the entire study population. All patients were examined in the left lateral decubitus position, and echocardiographic examinations were recorded on commercially available equipment (Vivid 7 GE Medical System, Horten, Norway) with a phased-array 3.5-MHz transducer and tissue Doppler imaging (TDI) software.

Laboratory tests

Blood specimens were collected for biochemical tests after 12-h fasting. Hemogram, blood urea nitrogen (BUN), creatinine, calcium (Ca), phosphorus (P), low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride and albumin values were investigated from these specimens. Protein excretion was measured from 24h urine using the immunoturbidimetric method. Glomerular filtration rate (GFR) was calculated according to the short Modification of Diet in Renal Disease (MDRD) formula (14).

ECG

All ECGs were evaluated by two cardiologists blinded to the patient data. fQRS was defined by the presence of various RSR' patterns (QRS duration <120 ms) with or without Q wave, which includes an additional R wave (R prime) or notching of the R wave or S wave, or the presence of more than one R prime (fragmentation) without typical bundle-branch block in two contiguous leads corresponding to a major lead set for major coronary artery territory (Fig. 1) (8, 9). Analysis of the standard 12-lead ECG was performed without using any magnification, and fragmentations were considered to be present if a visually identifiable signal was demonstrated in all complexes of a particular lead. QRS duration was determined by the longest QRS in any lead.

Two-dimensional echocardiography and pulsed-wave tissue Doppler imaging

Two echocardiographers with no knowledge of the study performed the examinations; they were blinded to the ECGs and clinical status of each patient. The conventional M-mode, B-mode and Doppler parameters were measured according to the American guidelines (15). Left ventricular ejection fraction (LVEF) was calculated using the Simpson biplane method (15). Measurements obtained directly in the M-mode by the two-dimensional image included: left atrial diameter (LAD), left ventricular diastolic diameter (LVDD), LV systolic diameter (LVSD), LV posterior wall (LVPW), interventricular septum (IVS) thick-

ness, transmitral filling velocities including peak early (E) and late (A) diastole and E-wave deceleration time (DT) (16). TDI was performed from the lateral mitral annulus. Tissue velocities including peak early (Em) and late (Am) diastolic mitral annular velocities and systolic mitral annular velocity (Sm) were analyzed. To calculate the Tei index, the time interval from the end to the onset of mitral annular velocity wave during diastole (a) and the duration of the Sm (b) were measured. Tei index was calculated as isovolumetric contraction time (IVCT) plus isovolumetric relaxation time (IVRT) divided by ET: (IVCT+IVRT)/ET=(a-b)/b. Tei index was calculated using the average values of three consecutive cardiac cycles (13, 17). At tricuspid annular plane systolic excursion (TAPSE) measurement by M-mode in apical four chamber view, the M-mode was placed through the lateral tricuspid annulus. Based on the images obtained, the distance was taken between the peak rise of the lateral tricuspid annulus toward the atrium and its descent to the ventricle. Measurements were performed at the end of expirium in order to reduce longitudinal changes in the tricuspid plane. The results were obtained by taking the mean amount of displacement of the lateral tricuspid annulus observed in three cardiac cycles from the end of diastole to the end of systole.

Statistical analysis

After investigating data compatibility with normal distribution using the Kolmogorov-Smirnov test, Student's t-test was used to compare normally distributed data between groups and the Mann-Whitney U test for non-normally distributed data. The chi-square test was used in the investigation of categoric variables. Pearson and Spearman analyses were used for correlation analysis. Multiple linear regression analysis was performed for parameters affecting presence of fQRS (proteinuria and Tei index). All the results are expressed as mean±standard deviations. $p<0.05$ was regarded as significant. SPSS (SPSS, 13.0, Chicago, IL, USA) was used for statistical analyses.

Results

fQRS was present in 17 of the patients in the study, and absent in the other 17. Mean age of the patients with fQRS was 49.82±10.93 years (12F/5M), and that of those without fQRS 43.94±12.12 (9F/8M). No significant age-related difference was determined between the two groups. Protein excretion in 24-h urine in the patients with fQRS was 3614.41±2229.97 mg/day, compared to 1448.32±1911.52 mg/day for those without ($p<0.05$). There was no significant difference between patients with or without fQRS in terms of blood pressure, BMI, types of primary disease, length of primary disease monitoring, comorbid diseases, drugs used, kidney function tests, Hb, Ca, P, lipid parameters or GFRs (Table 1).

Echocardiography

All echocardiographic data are shown in Table 2. There was no significant difference between patients with or without fQRS in terms of both conventional two-dimensional echocardiographic parameters (LVEF, LAD, LVDD, LVSD, LVPW, IVS thickness) and Doppler and tissue Doppler echocardiographic

Table 1. Clinical and laboratory characteristics of study population

	fQRS (-) (n=17)	fQRS (+) (n=17)	*P*
Age, years	43.94±12.12	49.82±10.93	NS
Gender, Female/male	9 F/8 M	12 F/5 M	NS
BMI	27.15±3.92	29.81±6.31	NS
Duration of primary disease, month	33.94±33.36	32.29±20.74	NS
SBP, mm Hg	115.00±10.00	120.00±10.00	NS
DBP, mm Hg	70.00±5.00	75.00±10.00	NS
Medications			
None	23.50%	17.60%	NS
Steroids+statins+ACEs	5.90%	23.50%	NS
ACEs+ARBs+statins	0%	5.90%	NS
ARBs+Antiplatelet	29.40%	23.50%	NS
Steroids+CsA+Statins+ACEs	29.40%	29.40%	NS
Steroids+cyclophosphamide+ Statins+ACEs	11.80%	0%	NS
Primary renal disease			
Unknown (%)	23.50%	35.30%	NS
Membranous nephropathy	23.50%	29.40%	NS
MPGN	0%	11.80%	NS
FSGS	17.60%	11.80%	NS
Wegener's granulomatosis	17.60%	0%	NS
Amyloid	0%	5.90%	NS
Ig A nephropathy	17.60%	5.90%	NS
Diabetes mellitus, %	17.60%	29.40%	NS
Hypertension history, %	64.70%	64.70%	NS
GFR, mL/min	59.43±38.18	61.37±20.90	NS
BUN, mg/dL	28.87±15.22	23.55±19.56	NS
Creatinine, mg/dL	1.71±1.43	1.83±1.47	NS
Calcium, mg/dL	9.02±0.56	9.07±0.49	NS
Phosphorus, mg/dL	3.90±0.62	3.65±0.86	NS
Albumin, g/dL	3.84±0.79	3.49±0.85	NS
LDL, mg/dL	160.06±71.17	153.64±74.79	NS
HDL, mg/dL	51.90±13.14	46.44±6.85	NS
Triglyceride, mg/dL	194.35±71.52	211.64±107.20	NS
Hemoglobin, g/dL	12.5±1.05	12.70±0.65	NS
Proteinuri, mg/day	1448.32±1911.52	3614.41±2229.97	0.005

ACEs - angiotensin-converting enzyme inhibitors; ARBs - angiotensin receptor blocker; BMI - body mass index; BUN - blood urea nitrogen; CsA - cyclosporine; DBP - diastolic blood pressure; FSGS - focal segmental glomerulosclerosis nephritis; GFR - glomerular filtration rate; HDL - high density lipoprotein; LDL - low density lipoprotein; MPGN - membranoproliferative glomerulonephritis; SBP - systolic blood pressure. Data are presented as a mean±SD and %. Statistical significance was set at $p<0.05$

parameters including E, A, Em, Am or Sm velocities. In addition, systolic (LVEF and Sm) and diastolic (E/A, Em/Am, E/Em) function indicators of LV were similar in both groups. However, the Tei index, which suggests the combined systolic and diastolic function of LV, was significantly higher in patients with fQRS than in those without (0.55±0.12 vs. 0.39±0.11, p<0.001). No significant difference was determined in TAPSE, one of the markers of right ventricular function, in patients with or without fQRS.

Relationship between fQRS and other parameters

At multiple linear regression analysis, proteinuria (p<0.05, β=0.30, R^2=0.22) and Tei index (p<0.05, β=0.45, R^2=0.32) were observed to affect presence of fQRS. There was also a positive correlation between Tei index and proteinuria (p<0.05 r=0.366).

Discussion

In this study of the presence of fQRS in a NS patient group and the factors affecting this, no demographic or biochemical factors affected incidence of fQRS, with the exception of proteinuria. fQRS incidence was higher in patients with a higher level of proteinuria. In terms of the association between fQRS and myocardial functions, a correlation was only determined between Tei index and fQRS. NS is a clinical picture accompanied by biochemical (hypoalbuminemia, hyperlipidemia) and metabolic (edema) abnormalities caused by massive proteinuria (3). Incidence of cardiovascular events increases in the NS patient group compared to the normal population. Intestinal edema developing secondary to massive proteinuria-associated hypoalbuminemia reduces nutrient absorption and leads to malnutrition and activation of inflammatory cascade. Various inflammatory mediators (such as TNF α) exhibit a negative inotropic effect on the myocardium (5, 18, 19). In this way, malnutrition and inflammation lead to an increase in cardiovascular events incidence in the NS patient group. Thrombosis frequency is known to increase in this patient group. In particular, deep vein thrombosis and pulmonary embolism secondary to this cause impairment in right ventricular functions (4). Hyperlipidemia, one of the diagnostic criteria for NS, is known to be a cardiovascular events risk factor. Therefore, dyslipidemia, which is frequently encountered in this patient group, causes a rise in coronary artery disease (CAD) frequency (20). Studies performed in the pediatric age group in particular have shown a greater incidence of cardiomyopathy and congestive heart failure (CHF) in patients with focal segmental glomerulosclerosis (FSGS). Researchers suggest this may be related to immune mechanisms (6). In conclusion, the causes of the increased incidence of cardiovascular events in the NS patient group may be listed as malnutrition, inflammation, predisposition to thrombosis, right ventricle function impairment, cardiomyopathy, CHF and dyslipidemia. We investigated the presence of fQRS in this patient group, which has not been investigated before, and showed the presence of fQFS in a NS patient group. The only biochemical and demographic parameter to affect the presence of fragmented fQRS was proteinuria.

Table 2. Two-dimensional echocardiographic and pulsed-wave Doppler tissue imaging measurements

	fQRS (-) patients (n=17)	fQRS (+) patients (n=17)	*P* value
LVDD, mm	43.88±6.90	44.35±3.70	NS
LVSD, mm	29.41±5.72	26.47±3.59	NS
IVS, mm	10.47±1.12	11.05±1.43	NS
LA diamater, mm	35.88±3.10	37.82±4.95	NS
LVEF, %	61.94±3.74	61.17±2.81	NS
E, m/s	83.52±17.88	68.94±28.91	NS
A, m/s	75.94±26.53	70.79±35.21	NS
DT, ms	203.47±54.43	237.82±47.28	NS
PW, mm	10.29±0.84	10.70±1.44	NS
Em, cm/s	12.59±0.03	14.65±0.16	NS
Am, cm/s	10.65±0.02	11.18±0.03	NS
Sm, cm/s	10.65±0.02	13.59±0.14	NS
E/A	1±0.27	1.2±0.36	NS
Em/Am	1.5±1.5	1.2±0.33	NS
E/Em	7.8±5.1	7.1±2.5	NS
Tei index	0.39±0.11	0.55±0.12	<0.001
TAPSE, cm	17.79±10.48	17.72±10.59	NS

A - late transmitral filling velocities; Am - late diastolic mitral annular velocities; DT - E-wave deceleration time; E - peak early transmitral filling velocities; Em - peak early diastolic mitral annular velocities; IVS - interventricular septum thickness; LAD - left atrial diameter; LVEF - left ventricular ejection fraction; LVDD - left ventricular diastolic diameter; LVSD - left ventricular systolic diameter; PW - posterior wall; Sm-systolic mitral annular velocity; TAPSE - tricuspid annular plane systolic excursion. Data are presented as a mean±SD, Statistical significance was set at p<0.05

Microalbuminuria and clear proteinuria are today accepted as being related to a rise in incidence of cardiovascular events, for which reason they constitute one of the risk factors for cardiovascular events (21, 22). Microalbuminuria is a marker of endothelial damage, which gives rise to inflammatory cascade activation. Proteinuria in NS patients causes inflammatory cytokine release during endothelial injury, tubular reabsorption and tubular catabolism (23, 24). In addition, malnutrition developing secondary to hypoalbuminemia leads to inflammatory cascade activation and cytokine release (5, 18, 19). Studies have shown that inflammatory cytokines cause myocardial injury (5). Although inflammation markers could not be assessed, due to this being a cross-sectional study, in the light of this information, one of the probable reasons for the relation between the fQRS and proteinuria may be a rise in inflammatory cytokines.

Previous studies have shown that fQRS is a predictor of cardiovascular events in a variety of populations (8, 11). The cardiovascular events increasing effect is thought to be associated with myocardial scarring and/or the presence of fibrosis, leading to nonhomogeneous myocardial electrical activity (9). Indeed, studies have revealed that the presence of fQRS is correlated with cardiac structural abnormality, ventricular arrhythmia, myocardial scarring and fibrosis (8-11). While there are no

studies showing an association between presence of fQRS and myocardial function and prognosis in patients with NS, Perlini et al. (25) demonstrated elevated fQRS in patients with AL amyloidosis and showed that this was correlated with prognosis. AL amyloidosis is a clinical picture observed together with renal and cardiac involvement and one that can lead to NS. There was a greater presence of fQRS in our patients with amyloidosis, though this did not achieve statistical significance. However, our patients had AA amyloidosis. While cardiac involvement is not an expected finding in this patient group, we think that the process leading to amyloidosis may also affect the myocardium.

We determined no significant difference in classic echocardiographic systolic and diastolic function markers at echocardiographic examinations performed in order to assess the relationship between fQRS and myocardial functions. We also determined no significant difference in TAPSE, a right ventricle function marker. However, there was a significant difference between Tei indices in patients with or without fQRS.

There are known to be many limitations to classic echocardiographic index evaluation of myocardial functions (13). New techniques are therefore being developed in order to be able to better evaluate cardiac functions. One such is the Tei index (12). Also known as the myocardial performance index, the Tei index is used in the analysis of myocardial systolic and diastolic functions (12, 13). We used the Tei index, shown in previous studies to provide a better analysis than older echocardiographic indices, to analyze myocardial functions. Our study supports the idea that the Tei index is more sensitive than classic echocardiographic parameters, particularly in showing subclinical myocardial function compromise. Although our patient numbers in this study were low, we identified fQRS at a level approaching 50% in this patient group, in which the presence of fQRS has not been investigated before. Presence of fQRS being relation with Tei index and no relation with other parameters being identified suggests that subclinical myocardial injury may be widespread in this patient group. Moreover, we determined a positive correlation between Tei index and proteinuria level. Based on these findings, we think that the presence of fQRS in an NS patient group can be a marker of impaired myocardial performance and is also correlated with proteinuria level.

Study limitations

There are a number of limitations to this study in which we investigate the presence of fQRS in patients with NS and its association with myocardial functions. The first is that the patient numbers are limited. Second, because the study is cross-sectional, the relationship between fQRS and cardiovascular event and renal progression could not be assessed. Finally, in this study in which we showed a correlation between presence of fQRS and proteinuria, we were unable to show whether proteinuria contributes to inflammation-mediated myocardial injury. However, since no previous similar studies have been performed in this patient group, when our study is supported by prospective studies with adequate patient numbers more powerful data on the subject will become available.

Conclusion

In conclusion, we have shown, for the first time in the literature, the presence of fQRS in an NS patient group and that this is affected by proteinuria level. Additionally, we think that fQRS, determined using ECG, an economic and easily accessible technique, can be an early marker of myocardial function impairment in this patient group. New clinical studies to support the findings in this study will help fQRS become a parameter that can be used in the analysis of myocardial functions.

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Peer-review: Externally peer-reviewed.

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