INTRODUCTION

Impairment of renal function is associated with increased cardiovascular risk.1 Cardiovascular diseases, such as coronary artery disease (CAD) and heart failure are the leading cause of death in patients with renal insufficiency.2 There is a strong correlation between the degree of renal dysfunction and the presence of CAD. However, the role of parameters showing renal function on predicting the extent and severity of CAD is still conflicting.3 Deterioration of renal function is associated with a number of predisposing risk factors for cardiovascular disease such as increased neurohormonal activation, inflammation, increased oxidant stress, insulin resistance, increased plasma asymmetric dimethylarginine (ADMA) level, hyperhomocysteinemia, higher serum lipoprotein (a) levels and increased prothrombotic factors.4

ABSTRACT

Objective: We aimed to evaluate the relationship between estimated glomerular filtration rate (eGFR) and QT dispersion (QTd) in patients with coronary artery disease (CAD).

Methods: Sixty patients (mean age 62.72 ± 12.48 years) included 46 male, (mean age 60.89 ± 12.70 years) and 14 female (mean age 68.71 ± 9.86 years) were enrolled in this study. Patients were divided into 2 groups according to their eGFR using the 6 variable MDRD equation. Group 1 consisted of patients with estimated eGFR < 60 ml/min/1.73m² and Group 2 consisted of patients with eGFR ≥ 60 ml/min/1.73m².

Results: Baseline patient characteristics were homogeneous in both groups except for age, gender and smoking. Also, the extent of CAD was similar in both groups (p > 0.05) QTd values were found higher in group 1 than those of group 2 (57.23 ± 40.65 ms vs. 31.23 ± 14.47 ms, p = 0.002). After adjustment for age, gender and smoking using one-way ANCOVA test, statistically significant difference in QTd still existed between the groups (p=0.038).

Conclusion: QTd tends to be higher in patients with poor renal function independent of severity of angiographical CAD. QTd may be a potentially useful non-invasive test in the management of patients with poor renal function, especially those with CAD.

KEY WORDS: Coronary artery disease, Glomerular filtration rate, QT dispersion.

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However, it is not yet well understood that whether impairment of renal function increases the cardiovascular risk independently or together with associated risk factors.

QT dispersion (QTd) is defined as the difference between the longest and shortest QT interval recorded from surface electrocardiogram (ECG) and is an indirect, non-invasive parameter of ventricular repolarization and homogeneity. The prognostic value of QTd has been investigated in a number of cardiovascular diseases and conditions, such as hypertension, angina pectoris, paroxysmal atrial fibrillation and coronary artery bypass graft (CABG) operation. QTd is a well-established predictor of morbidity and mortality with an ever-growing use in clinical practice.

In previous studies, it was shown that QTd increased significantly in patients with chronic end-stage renal failure, particularly in patients receiving hemodialysis, which increases QTd after each session. However, there is limited data in literature investigating the relationship between estimated glomerular filtration rate (eGFR) and QTd in patients with mild to moderate renal insufficiency and/or chronic renal failure not receiving hemodialysis. In this study, we aimed to investigate the role of eGFR on QTd in patients with CAD.

METHODS

Patients: Patients in whom coronary angiography (CAG) was performed due to a high clinical suspicion of CAD were included in the study. Patients with CAD were evaluated. Acute myocardial infarction, in the last one month, unstable angina pectoris, type 1 diabetes mellitus, uncontrolled hypertension (systolic blood pressure > 190 mm Hg), atrial fibrillation, bundle branch block, presence of permanent pacemaker or automatic implantable cardioverter device, use of antiarrhythmic drugs that may affect the QT interval, previous CABG operation, severe systemic inflammatory disease, hepatic failure and receiving hemodialysis were regarded as exclusion criteria. Sixty patients met the inclusion criteria and constituted the study population. On admission, arterial blood pressure and heart rate measurement, resting 12-lead electrocardiography (ECG), transthoracic echocardiography, whole blood count and standard biochemical tests were performed in all patients. CAG was performed in all patients. To prevent the contrast-induced nephropathy, periprocedural IV hydration with normal saline was started and administration of oral NAC at 600 mg twice daily on the day before and the day of the procedure was given in patients with reduced eGFR. Also, attention was paid to the use of low-osmolality contrast media in these patients. Patients were divided into two groups according to their eGFR values measured using the six variable modifications of diet in renal disease (MDRD) equation. Group 1 consisted of 30 patients with CAD and eGFR < 60 mL/min/1.73m² and Group 2 was consisted of 30 patients with CAD and eGFR > 60 mL/min/1.73m². The regional ethics committee approved the study protocol.

Surface electrocardiography and QT analyses: A resting 12-lead surface ECG with a paper speed of 50 mm/s and a signal size of 10 mm/mV (Hewlett Packard M1700A; Hewlett Packard, Houston, TX) was recorded before CAG in the morning period in order to prevent circadian variation. Then, all ECGs were scanned using a high-resolution scanner (HP Deskjet F2480 All-in-One Printer, 4800 × 1200 dpi; Hewlett Packard) and transferred to the computer. The measurements were performed on screen using digital magnification with a high-performance graphic program (Adobe Photoshop CS2; Adobe, San Jose, CA). The ECGs were zoomed in times and ECG gridlines were assessed appropriately to provide correct conversion to milliseconds and to confirm that the image was perpendicular to the measuring tool. QT interval was measured from the onset of QRS complex to the end of T wave defined by the return of the T wave to the isoelectric TP baseline and averaged in every lead. When T wave was negative, the point where the T wave returned to the isoelectric TP baseline was taken as the end of T wave. When U wave was present, the nadir of the curve between T and U wave was taken as the end of T wave. If the end of T wave was not determined properly in any lead, then this particular lead was excluded from analysis. After these analyses, the difference between the maximum and minimum QT interval was defined as QTd (QTd (ms) = QTmaximum - QTminimum). All measurements were performed by two separate investigators blinded to each other’s results and patients’ clinical data.

Statistical analysis: After all error controls and corrections, statistical analyses and calculations were performed using the SPSS 16.0 Statistical Package Program for Windows (SPSS, Chicago, IL). We used one-sample Kolmogorov–Smirnov and Levene tests to determine the distribution characteristics of variables and homogeneity of variance. All results for continuous variables
with normal distribution were expressed as mean ± standard deviation (SD), skewed variables as median (interquartile range — IQR) and categorical variables as percentages. Independent samples t-test was used to compare the continuous variables with normal distribution, Mann-Whitney U-test was used for skewed variables between two groups, and χ² test and χ² likelihood ratio were used for categorical variables. Analysis of covariance (ANCOVA) was used to analyze the confounding effects of variables on QTd values. The variables for ANCOVA were age, gender and smoking. Intra- and inter-observer variabilities were calculated in terms of relative error. Differences were considered significant at p< 0.05.

RESULTS

A total of 60 patients (46 male) aged 35–88 years (mean age 62.72 ± 12.48 years) 14 female (mean age 68.71± 9.86 years) were enrolled in this study. The mean age of patients was 69.3 ± 12.06 years in group 1 and 56.13 ± 9.03 years in group 2 (p < 0.001). The baseline socio demographic and clinical characteristics of the study population are presented in Table-I. The two groups were similar with regard to systolic blood pressure, diastolic blood pressure, echo cardiographic findings and risk factors (smoking, HT, HL, DM, previous CAD). However, there were statistically significant differences for age, gender and smoking between the groups. Coronary angiography findings of patients included in the study are presented in Table-II. Number of diseased vessel and number of totally occluded vessel did not differ significantly between the groups (p=0.355 and p=0.301, respectively).

Patients with low eGFR (< 60 mL/min/1.73m²) and CAD had higher QTd values compared with those of normal eGFR (>60 mL/min/1.73m²) and CAD (57.23 ± 40.65 ms vs. 31.23 ± 14.47 ms, p value 0.002). However, QTmax and QTmin values did not differ significantly between the groups (for QTmaximum 456.97 ± 53.66 ms vs. 426.97 ± 43.45 ms, p value 0.084 and for QTminimum 400 ± 52.47 ms vs. 396.67 ± 42.86 ms, p value 0.293) (Table-III).

After adjustment for age, sex and smoking using one-way ANCOVA (Analysis of covariance) test, statistically significant difference for QTd still

### Table-I: Baseline sociodemographic and clinical characteristics.

|                  | Group 1 (n=30) | Group 2 (n=30) | p    |
|------------------|----------------|----------------|------|
| Age (years)      | 69.3 ± 12.06   | 56.13 ± 9.03   | <0.001 |
| Male n(%)        | 19 (%63)       | 27 (%90)       | 0.037 |
| Systolic blood pressure [mmHg] | 132.30 ± 23.81 | 126.80 ± 20.65 | 0.343 |
| Diastolic blood pressure [mmHg] | 72.23 ± 12.45  | 73.43 ± 13.96  | 0.727 |
| Left ventricular internal dimension-diastole (mm) | 52.63 ± 8.22 | 51.73 ± 6.48 | 0.640 |
| Left ventricular ejection fraction (%) | 44.83 ± 13.23 | 49.15 ± 12.66 | 0.202 |
| Glomerular filtration rate (mL/min) | 36.62 ± 16.63 | 84.66 ± 16.65 | <0.001 |

### Table-II: Coronary angiography findings of patients.

|                  | Group 1 (n=30) | Group 2 (n=30) | p    |
|------------------|----------------|----------------|------|
| Number of diseased vessels, n(%) | 0 (0%) | 0 (0%) | 0.355 |
| Number of totally occluded vessels, n(%) | 0 (0%) | 0 (0%) | 0.301 |

### Table-III: Differences in QT interval measurements between two groups according to GFR values.

|                  | Group 1 (n=30) | Group 2 (n=30) | p     |
|------------------|----------------|----------------|-------|
| Heart rate (bpm) | 77.53 ± 16.37  | 73.20 ± 12.23  | 0.250 |
| QTmax (ms)       | 456.97 ± 53.66 | 426.97 ± 43.45 | 0.084 |
| QTmin (ms)       | 400 ± 52.47    | 396.67 ± 42.86 | 0.293 |
| QTd              | 57.23 ± 40.65  | 31.23 ± 14.47  | 0.002 |

Values are expressed as mean values ± s.d.
existed between the groups. After adjustment, QTd value for group 1 was 54.90 ± 35.59 and QTd value for group 2 was 33.57.

DISCUSSION

In this study, significant relationship between QTd and eGFR was observed in patients with CAD. We found that, QTd was significantly higher in patients with low eGFR than those of normal eGFR and CAD.

Patients with renal failure are more predisposed to cardiovascular disease compared to patients with normal kidney function. In HDFP (the Hypertension Detection and Follow-up Program) study, it was shown that cardiovascular mortality increased depending on the elevations of serum creatinine level. This observed increase in mortality rate was primarily related to level and duration of renal failure, however, can also occur in early stage of the disease.

eGFR is the most appropriate and simple way of assessing renal function. Besides, Aras et al. showed that eGFR is a useful diagnostic parameter for predicting presence of CAD in women. An eGFR level of ≤ 60 ml/min/1.73m² represents moderately renal failure. Most of the prospective cohort studies demonstrated an inverse relationship between the degree of renal dysfunction and cardiovascular morbidity and mortality, even in patients with moderate renal failure. This inverse correlation was more evident in patients with eGFR < 60 ml/min/1.73m² when compared with patients with GFR > 60 ml/min/1.73m². In addition, moderately decreased eGFR was accepted as major cardiovascular risk factor and all patients with moderately decreased eGFR were considered as high risk according to JNC VII report (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). Therefore, eGFR of 60 ml/min/1.73m² was used as a threshold limit value in our study.

Description of the abnormalities of cardiac repolarization and myocardial homogeneity from the surface ECG has long been the focus of attention. QTd has been shown as a non-invasive, cheap, simple and significant clinical index indicating repolarization heterogeneity of ventricular myocardium. QTd has been widely investigated, and found as a risk factor for severe malignant ventricular arrhythmias and sudden cardiac death in a number of cardiac (long QT syndrome, acute myocardial infarction, heart failure, left ventricular hypertrophy, idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, aortic stenosis, etc.) and non-cardiac (diabetes mellitus, rheumatoid arthritis, ankylosing spondylitis, anorexia nervosa, electrolyte imbalance, severe burns, etc.) disease and conditions. Cardiovascular mortality was found to be increased by 34% for each 17 ms increase in QTd in multivariate analyzes. Patients with chronic renal failure had a greater QT interval and QTd compared with the control subjects, and it is shown that increase in QTd was more pronounced in patients with chronic end-stage renal disease receiving renal replacement therapy such as hemodialysis or peritoneal dialysis. However, there is no clinical study analyzing the impact of early stages of chronic renal failure on QTd. In this study, we found a statistically significant QTd prolongation in CAD patients with low eGFR < 60 ml/min/1.73m² compared with those of CAD and eGFR ≥ 60 ml/min/1.73m².

Deterioration of renal function has a negative effect on cardiovascular biology and physiology and can lead to deterioration of ventricular repolarization and myocardial homogeneity. In patients with renal failure, QTd prolongation may occur due to several mechanisms. Ventricular dilation, myocardial fibrosis (especially parathormone-dependent intermyocardiocytic fibrosis), myocardial calcification, myocyte hypertrophy, increased collagen interstitial matrix, uremic autonomic neuropathy, impaired metabolism of potassium, calcium, and phosphate have been suggested as potential mechanisms for QTd prolongation in patients with chronic renal failure. Also, cardiovascular risk factors, which are almost always
present in all stages of renal failure, may have a negative impact on cardiovascular physiology. Besides, the presence of cardiovascular risk factors are associated with increased atherosclerotic burden and may lead to some pathological processes, such as medial thickness and calcific lesions resulting in loss of vessel wall compliance.\textsuperscript{26} Depending on these, systolic blood pressure and pulse pressure are increased, left ventricular hypertrophy develops, functional reserve and perfusion of coronary artery are decreased, and myocardial microcirculatory reserve can be compromised.\textsuperscript{26} QTd prolongation easily measured by surface ECG can be a useful indicator of impaired myocardial microcirculation and repolarization heterogeneity of ventricular myocardium in patients with all stages of renal failure.

**Limitations of the study:** The small number of patients is the major limitation of this study, and might obscure the definite impact of GFR on QTd. Also, measurement of QTd has some technical limitations. Firstly, the reproducibility of QTd measurement is limited due to intrinsic (T-wave inversion and presence of U-wave, etc.) and extrinsic (interference in the ECG, amplitude, and timing of recording, etc.) factors.\textsuperscript{27} Secondly, there is not a certain consensus about the normal range of QTd measured by standart 12-lead surface ECG. The normal QTd values reported in literature range from 31±11 ms to 54±27 ms. So, abnormal QTd values distinctly outside of the potential calculation errors (e.g. QTd> 100ms) are suggested as a marker of abnormal ventricular repolarization and heterogeneity.\textsuperscript{27}

In conclusion, this study showed that patients with CAD and poor renal function have increased QTd compared with patients with CAD and good renal function. In order to decrease the frequency of malignant ventricular arrhythmias and sudden cardiac death, QTd should be used as a beneficial, non-invasive, easy reproducible and inexpensive test in the care of patients with poor renal function, especially those with pre-existing cardiac diseases. Further large-scale randomized clinical studies with long follow-up are required to assess more clearly the relationship between eGFR and QTd.

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