Original Article

Evaluation of myocardial repolarization in patients with chronic renal failure

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Summary:

Back ground: Patients with chronic renal failure (CRF) are at increased risk of cardiovascular diseases and 60% of cardiovascular mortality in CRF is attributed to sudden death. Various abnormalities in myocardial repolarization assessed by QT variability index (QTVI) are associated with high risk of ventricular arrhythmia.

Objectives: The aim of the present study was to estimate and evaluate an index of myocardial repolarization instability (QTVI) of patients with CRF on haemodialysis, continuous ambulatory peritoneal dialysis (CAPD) or conservative treatment in comparison with healthy individuals.

Patients and Methods: The study was conducted on middle-aged; sixty eight (68) patients with chronic renal failure (CRF) of either sex in addition to age-matched healthy subjects (32) served as control, during the period between October 2009 to November 2010 in Al-Kadhimya Hospital. 36 patients were on haemodialysis, 21 were on continuous ambulatory peritoneal dialysis, and 11 on conservative treatment. Holter monitoring for 30 minutes was performed for each subject, and QTVI was calculated as the logarithm of the ratio between the variances of the normalized QT and RR intervals.

Results: QTVI was significantly increased in patients with CRF as compared with the control healthy subjects (0.82± 0.56, 1.54± 0.27 respectively; P<0.01). However, QTVI did not differ significantly among patients on dialysis or conservative treatment.

Conclusion: the present study concludes an elevated QTVI in patients with chronic renal failure when compared with that of control.

Key words: QT variability index, chronic renal failure, ventricular arrhythmia.

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Introduction:

Cardiovascular disease is the largest single cause of death in patients with CRF, accounting for approximately 50% of total mortality (1, 2). Patients with CRF are at an increased risk for ventricular arrhythmia and sudden death, and this may cause up to 60% of cardiac deaths in dialysis patients (2). The QT interval of the ECG is a measurement of the duration of ventricular depolarization and repolarization. Disturbed myocardial repolarization in terms of increased difference in the QT interval corrected for heart rate between different ECG leads (QT dispersion) had been associated with increased risk for ventricular arrhythmia and mortality both in patients with CRF and in the general population (3). An elevated QT dispersion may reflect spatial inhomogenesity in myocardial repolarization, despite the validity and reliability of the method has been questioned (4). Several studies reporting an elevated QT dispersion in patients on haemodialysis treatment compared with healthy subjects (5, 6). Using a computer algorithm, the temporal QTVI can be calculated, it provides an estimation of the temporal variability in the myocardial repolarization process (7, 8). However, this method of assessing myocardial repolarization is fewer operators dependent when compared with the measurement of QT dispersion. Although there are few prospective studies regarding the prognostic value of QTVI, published data indicates that an elevated QTVI is associated with an increased risk for ventricular arrhythmia(7). The aim of the present study was to estimate and evaluate an index of myocardial repolarization instability (QTVI) in a large group of patients with CRF on haemodialysis, continuous ambulatory peritoneal dialysis (CAPD) or conservative treatment in comparison with healthy individuals.

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Patients and Methods:

Sixty eight patients (68) of either sex with CRF, mean age of 57±14 years were involved in this study. Male to female ratio was (2.1:1). In addition, thirty two (32) age-matched healthy subjects served as control, they were non-smokers, normotensive, neither with significant relevant past medical history nor on any regular medications, they had normal ECG. This study was carried out during the period from October 2009 to November 2010 at Al Kadhimya Hospital.

Concerning exclusion criteria, patient with atrial fibrillation, permanent pacemaker, myocardial infarction or stroke within the preceding 3 months and more than 5% extra systoles was excluded. Each subject was submitted for complete medical history and a thorough clinical examination. Medications and laboratory data are shown in tables 1 and 2. Patients on haemodialysis were investigated on the day when they did not receive dialysis treatment. On arrival at the laboratory, subjects rested supine in a quiet comfortable room for about 10 min. After the resting period, a surface ECG was performed, lead II was acquired for 30 min. (Schiller Holter monitoring) in patients with CRF and 20 min in healthy subjects. RR interval mean (RRm) and variance (RRv), and QT interval mean (QTm) and variance (QTv) were derived from the respective time series. QTVI which represents the log ratio between normalized QT and RR interval variability, was calculated according to Berger, R. D., et al. (2007) [8], the following equation:

QTVI = Log 10 [(QTv/QTm2)/(RRv/RRm2)]

Thus, a difference of 1 between two individuals implies a 10 times difference in temporal QT variability normalized to the QT interval, RR variance (heart rate variability calculated in the time domain) and the RR interval. The squared coherence function, which is a measure of the degree of linear interaction between RR and QT interval fluctuations, was calculated from power spectra of the RR and QT interval time series, and the cross spectrum between these two series. The mean squared coherence was obtained by averaging the coherence function over the frequency band from 0 and 0.45 Hz. The coherence provides a measure of the degree of linear interaction between the RR and QT interval fluctuations as a function of the frequency of those fluctuations[3].

Statistics:

Numerical distributions are presented by their mean ± S.D. Student's t-test for unpaired comparisons was used for continuous data with a normal distribution. QTVI values showed a non-normal distribution and, hence, the Mann–Whitney U test for unpaired comparisons was used. The χ^2 test was used for binomial data. The relationship between two variables was assessed from bivariate scatter plots, and calculation of the rank correlation coefficient was performed according to Spearman. A multiple forward stepwise linear regression analysis was performed with QTVI as the dependent variable. All variables with significant association to QTVI were added to the model. Statistical significance was defined as $P < 0.05$.

Table 1: Medications of patients with CRF.

Parameter	No. of patients	% of patients
β-Blocker (%)	33	48.5
ACE inhibitor (%)	18	26.4
Angiotensin II receptor antagonist (%)	21	30.8
Calcium antagonist (%)	34	50
Diuretics (%)	42	61.7
More than three antihypertensive drugs (%)	26	38.2

Table 2: Laboratory data of patients with CRF.

Investigation	Value
Haemoglobin (g/l)	118±14
Serum sodium (mmol/l)	141±6
Serum potassium (mmol/l)	4.2±0.3
Serum calcium (mmol/l)	8.9±0.6
Plasma albumin (g/l)	38±7
Blood urea (mmol/l)	21±6
Serum creatinine	428±91

Results:

Ten patients with CRF had a previous history of congestive heart failure. A normal ECG was found in 65% of the patients, whereas 17% fulfilled criteria of left ventricular hypertrophy, 10% had bundle branch blocks and 9% had pathological Q waves suggesting previous myocardial infarctions. QTVI, QT or RR variance did not significantly differ among subgroups of patients on haemodialysis, CAPD or conservative treatment ($p=0.851$) There was no significant difference in QTVI between patients on conservative treatment and those treated by dialysis (0.86± 0.47 compared with 0.77± 0.52; $P > 0.05$). There was no significant difference regarding age between the patients and healthy subjects (Table 3). The heart rate and systolic and diastolic blood pressures values of the patients were significantly elevated in patients compared with healthy controls ($P < 0.05$; Table 2). Table 4 shows, QTVI and the QT variance were increased significantly ($P < 0.01$), whereas the RR variance was reduced significantly ($P < 0.01$) of patients when compared with that of healthy subjects. Patients on haemodialysis, CAPD or conservative treatment all showed significant elevation in QTVI compared with healthy subjects ($P < 0.01$). Mean QT intervals were similar in both groups, whereas the mean squared coherence between QT and RR time series was reduced significantly in the patient group as compared with that of healthy subjects ($P < 0.01$) as it was illustrated in table 4. The data in table 5 revealed that patients with overt coronary artery disease (24%) showed

elevated QTVI and QT variance compared with the other CRF patients (QTVI, −0.49± 0.67 compared with −0.98± 0.51 respectively; QT variance, 65± 112 compared with 19± 21 ms^2 respectively; P<0.01), whereas the variance of the RR intervals was reduced in the former group (489± 542 compared with 917± 1099 ms^2; P<0.05). When including only CRF patients without a history of coronary artery disease in the analysis, QTVI was still elevated compared with that of healthy subjects (−0.98± 0.51 compared with −1.54± 0.27; P<0.01). Patients with an abnormal ECG (left ventricular hypertrophy, bundle branch block or pathological Q waves) had elevated QTVI when compared with the patients with normal ECGs (−0.64± 0.63 compared with −0.90± 0.51 respectively; P<0.05). Patients receiving treatment with a β-blocker showed similar QTVI values, but lower heart rate than patients without β-blocker treatment (68± 1 compared with 75± 1 beats/min respectively; P<0.001). There were no differences in QTVI between patients on or off treatment with an ACE (angiotensin-converting enzyme) inhibitor, angiotensin II receptor blocker, calcium channel blocker or diuretics.

Table 3: Demographic, Blood pressure and heart rate values of studied groups.

Parameters	CRF patients (n=68)	Control (n=32)	P value
Age (years)	57±14	59±9	0.087
Gender (females/males)	29/39	18/14	NS
Systolic blood pressure (mmHg)	153±18	121±12	0.032
Diastolic blood pressure (mmHg)	88±17	76±11	0.029
Heart rate (beats/min)	76±16	68±12	0.044

Values are expressed as means±S.D.
P value less than 0.05 was considered to be significant.

Table 4: Measurements of temporal QTVI in the studied patients.

Parameter	Healthy subjects (n=32)	CRF patients (n=68)	P values
QTVI	−1.54±0.27	−0.82±0.56	0.0083
Mean QT interval (ms)	507±58	492±71	0.977
QT variance (ms^2)	12.3±8.2	30.3±56.4	0.0001
Mean RR interval (ms)	996±129	867±134	0.093
RR variance (ms^2)	1815±1539	602±684	0.0001
Mean QT–RR coherence	0.39±0.10	0.27±0.11	0.0091

Values are expressed as means±S.D.
P value less than 0.05 was considered to be significant.

Table 5: Measurements of QTVI in CRF patients with and without CAD.

parameter	CRF patients (n-68)	CRF patients		
		With CAD (n=21)	Without CAD (n=47)	P value
QTVI	−0.82±0.56	−0.49± 0.67	−0.98± 0.51	0.004
Mean QT interval (ms)	492±71	491±63	483±71	0.763
QT variance (ms^2)	30.3±56.4	65± 112	19± 21	0.001
Mean RR interval (ms)	867±134	866±145	868±129	0.963
RR variance (ms^2)	602±684	489± 542	917± 1099	0.0079
Mean QT–RR coherence	0.27±0.11	0.33±0.11	0.19±17	0.003

Values are expressed as means±S.D.
P value less than 0.05 was considered to be significant.

Discussion:

The present study demonstrates an elevated QTVI in patients with CRF on haemodialysis, CAPD or conservative treatment. These findings reflect myocardial repolarization instability, which may predispose to ventricular arrhythmia, events that occur frequently in patients with CRF (12). Patients with coronary artery disease in addition to renal failure appear to be at particularly high risk: these individuals have QTVI values comparable with those reported previously in ischemic or dilated cardiomyopathy (8). To our knowledge, the present study in Iraq is the first to investigate beat-to-beat QT variability in patients with CRF. The augmentation of QTVI (the quotient) was the result of both reduced RR interval variance (the denominator) and increased QT interval variance (the numerator). Reduced heart rate variability corroborates previous reports of reduced autonomic control of heart rate in CRF patients (6, 13). The present data expands previous reports of elevated QT dispersion in patients with CRF on dialysis treatment to show that QTVI, an index of temporal instability of myocardial repolarization, is also increased (9, 10). Moreover, an elevated QTVI was also seen in patients with CRF on conservative treatment. Whereas Berger et al.(8) reported no correlation between the two measurements in patients with dilated cardiomyopathy, Piccirillo et al.(11) reported a positive relationship between the two measurements in a mixed population of normotensive patients with primary hypertension and hypertrophic cardiomyopathy. Furthermore, in patients with

ischemic or dilated cardiomyopathy, a graded relationship between NYHA function class and QTVI has been reported, whereas no such relationship could be demonstrated for QT dispersion (9, 10). Although there have been few reports regarding the prognostic value of QTVI, Atiga et al. (12) reported that QTVI predicted the subsequent risk of sudden death or ventricular arrhythmia in patients who underwent electrophysiological investigations, whereas QT dispersion did not. Future prospective studies are needed to establish whether QTVI or QT dispersion is the most valuable variable in predicting the risk for cardiovascular morbidity (14, 15). The mechanisms behind elevated temporal QT variability have yet to be elucidated. Several factors are involved in the regulation of myocardial repolarization and their interaction is complex and incompletely understood. There is evidence that temporal repolarization instability arises at the level of the single cell, and explanations such as altered repolarization currents, abnormal intracellular ionic cycling and disease-induced changes in intercellular coupling have been proposed (6,17). The RR–QT interval coherence was reduced in patients with CRF. However, the slightly reduced RR–QT interval coherence among CRF patients could only have partly contributed to the markedly elevated QTVI observed. Structural changes of the left ventricle, such as dilation and scarring in ischemic or dilated cardiomyopathy or left ventricular hypertrophy in hypertension, are associated with elevated QTVI (17-20). Coronary disease is often silent and ischemic heart disease with fibrosis and scarring is probably one of several mechanisms causing the elevated QTVI in patients with CRF (19-23).

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