

## Influence of Diabetes Mellitus on myocardial repolarization by measurement of QT variability Index

Abbas F. Al-Hashimi\*      MBChB., MSc  
 Najeeb H. Mohammed\*\*    MBChB., MSc, DM, PhD  
 Ammar A. Thamer\*\*        MBChB., MSc

### Summary:

**Background:** Various abnormalities in myocardial repolarization assessed by QT variability index (QTVI) in diabetics are associated with high risk to ventricular arrhythmia. The increase in cardiovascular morbidity and mortality appears to relate to the synergism of hyperglycemia with dyslipidemia, hypertension and obesity in addition to disturbed myocardial repolarization.

**Objectives:** The aim of the present study was to estimate and evaluate an index of myocardial repolarization instability (QTVI) in patients with DM on insulin or oral hypoglycemic drugs in comparison with healthy individuals.

**Patients and Methods:** The study was conducted on fifty six (56), middle-aged patients with DM of either sex in addition to age-matched healthy subjects (32) served as control, during the period between December 2009 to January 2011 in Al-Kadhimya Hospital. 21 patients were on insulin therapy and 35 were on oral hypoglycemic drugs (OHD). 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 DM as compared with the control healthy subjects ( $-0.82 \pm 0.56$ ,  $-1.54 \pm 0.27$  respectively;  $P < 0.01$ ). However, QTVI did not differ significantly among patients on insulin or OHD treatment.

**Conclusion:** the present study concludes an elevated QTVI in patients with DM when compared with that of control.

**Key words:** QT variability index, diabetes mellitus, ventricular arrhythmia.

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### Introduction:

Cardiovascular disease is the largest single cause of death in patients with DM, accounting for approximately 50% of total mortality (1, 2). The increase in cardiovascular morbidity and mortality appears to relate to the synergism of hyperglycemia with dyslipidemia, hypertension and obesity (3). Patients with DM are at an increased risk for ventricular arrhythmia and sudden death, and this may cause most of cardiac deaths in diabetic patients (3). 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 DM and in the general population<sup>4</sup>. An elevated QT dispersion may reflect spatial inhomogeneity in myocardial repolarization, despite that the validity and reliability of the method has been questioned<sup>5</sup>. Several studies reporting an elevated QT dispersion in patients on insulin treatment compared with healthy subjects (4, 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 (9). The aim of the present study was to estimate and evaluate an index of myocardial repolarization instability (QTVI) in a group of patients with DM on insulin or OHD treatment in comparison with healthy individuals.

### Patients and Methods:

Fifty six patients (56) of either sex with DM, mean age of  $62 \pm 13$  years were involved in this study. Male to female ratio was (1.5:1). 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, and they had normal ECG. This study was carried out during the period from December 2009 to January 2011 at Al-Kadhimya Hospital.

\* Dept. of Physiology, College of Medicine, Al-Nahrain University.

\*\* Dept. of Physiology, College of Medicine, Baghdad University.

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. Clinical variables, laboratory data and medications are shown in Table (1). 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 DM patients 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 the following equation:

$$QTVI = \text{Log } 10 [(QTv/QTm^2) / (RRv/RRm^2)] \dots\dots$$

Berger, R. D. 1997. (10)

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 were 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. Statistical significance was defined as P<0.05.

**Table 1: Clinical, laboratory data, and medications of patients with DM.**

Criteria	No. of Patients N= 56	Ratio %
Insulin treatment	21	37.5
OHD treatment	35	62.5
β-Blocker	26	46.4
ACE inhibitor	23	41
Angiotensin II receptor antagonist	5	8.9
Coronary artery disease	39	69.6

OHD = oral hypoglycemic drug.

**Results:**

There was no significant difference in QTVI between patients on insulin therapy and those treated by OHD (−0.83± 0.42 compared with −0.78± 0.49; P >0.05). There was no significant difference regarding age between the patients and healthy subjects (Table 2). As shown in table 3, QTVI and the QT variance were increased by 47% and 146% respectively (P<0.01), whereas the RR variance was reduced by 69% (P<0.01) of patients when compared with that of healthy subjects. Patients on insulin therapy or OHD 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 by 18% in the patient group as compared with that of healthy subjects (P<0.01). As shown in table 4, patients with coronary artery diseases (CAD) had elevated QTVI when compared with the patients with normal ECGs (−0.64± 0.63 compared with −0.91± 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, and calcium channel blocker.

**Table 2: Demographic, clinical variables of studied groups.**

Parameters	Patients N=56	Control N=32	P value
Age (years)	62±13	59±9	0.087
Gender (males/females)	33/23	18/14	NS
Systolic BP (mmHg)	151±16	120±13	0.031
Diastolic BP(mmHg)	89±18	78±9	0.028
Heart rate (beats/min)	78±14	70±14	0.046

Values are expressed as means ± S.D.

P value less than 0.05 is considered to be significant.

BP = Blood pressure.

**Table 3: Measurements of QTVI in diabetic patients and healthy subjects.**

parameter	Healthy subjects	Diabetic patients	P values
QTVI	−1.76±0.32	−0.82±0.56	0.0083
Mean QT interval (ms.)	531±61	506±68	0.977
QT variance (ms <sup>2</sup> )	12.3±8.2	30.3±56.4	0.0001
Mean RR interval (msec.)	973±124	857±131	0.0093
RR variance (ms <sup>2</sup> )	1815±1539	602±684	0.0001
Mean QT–RR coherence	0.41±0.10	0.29±0.11	0.0091

Values are expressed as means ± S.D.

P value less than 0.05 is considered to be significant.

**Table 4: Measurements of QTVI in DM patients with CAD and without CAD**

parameter	Diabetic patients N= 56	Diabetic patients		p value
		With CAD N= 39	Without CAD N= 17	
QTVI	-0.82±0.56	-0.64± 0.63	-0.91±0.51	0.018
Mean QT interval (ms)	506±68	494±68	490±72	0.763
QT variance (ms <sup>2</sup> )	30.3±56.4	31.9±65.6	30.0±51.9	0.977
Mean RR interval (ms)	857±131	866±145	868±129	0.963
RR variance (ms <sup>2</sup> )	602±684	380±543	706±721	0.0079
Mean QT-RR coherence	0.29±0.11	0.30±0.09	0.33±0.11	0.766

Values are expressed as means± S.D.

P value less than 0.05 is considered to be significant.

**Discussion:**

The present study demonstrates an elevated QTVI in patients with DM on insulin therapy or OHD treatment. These findings reflect myocardial repolarization instability, which may predispose to ventricular arrhythmia (6). Patients with coronary artery disease in addition to DM appear to be at particularly high risk: these individuals have QTVI values comparable with those reported previously in ischemic or dilated cardiomyopathy(11). Reduced heart rate variability corroborates previous reports of reduced autonomic control of heart rate in diabetic patients (12, 13). The present data expands previous reports of elevated QT dispersion in diabetics on OHD treatment to show that QTVI, an index of temporal instability of myocardial repolarization, is also increased (11, 14). Moreover, an elevated QTVI was also seen in diabetic patients on insulin therapy. It is unclear whether QT dispersion and QTVI provide information about myocardial repolarization that is redundant or complementary. Whereas Berger et al. (13, 15) reported no correlation between the two measurements in patients with dilated cardiomyopathy. Furthermore, in patients with ischemic or dilated cardiomyopathy, a graded relationship between NYHA function class (New York Heart Association) and QTVI has been reported, whereas no such relationship could be demonstrated for QT dispersion (16). Although there have been few reports regarding the prognostic value of QTVI, Future prospective studies are needed to establish whether QTVI or QT dispersion is the most valuable variable in predicting the risk for cardiovascular morbidity (17). 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 (16-18). The RR–QT interval coherence was reduced in patients with diabetes. However, the slightly reduced RR–QT interval coherence among diabetics could only have partly contributed to the markedly elevated QTVI observed. Hence co-existing cardiovascular diseases in DM including hypertension and coronary artery disease could have induced structural changes within the myocardium that may explain some of the observed increase in QTVI. 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 DM (18). Furthermore, cardiomyopathy and/or neuropathy of the cardiac autonomic nervous system could also have contributed to the elevated QTVI observed in the diabetic subgroup (18).

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