The Relationship between QT Dispersion and Ischemic Injuries in Myocardial Isotope Scan

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Abstract- The relationship between QT dispersion and myocardial ischemia is still controversial. Therefore, we aimed to investigate the relationship between QTd and the severity and extent of myocardial ischemia. In this cross-sectional study, 141 patients having symptoms of CAD who referred to our medical center during 2009-2010, and were examined with myocardial isotope scan and ECG, were enrolled. Based on the Electrocardiography and Single-Photon Emission Computed Tomography results, the patients were categorized as having normal, mild, moderate, and severe ischemia. QTd was measured at rest and under stress as the maximum difference between QT intervals in 12-lead ECG. Ultimately, the correlation between rest and stress QTd and the severity and extent of ischemia (number of ischemic segments and summed ischemic score) were investigated, and the rest and stress QTd was compared between the groups. QTd under stress was positively correlated with the number of ischemic segments and summed ischemic scores in all patients. In normal patients, stress and rest QTd were the same. The QTd under stress significantly increased in patients with ischemia. There was no significant difference between the groups regarding QTd at rest. Stress QTd was significantly greater in patients with severe ischemia and greater in patients with mild and moderate ischemia compared with the normal patients. Stress QTd difference between mild and moderate ischemic groups was not significant. QTd under stress is related to the severity and extent of myocardial ischemia and is clinically useful for identifying ischemic myocardial injuries.
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Introduction

Myocardial ischemia is an imbalance between the amount of oxygen that is available to the myocardium and its required amount of oxygen. It may result from low blood flow in the coronary arteries (coronary artery disease), reduction in the oxygen-carrying capacity or increased oxygen consumption in the myocardium (1). Recently, coronary artery disease (CAD) is considered as one of the main causes of mortality and morbidity worldwide (2).

Different methods have been introduced and used for diagnosing CAD and investigating the need for revascularization such as the exercise tolerance test (ETT) and imaging techniques, i.e. SPECT (Single-Photon Emission Computed Tomography) (3-5). ETT is used as a routine and common method in clinical assessments throughout the world (4, 5).

However, currently it seems that cardiac SPECT is replacing ETT in many centers. Although the results obtained by SPECT can provide important and reliable information about patients' prognosis, this method also has some shortcomings including exposure to ionizing radiation, and controversial reports about its amount of accuracy (6-8). Moreover, ETT is faster and cheaper.

During the ETT, ST segment changes in the electrocardiogram are used as the standard criterion for diagnosing CAD (4, 5). Previous studies show that several factors can affect this electrocardiographic parameter. Also, the overall accuracy of ST segment changes in exercise tests has been set at 70-80% (9, 10). Because of such problems, in recent years some researchers have suggested to use QT interval (QTI) changes in response to exercise-induced ischemia instead of ST segment changes in order to increase the diagnostic accuracy of ECG (10-12). The underlying reason for using QTI for diagnosing ischemia is that exercise-induced ischemia causes heterogeneity in the

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ventricular repolarization (4).

QT dispersion (QTd) is one of the QTI parameters used more frequently than the other parameters (13,14). QTd is measured as the difference between the maximum and minimum QT intervals using a 12-lead ECG. Since initially introduced by in 1990 by Day and colleagues (15), it has been considered as a criterion for predicting the risk of arrhythmias in patients with prolonged QT intervals (15-17). In fact, QTd measures the homogeneity of the ventricular repolarization indirectly and non-invasively. Various studies have shown that QTd increases in heart problems such as heart failure, cardiomyopathy, and myocardial infarction. QTd is used in assessing the risk of stroke, its increase (QTd>80 ms) is associated with poor prognosis of cardiac disease, and can indicate the possible incidence of ventricular arrhythmias and sudden death (13,16,18-27).

Although some studies have evaluated QTd in patients suffering from CAD (28-36), it is still unclear whether it is useful in identifying patients with CAD (37). QTd is associated with and determined by the amount of viable myocardial tissue in patients with chronic Q-wave myocardial infarction (36). However, another study, showing that a hibernated myocardium did not affect QTd, did not confirm this finding (38). Other reports state that QTd values during exercise can provide more information about detecting myocardial ischemia than ST segment abnormalities; and that the extent of myocardial ischemia is an important factor in increasing the risk of cardiac problems and events (39,40).

Currently, we have limited information about the relationship between QTd and myocardial ischemia (21). Considering the lack of sufficient information in this regard and the need for inexpensive diagnostic methods for examining the extent of myocardial ischemia, we aimed to investigate the value of using QTd in diagnosing cardiac ischemia and its severity.

Materials and Methods

In this cross-sectional study, 141 patients having symptoms of CAD who referred to Taleghani Hospital affiliated to Shahid Beheshti University of Medical Sciences in Tehran during 2009-2010, and were examined with myocardial isotope scan and ECG, were enrolled. Then, the routine procedures including blood pressure measurement, blood tests, chest radiography, echocardiography, and ECG were done to assess the patients' cardiovascular system.

Patients with stage 4 and 5 chronic renal failure (GFR <30 mL/min/1.73), acute coronary syndrome, moderate and severe valvular disease, atrial fibrillation, other arrhythmias, left and right bundle branch blocks (RBBB and LBBB), morning headaches, important neurological or respiratory disease and myocardial infarction in the last three months were excluded from the study. The patients who were pregnant, immobile, or consumed class I and III antiarrhythmic drugs were also excluded.

Written informed consent was obtained from the remaining 100 patients and they were then assessed using myocardial isotope scan. During isotope scan, electrocardiograms were serially taken in different stages; therefore, electrocardiograms taken at the beginning of the scan were used to calculate QTd at rest and those taken at the time of maximum heart rate for calculating QTd under stress. To calculate the number of segments involved in ischemic damage, we used the conventional 17-Segment categorization. The summed ischemic score was also determined based on Cedars-Cinai calculations which show the total severity of ischemia and the number of damaged segments. The severity of ischemia in each segment was also determined based on the same calculations between zero to 4 (normal, mild, moderate, and severe ischemia and infarction).

Stress was induced using dipyridamole for 78 (78%) patients and exercise for 22 (22%) patients. 12-lead ECG was performed with a frequency of 50 HzAc. ECG analysis and QTd calculations were done manually. QTd was defined and calculated as the mean difference between the maximum and minimum QT interval in the 12 electrodes in all cycles.

Data were analyzed using SPSS software, version 16. To investigate the correlation between QTd and the scan results, Spearman's correlation test was used. Also, to compare QTd values of different groups, non-parametric Kruskal-Wallis and Mann-Whitney tests were used. The significance level was set at p<0.05.

Result

Totally 58 women and 42 men participated in our study (mean±SD age: 63.7±12.4 years, range: 35-90).

Myocardial isotope scan showed that 58 patients (58%) had normal myocardium, whereas 42 patients (42%) suffered from myocardial ischemia. Of patients suffering from myocardial ischemia, 16, 20, and 6 patients had mild, moderate, and severe ischemia, respectively. The mean (±SD, range) QTds at rest for patients with normal myocardium and those with

myocardial ischemia were 48.6 (±12.3, 0-90) ms and 43.2 (±18.7, 0-130 ms) [P=0.052]. The mean (±SD, range) QTd for all the patients was 46.4 (±15.5, 0-90 ms) at rest and 53.8 (±20.7, 0-130 ms) under stress (P<0/001, t test). The mean (±SD, range) ischemic segments were 4 (±2.6, 1-13) in patients with ischemia, and the mean (±SD, range) summed ischemic score was 7.3 (±6.5, 2-26).

Spearman correlation test was used to evaluate the correlation between QTd values and scan parameters (number of ischemic segments and summed ischemic score) in all patients as well as patients with ischemia (Table 1). We found a statistically significant and positive correlation between the QTd value under stress in all patients and the number of ischemic segments and summed ischemic score. Our results indicate that under stress, QTd values rise as the severity and extent of ischemic injury increases.

Table 1. Correlation between the QTd value and scan parameters in all patients and patients with myocardial ischemia

Group		All patients		Patients with ischemia	
QTd		Correlation coefficient	P value	Correlation coefficient	P value
At rest	number of ischemic segments	-0.21	0.142	-0.073	0.65
	summed ischemic score	-0.22	0.372	-0.15	0.33
Under stress	number of ischemic segments	0.5	0.0001	0.25	0.11
	summed ischemic score	0.49	0.0001	0.2	0.2

In the normal group, QTd under stress decreased compared with QTd at rest (P=0.651). Whereas in the group with ischemic injury, QTd increased significantly under stress. By comparing the QTd values at rest and under stress in patients with a normal myocardium and those with ischemic injury, we found that the two groups differed significantly with respect to their QTd values under stress (Table 2).

Table 2. Comparison of QTd mean (±SD) between normal patients and patients with myocardial ischemia

Group QTd (ms)	Normal	Ischemic	P value
At rest	48.6±12.3	43.2±18.7	0.052
Under stress	45.6±14	٢65±23.2	<0.0001
P value(Intra-group comparisons)	0.651	٠<0.0001	--

For further investigation, the QTd values at rest and under stress were observed and compared between the 4 groups of patients with normal, mild, moderate and severe ischemia using the Kruskal–Wallis test. We found no significant difference between the 4 groups. Although the P value at rest was close to a significant level, but the difference between the groups was not significant (table 3). Therefore, the maximum QTd value under stress is observed in the group with severe ischemia and followed by the groups with mild and moderate ischemia and finally in the normal group, respectively.

We determined a new parameter called QT difference which is in the difference between (QTd) at rest and under stress, and compared it between normal and ischemic groups. We found that the mean±SD QTd was significantly lower in normal patients (-3.3±13.3 ms) than in patients with myocardial ischemia (21.8±18.9 ms) [P<0.0001].

Discussion

We investigated the relationship and correlation between QTd and the parameters indicating myocardial ischemia in SPECT. Our most important finding was that QTd values at rest had no significant relationship with the extent and severity of ischemic myocardial injury. However, our findings show that the value of this electrocardiographic parameter under dipyridamole or exercise-induced stress is significantly correlated with the severity and extent of myocardial ischemia in isotope scans, and rises with an increase in the severity

and extent of ischemia.

Some researchers have not considered QTd as a standard criterion for assessing the homogeneity of ventricular repolarization. They state that not only the accuracy and repeatability of the standards relating to the dispersion, but also the existence of a direct correlation between homogeneity of ventricular repolarization and QTd is in question (40). In contrast, other researchers believe that QTd is a reliable measure for investigating abnormalities of myocardial repolarization and is able to predict severe arrhythmias after myocardial infarction and also mortality because of cardiovascular diseases (42).

Previous studies have shown that an increase in the heterogeneity of ventricular repolarization in myocardial ischemia results in an increase in QTd value (32-34, and 43). In patients without chest pain or ST segment depression during stress induction, QTd calculation immediately after stress induction can be very useful for diagnosing CAD (44, 45). Moreover, QTd increase to more than 60 ms under stress, with 70% sensitivity and 95% specificity can be useful in diagnosis of CAD (34).

Teragawa and his colleagues also observed that stress induction using ATP infusion was associated with increased QTd only in patients with ischemia (ischemia and ischemia with scar), whereas in normal patients or those who suffered from scars, ischemia as the result of ATP infusion caused reduced QTd. They stated that in the normal group, ATP infusion may simultaneously cause a significant reduction of the maximum and minimum QT segment duration. In the group with myocardial ischemia, although the minimum duration of QT segment reduced considerably, it had a very small reduction during the maximum QT segment. Therefore, the induction of ischemia was associated with an increase in QTd in the group with ischemic injuries, and a decrease in QTd in the group without ischemic injuries (37).

Takase and colleagues also observed that QTd at rest in patients with simultaneous reversible and irreversible injuries and those with only irreversible injury was significantly higher than the normal group and the group with reversible injury. However, QTd under stress increased in the group with reversible injury but decreased in the three other groups (5).

We compared the QTd value in patients who suffered from ischemia with normal people based on myocardial scanning and found that this parameter was identical in both groups at rest, but significantly increased with the induction of stress in the ischemic group compared with the normal group. Further

investigations based on the severity of ischemic damage (normal, mild, moderate, and severe) also showed that QTd value is identical between groups at rest, but under stress, the QTd was higher in all ischemic groups. In the group with severe injury, the QTd was significantly higher than the groups with mild and moderate injury; and the same between the groups with mild and moderate injuries. The considerable point in our study was that the QTd value decreased with the induction of stress in the normal group, although the difference was not significant, and significantly increased in the ischemic group.

In our study, as the severity and extent of ischemic damage increased, the QTd under stress also increased, while no significant relationship was found between the two groups at rest. It should be noted that the correlation between QTd and ischemic parameters in the scan is much smaller at rest than under stress. As mentioned, such QTd increase under stress might be because of the increase in the heterogeneity of ventricular repolarization caused by the incorrect reaction of the ischemic myocardium to catecholamine or the abnormal flow of calcium ions (46). Some studies confirm the findings of our study (4,5,37) while the findings of Schmidt and his colleagues are not consistent with ours (21).

Carluccio and his colleagues observed a significant increase in QTd value using dipyridamole upon the induction of abnormal ventricular wall motion and concluded that ischemia could change QTd value (47). Takase and co-workers stated that QTd and QTcd after stress and in the recovery phase were sensitive to ventricular repolarization and myocardial ischemia, and they could be used to determine stress-induced myocardial ischemia. They also found that the proper cut-off value for the diagnosis of stress-induced myocardial ischemia was 41.6 ms for QTd and 40.4 ms for QTcd. Therefore, the sensitivity and specificity of QTd for detecting ischemia were 60% and 58%, respectively. The corresponding figures for QTcd were 57.8% and 80%, respectively.

Furthermore, logistic regression analysis showed that QTd, QTcd, and ST segment changes were correlated significantly with myocardial ischemia (5). Masaki and his colleagues also stated that not QTd, but QT peak dispersion (QTpd) can be useful in detecting stress-induced myocardial ischemia (4).

In contrast, Schmidt and others investigated the QTd value in the diagnosis of myocardial ischemia compared with myocardial scan using thallium 201 (Tl-201 SPECT). They observed that there was no significant

correlation between QTd at rest and under stress and scanning parameters such as the degree of myocardial ischemia, the number of ischemic segments, and summed ischemic stress score. The researchers also noticed that there was no significant difference between different groups with respect to QTd values based on the severity of ischemia. It was concluded that QTd could not be used in determining the extent or degree of ischemic myocardial damage. They stated that according to their study myocardial ischemia did not affect QTd (21). Coronel and co-workers concluded that myocardial ischemia did not affect the duration of action potential (48). Considering the findings of the mentioned study, Schmidt and colleagues stated that ischemia could not alter the value of QTd (21).

We introduced a new index called QT difference that actually shows the difference between QTd at rest and under stress. The comparison of this index between the normal and ischemic groups indicates that its value increases significantly in patients with myocardial ischemia. Schmidt and colleagues also examined this factor in their study; in fact, what they assessed as QTd was the difference between QTd at rest and under stress or QT difference (21). Since QT difference gives a resultant of the two values of stress and rest QTd, this can possibly be a more appropriate index for diagnosis of myocardial ischemia and the homogeneity rate of repolarization of ventricular cells. Further studies are needed to determine its diagnostic capabilities, including its sensitivity and specificity which are currently under investigation by the same researchers.

Considering the different results obtained from different studies regarding the QTd value, and based on the findings of this study we can conclude that under dipyridamole or exercise-induced stress, the QTd can be clinically useful in identifying ventricular ischemic myocardial injuries. For the accurate use of this parameter, the further studies should focus on determining its cut-off value. Therefore, the sensitivity and specificity of QTd in the diagnosis and determination of the severity and extent of ischemic injury can also be assessed.

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