

NEARLY TWO DECADES OF QTc DISPERSION IN CARDIOLOGY

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Summary. *Heterogeneous ventricular repolarization was recognized from standard ECG as early as 1934. QT interval dispersion was recognized as a marker of arrhythmia risk in the 1990, and the first prognostic significance of QT interval dispersion was shown in the 1994. The QT interval dispersion is the range of QT interval duration in all measurable ECG leads. It represents the difference between the longest and the shortest QT interval. There is a methodological problem associated with QT dispersion measurements, because normal values for QT dispersion have not been well defined. Values between 30ms and 60ms are considered normal. Increased QTc interval dispersion can be seen in patients with various cardiac diseases: myocardial infarction, left ventricular hypertrophy, long QT syndrome, heart failure, and aortic stenosis. The QTc interval dispersion has obvious predictive value, but inter- and intraobserver variability limits its larger clinical use. In perspective, it is important to decrease measurement error by improving measurement technique, more precisely define normal values and prove predictive value in different diseases and drug use in studies with great number of patients.*

Key words: *Electrocardiogram, QTc interval dispersion, measurement, prognostic value*

Heterogeneous ventricular repolarization was recognized from standard ECG as early as 1934 (1). Unfortunately, new interest for QTc interval dispersion was born again in the 1990, when Day reported that QTc interval dispersion was a marker of arrhythmia risk in patients with long QT interval (2). The first prognostic significance of QTc interval dispersion was shown by Barr et al. in 1994. They found bad outcome in patients with heart failure and QTc interval dispersion greater than 100 ms (3). Darbar et al. confirmed prognostic significance of QTc interval dispersion in patients with peripheral arterial disease. Those patients had greater cardiovascular mortality if their QTc interval dispersion was equal or greater than 60 ms. Sensitivity of this marker was 92% and specificity 81% (4). Up to date QTc interval dispersion has been examined in different medical disciplines and now, we know much more about it. Nowadays, QTc interval dispersion is a marker for vulnerability of ventricular arrhythmias and for sudden cardiac death.

How is QTc interval dispersion measured?

The QTc interval dispersion is a difference between maximal and minimal QTc intervals which are obtained from 12 electrocardiographic leads (figure 1). This is a unit of heterogeneous ventricular repolarization. QT dispersion is the range of QT interval duration in all measurable ECG leads. It represents the difference between the longest and the shortest QT interval (5).

The **first** problem is how much measurable leads are enough. In the study of Yi et al. only 11 leads were used

to measure QT dispersion as VI was excluded on the basis that flat T waves are commonly encountered in this particular lead (6). The lead III is the second lead with such a problem. However, other leads could be omitted from the calculation of QT dispersion essentially if their T wave amplitudes were low. This manner leads to underestimating of QT dispersion, and it was shown in our study (7). QTc interval dispersion calculated from three leads may be as useful a measurement as QTc interval dispersion calculated from all leads of the standard ECG. Its advantages over the standard measurement are its simplicity and the lack of problems with lead adjustment (8).

The **second** problem is how we can exactly identify the end of T wave. The main difficulty is the persistence of U wave. Cowan *et al* showed that variation in QRS onset in a single 12 lead ECG could vary by up to 24 ms (9). For manual measurement methods, increasing the paper speed is not helpful to decrease measurement error. Therefore, ECG paper recording at 50 mm/s is recommended. The facts above noticed as a source of error are certainly not negligible. Relative errors of 25-40% of inter- and intraobserver variability of manual measurement of QT dispersion have been reported (10). Nowadays, the "gold standard" is manual measurement using the digitising board. Manual measurement using calipers or ruler carries the highest potential for error. The currently available automated algorithms unfortunately do not perform much better than human observers (11).

The **third** problem is that, a relatively small error in QT measurement magnifies the error in QT dispersion. Additional difficulty is the circadian variation of QT interval.

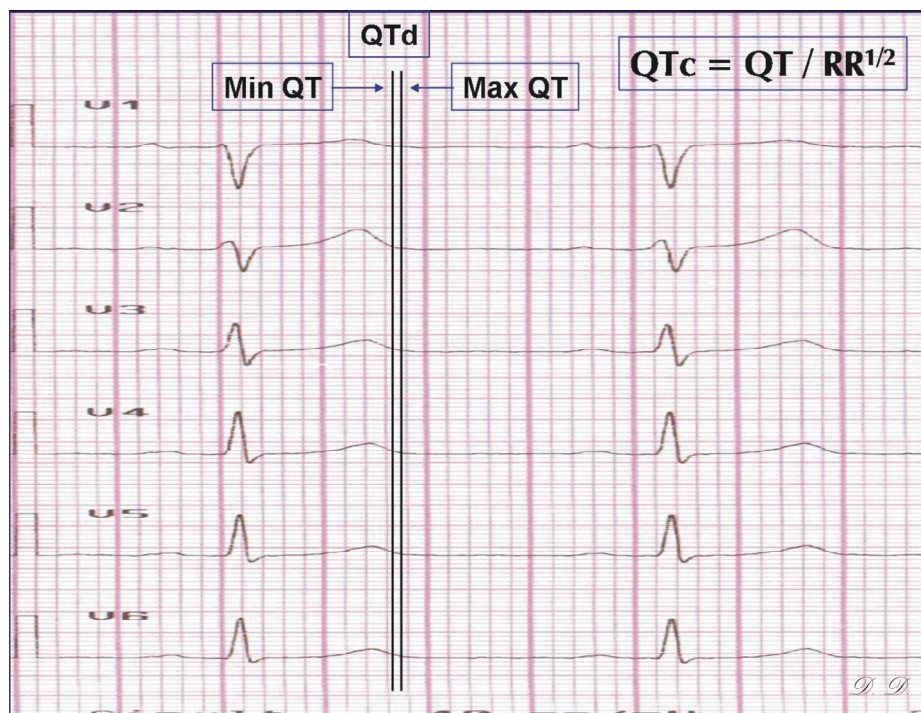


Fig. 1. Measuring QT intervals, QT dispersion and Bazett's formula for rate correction QT interval (precordial leads)

The *forth*, it is not clear whether QT dispersion measurements must be corrected for rate. In studies, Bazett's formula is the most accepted for correction of QT interval, but clinical study in 35 patients demonstrated that QT dispersion is independent of the heart rate (12).

Which values of QT dispersion are normal?

According to the methodological problem associated with QT dispersion measurements, normal values for QT dispersion have not been well defined. In an analysis of 8,455 healthy subjects from 51 studies, mean QT dispersion ranged from 11 ± 10 to 71 ± 7 ms (13). In the Rotterdam Study, 5812 adults > 55 years old were followed up to for 4 years. Subjects with QTc interval dispersion > 60 ms had a twofold risk for cardiac death or sudden death and a 40% increased mortality risk when compared to those subjects with a QTc interval dispersion < 30 ms (14).

In the Strong Heart Study, 1839 American Indians were followed up to nearly 4 years (15). The QTc interval dispersion > 58 ms was associated with a 3.4-fold increased risk for cardiovascular death in Indians aged 45 to 74 year.

The prognostic value of QT dispersion was also evaluated in the substudy of West of Scotland Coronary Prevention Study (WOSCOPS), in which 6595 middle-aged men were evaluated with a moderately raised cholesterol but not prior to myocardial infarction. The QT dispersion > 44 ms was associated with a 36% increased risk death or nonfatal myocardial infarction. The sensi-

tivity of this marker was 8.8% and the specificity was 93.8%. The cut-off provided little predictive value according to low sensitivity (16).

So, there is a general agreement that values between 30 ms and 60 ms are considered normal. The great interobserver variability suggests that examiner has to obtain itself normal values, based on numerous ECG of healthy people.

Clinical significance of QTc interval dispersion

Increased QTc interval dispersion can be seen in patients with various cardiac diseases: myocardial infarction, left ventricular hypertrophy, long QT syndrome, heart failure, and aortic stenosis. Increased QTc interval dispersion can be also seen in some non-cardiac diseases.

It was shown that QT dispersion could predict inducibility of ventricular arrhythmias during electrophysiology study (17). In the group of patients with a history of sustained ventricular tachycardia or ventricular fibrillation, QT and QTc interval dispersion were significantly greater in the subgroup of patients with dilated cardiomyopathy than in patients with a previous myocardial infarction, established coronary artery disease without a myocardial infarction, or hypertensive left ventricular hypertrophy (18). Although QT dispersion is not an alternative to invasive methods of electrophysiology study, it is a useful and simple parameter for electrophysiological evaluation. Torres et al reported that a prolonged QT with amiodarone was associated with an improved outcome, but many investigators ob-

served that a prolonged QT with quinidine, sotalol, dofetilide, propafenone and terfenadine is associated with an increased propensity for arrhythmias, especially of the torsades de pointes variety. This difference appears to be a result of different effects of the agents on dispersion in repolarization. Thus, measuring QT dispersion on a 24-hour basis may be a very helpful way of assessing drug effects in an individual patient (19).

In patients with acute myocardial infarction QTc interval dispersion is changed during the time. Ciolli et al. studied 101 patients with acute myocardial infarction and a control group of 97 healthy subjects. They determined QT and QTc interval dispersion on the electrocardiograms performed 12 hours and 3 and 10 days after the onset of symptoms in myocardial infarction patients and on the control group. Data suggest that QT dispersion: 1) increases during acute myocardial infarction; 2) peaks in the early hours after symptom onset; 3) drops late after infarction in patients treated with thrombolytic agents; 4) is associated with early severe ventricular arrhythmias (20). Moreno et al. support the hypothesis that QTd after acute myocardial infarction depends on reperfusion status as well as infarct site and size (21). But, there is a study with an opposite conclusion. In the study of De Sutter et al. QT parameters are not influenced by infarct size and do not predict inducibility during electrophysiological study in patients with coronary artery disease and malignant ventricular arrhythmias. In contrast, the amount of scar tissue determined by perfusion imaging is strongly correlated with inducibility (22). QT dispersion measured on an ECG recorded 2 or 3 days after acute myocardial infarction does not predict mortality during the next 5 years (23).

In acute coronary syndromes there are patients with initially non-diagnostic ECG. In our preliminary study 75% of 16 patients with acute coronary syndrome had QTc interval dispersion greater than ≥ 60 ms (24). In the study of the 137 patients with an initially non-diagnostic ECG, 51 were finally diagnosed with acute coronary syndrome (37%). For patients with chest pain and non-diagnostic initial ECG, acute coronary syndrome risk is high if QT and QTc interval dispersion values are greater than 40 ms. Therefore, QT and QTc interval dispersion can help to identify patients with acute coronary syndrome with present chest pain and a non-diagnostic initial ECG. However, poor operator characteristics of QT dispersion could limit its value as a diagnostic test in the clinical setting (25).

The QT dispersion is increased in association with an increased left ventricular mass index in hypertensive individuals. Antihypertensive therapy with ramipril and felodipine reduced this parameter. If an increased QT dispersion is a predictor of sudden death in this group of individuals, then the importance of its reduction is evi-

dent (26). Predictive value of QTc interval dispersion for adverse cardiovascular diseases was proven in hypertensive patients during five year follow-up (27). Regression of left ventricular mass during seven years follow-up was associated with decreasing of QTc interval dispersion (28).

The QT and QTc interval dispersion are increased in patients with systolic heart failure in comparison with matched controls, regardless of the method of measurement and independently of possible confounding factors. Beta blockers are associated with a reduction in both QT and QTc interval dispersion, raising the possibility that a reduction in dispersion of ventricular repolarization may be an important antiarrhythmic mechanism of beta blockade (29). Opposite facts were seen in Losartan Heart Failure Survival Study--ELITE II clinical trial. This study prospectively investigated 3,118 standard 12-lead ECGs recorded in 1,804 patients. Neither losartan nor captopril significantly modified QT or JT dispersion. Increased QT dispersion was not associated with increased mortality in patients with heart failure, and was not suitable to examine drug efficacy in these patients (30).

In aortic stenosis, multivariate logistic regression analysis showed that increased QTc interval dispersion had significant value for the risk of syncope. An increased QTc interval dispersion caused a 10.4% increase in the occurrence of syncope in aortic stenosis (31). Several authors reported a significantly higher QT dispersion in hypertrophic cardiomyopathy patients with ventricular arrhythmias compared with those without arrhythmias (32). In long QT syndrome, patients not responding to beta-blockers had a significantly higher QT dispersion than responders (33).

In the end, there are > 1000 articles in the literature on QT dispersion, but that is not enough for a full explanation of the role of QTc interval dispersion in clinical practice. A larger prospective study for evaluating prognostic significance of this parameter in different cardiovascular and non-cardiovascular diseases is needed.

Conclusion

After nearly two decades of QTc dispersion in cardiology, we can conclude that the QTc interval dispersion has obvious predictive value, but inter- and intraobserver variability limits its clinical use. In perspective, it is important to decrease measurement error by improving measurement technique, more precisely define normal values and prove predictive value in different diseases and drug use in studies with a great number of patients.

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BLIZU DVE DECENIJE DISPERZIJE QTC INTERVALA U KARDIOLOGIJI

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Kratak sadržaj: *Heterogena ventrikularna repolarizacija zapažena je na standardnom elektrokardiogramu još pre 1934. godine, kao marker za ventrikularne aritmije QT disperzija je otkrivena 1990. godina, a prvi prognostički značaj QT disperzije dokazan je 1994. godine. Disperzija QT intervala je raspon trajanja QT intervala u svim odvodima u kojima se može izmeriti. To znači razlika između najdužeg i najkraćeg QT intervala. Normalne vrednosti QT disperzije još uvek nisu definisane zbog metodoloških problema vezanih za merenje QT intervala. Normalnim vrednostima smatraju se vrednosti između 30 i 60 ms. Povećana disperzija QT intervala može se videti kod bolesnika sa različitim srčanim oboljenjima kao što su infarkt miokarda, hipertrofija leve komore, sindrom dugog QT intervala, srčana insuficijencija i aortna stenozna. Disperzija QTc intervala ima očiglednu prognostičku vrednost, ali varijabilnost rezultata merenja kod jednog istog ili različitih ispitivača ograničava njenu širu kliničku upotrebu. U budućnosti, važno je da se smanji greška merenja razvojem tehnike merenja, preciznije definisanje normalnih vrednosti i treba potvrditi prognostički značaj kod različitih bolesti i upotrebe lekova u studijama sa velikim brojem bolesnika..*

Ključne reči: *elektrokardiogram, disperzija QTc intervala, merenje, prognostička vrednost*