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Review article

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DRUGS AND QTc INTERVAL DISPERSION

SUMMARY

The measure of delayed ventricular repolarization most frequently used clinically is the ability of the new chemical entity to prolong the QTc interval on surface electrocardiogram. Intramyocardial dispersion of repolarization appears to play a more important role both in electrical stability of the ventricles and in arrhythmogenesis. The potential importance of myocardial dispersion of refractoriness in arrhythmogenesis has led to a number of attempts to assess it from the surface electrocardiogram. The QTc interval dispersion is the difference between maximal and minimal QTc intervals obtained from 12 electrocardiographic leads. Drugs which prolong QTc interval have different effect on QTc interval dispersion. Beta blockers decrease QTc interval and QTc dispersion. Amiodarone and sotalol increase QTc inerval but decrease QTc dispersion. Quinidine and flecainide increase QTc interval and QTc interval dispersion. Propafenone increases QTc interval dispersion in patients with myocardial ishemia. Treatment of patients with drugs which can improve inhomogenous ventricular repolarization leads to better prognosis. We should consider this more seriously when prescribing drugs.

Key words: **electrocardiogram, QTc interval, QTc dispersion, drug**

INTRODUCTION

Drug-induced delay in ventricular repolarization and proarrhythmias have attracted considerable regulatory attention. The measure of delayed ventricular repolarization most frequently used clinically is the ability of the new chemical entity to prolong the QTc interval on surface electrocardiogram. Before they can be approved, new chemical entities with systemic bioavailability require characterization for their potential to prolong the QTc interval. Intramyocardial dispersion of repolarization appears to play a more important role both in electrical stability of the ventricles and in arrhythmogenesis. The potential importance of myocardial dispersion of refractoriness in arrhythmogenesis has led to a number of attempts to assess it from the surface electrocardiogram. Although the concept of QT dispersion is the best known and most widely investigated, it has also proved to be the least successful in predicting the risks of drug-induced Torsade de Points (1).

The QTc interval dispersion is the difference between maximal and minimal QTc intervals obtained from 12 electrocardiographyc leads (Figure 1). That is the unit of heterogeneous ventricular repolarization. Heterogeneous ventricular repolarization was recognized from standard ECG as early as 1934 (2). Unfortunatelly, new interest for QTc dispersion was raised again in 1990, when Day reported that QTc dispersion was a marker of arrhythmia risk in patients with long QT interval (3).

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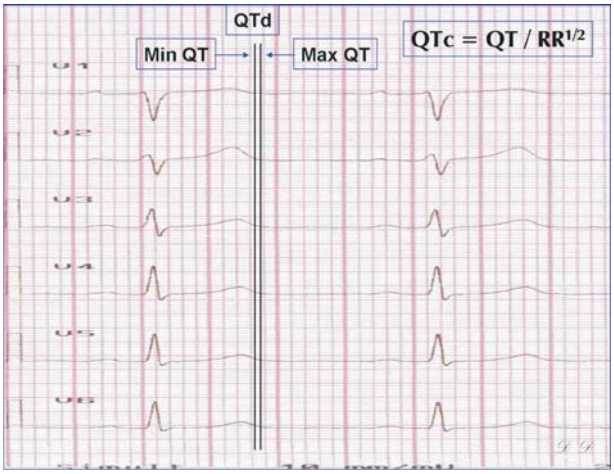

Figure 1: QT interval dispersion and Bazett's formula for QT interval correction (only precordial leads showed).

There is a methodological problem associated with QT dispersion measurements expressed through great intra- and inter-observer variability. In addition, 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 (4). In the Rotterdam Study, 5812 adults > 55 years old were followed up for 4 years. Subjects with QTc 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 dispersion < 30 ms (5). In the Strong Heart Study, 1839 American Indians were followed up for nearly 4 years (6). The QTc dispersion > 58 ms was associated with a 3.4-fold increased risk of cardiovascular death in Indians aged 45 to 74 years. There is a general agreement that values between 30 ms and 60 ms are considered normal.

Drug influence on QTc interval dispersion in different clinical conditions

Beta blockers are often used in clinical practice, especially in patients with coronary artery diseases. In the study of Puljevic et al., eighty-five patients, 3 months after myocardial infarction, were randomized in 2 groups. The first group received atenolol 50 mg daily during 7 days and the second group propafenone 300 mg per os twice a day. Both atenolol and propafenone significantly decreased QTc dispersion. Atenolol also decreased QTc interval, while with propafenone it was not changed (7). Similar results were found for methoprolol in patients with healed myocardial infarction (8). QT and QTc dispersion were increased in patients with systolic heart failure in comparison with matched controls, regardless of the method of measurement and apart from possible confounding factors. Beta blockers were associated with a reduction in both QT and QTc dispersion, raising the possibility that a reduction in dispersion of ventricular repolarization may be an important antiarrhythmic mechanism of beta blockade (9). New beta blocker, nebivolol reduced increased QT dispersion in hypertensive subjects after four weeks *(Table 1)*. This effect, having occurred without any change in the left ventricular mass, did not seem to be related to the blood pressure lowering and could contribute to reduce arrhythmias as well as sudden cardiac death in at-risk hypertensive patients (10).

Table 1: Effect of drugs on QTc interval and QTc interval dispersion

Drug	QTc interval	QTc dispersion
Atenolol	↓	↓
Methoprolol	↓	↓
Nebivolol	↓	↓
Quinidine	↑	↑
Flekainide	↑	↑
Propafenone	↔	↑, ischemia ↑
Amiodarone	↑	↓
Sotalol	↑	↓
Trimetazidine	↓	↓
Antipsychotic drugs	↑	↑
Ramipril	↔	↓
Irbesartan	↔	↓

Legend: ↑increase, ↓decrease, ↔no change

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 evident (11). Irbesartan improved QT dispersion during 6 months of treatment (12). Regression of left ventricular mass during seven-year treatment by hypertensive drugs and follow-up was associated with decreasing of QTc interval dispersion (13).

It is well-known that ***quinidine*** has great proarrhythmic effect especially in patients with ischemia. Mathis et al. examined a relationship between serum quinidine concentrations and QT interval dispersion, compared with corresponding QT intervals, in order to identify a reason why many reports describe torsade de pointes as occurring at subtherapeutic concentrations. Despite QT interval lengthening with increasing serum quinidine concentrations, QT dispersion was numerically greatest at subtherapeutic serum quinidine concentrations. Further study is required to

determine the value of QT dispersion as a tool for identifying proarrhythmic risk with drugs that prolong the QT interval (14). Amiodarone and quinidine both increased the corrected and uncorrected QT and JT intervals; amiodarone decreased and quinidine increased the dispersion of these intervals, and these data suggested an improvement in the homogeneity of myocardial refractoriness as a result of amiodarone treatment and the converse as a result of quinidine treatment. Quinidine increased the QTS interval more than amiodarone, and the data indicate that in patients with intraventricular conduction defects, the monitoring of the JT interval might more accurately reflect changes in myocardial repolarization (15).

The proarrhythmic risk of ***class Ic antiarrhythmic*** agents in combination with myocardial ischemia is mainly the result of their effects on ventricular repolarization. During myocardial ischemia, particularly during LAD occlusion, propafenone results in a significant increase in QT dispersion. The results indicate that QT interval prolongation and enhanced QT dispersion reflect inhomogeneous ventricular repolarization generated by the ischemic anterior wall of the myocardium. These observations may demonstrate a clinically important interaction between myocardial ischemia, repolarization variables and propafenone (16).

Class III atiarrhythmic agents such amiodarone, sotalol and dofetilide have different effect on survival in patients with heart failure or ischemia. In patients with a recent myocardial infarction, left ventricular dysfunction, and a short baseline QTc interval, dofetilide is associated with significant survival benefit. This benefit is not seen in a longer QTc interval. QT dispersion is not a risk factor in this population (17). After initiation of amiodarone, Grimm et al. concluded that amiodarone increased QT intervals and QTc intervals during sinus rhythm, but did not significantly changed measures of QT dispersion; and QT dispersion measured in the 12-lead standard ECG after initiation of amiodarone therapy did not appear to be a useful marker for subsequent arrhythmic events (18). In the study of Sarubbi et al., sotalol treatment prolonged ventricular repolarization times in an homogeneous fashion, as showed by the significant decreased in QTc dispersion. On the contrary, flecainide treatment was associated with an increase in QTc dispersion, mean QT, QTc, and QRS. Propafenone treatment did not affect repolarization time indexes, affecting only depolarization time as expressed by an increase in QRS (19). Effect of class III agents on QT/QTc dispersion in patients with heart disease and cardiac arrhythmias, QT dispersion and QRS and RR intervals were compared in patients before and after treatment with amiodarone, sematilide and sotalol. The mean baseline values for QT/QTc dispersions were not significantly different among all 3 groups. However, only amiodarone significantly reduced the QT dispersion and QTc dispersion in patients with myocardial infarction (20).

Trimetazidine has been suggested to exert anti-ischemic properties on myocardium without affecting myocardial oxygen consumption or supply. It is concluded that trimetazidine decreases QT and QTc dispersion after acute myocardial infarction. Further investigations are needed to evaluate the mechanism and the clinical implications of this effect (21).

Long-term treatment with ***antipsychotic drugs*** in conventional doses prolongs QTc dispersion and increases ventricular tachyarrhythmias in patients with schizophrenia in the absence of cardiac disease. Long-term treatment with antipsychotic drugs in conventional doses prolonged both QTc and QTc dispersion in patients with schizophrenia, but did not increase ventricular tachyarrhythmias in patients with schizophrenia in the absence of cardiac disease. However, despite the negative findings, ventricular tachyarrhythmias may occur as a rare side-effect of antipsychotic drugs, particularly if a patient has additional risk factors (22). QT interval dispersion may be increased in patients who develop haloperidol-induced Torsades de Pointes compared with those who do not. However, these effects depend on the method of measurement (12 leads vs. precordial leads). In addition, the odds of haloperidol-induced Torsades de Pointes are higher in patients with QTc interval prolongation compared with increased QT interval dispersion. Therefore, QTc interval determination remains preferable to QT interval dispersion as a mean assessment of risk of haloperidol-induced Torsades de Pointes (23).

CONCLUSION

Drugs which prolong QTc interval have different effect on QTc interval dispersion. Beta blockers decrease QTc interval and QTc dispersion. Amiodarone and sotalol increase QTc interval, but decrease QTc dispersion. Quinidine and flecainide increase QTc interval and QTc interval dispersion. Propafenone increases QTc interval dispersion in patients with myocardial ischemia. Treatment of patients with drugs which can improve inhomogeneous ventricular repolarizatin lead to better prognosis. We should consider that more seriously when prescribing drugs.

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LEKOVI I DISPERZIJA QTc INTERVALA

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SAŽETAK

Sposobnost novih hemijskih materija da produže QTc interval na standardnom elektrokardiogramu, klinički se najčešće koristila kao mera produžene ventrikularne repolarizacije. Izgleda da intramiokardna disperzija repolarizacije ima značajniju ulogu kako u pogledu električne stabilnosti komora tako i u pogledu aritmogeneze. Mogući značaj refraktarnosti miokardne disperzije u aritmogenezi vodi u brojne pokušaje da se to izmeri na standardnom elektrokardiogramu. Disperzija QTc intervala je razlika između maksimalnog i minimalnog QTc intervala koji se dobija iz 12 odvoda standardnog elektrokardiograma. Lekovi koji produžuju QTc interval imaju različiti uticaj na disperziju QTc intervala. Beta blokatori smanjuju QTc interval i QTc disperziju. Amiodarone i sotalol produžuju QTc interval ali smanjuju QTc disperziju. Hinidin i flekainid produžuju QTc interval i disperziju QTc intervala. Propafenon povećava disperziju QTc intervala kod bolesnika sa miokardnom ishemijom. Lečenje bolesnika lekovima koji mogu popraviti inhomogenu ventrikularnu repolarizaciju vodi u bolju prognozu. Trebalo bi da više mislimo o tome pri propisivanju lekova.

Ključne reči: **elektrokardiogram, QTc interval, QTc disperzija, lekovi**