

ORIGINAL ARTICLE

Effect of Transient Myocardial Ischemia on QT Interval Dispersion Among Patients With Unstable Angina

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ABSTRACT

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KEY WORDS: ventricular repolarization; acute coronary syndrome; QT dispersion

ABBREVIATIONS

QT_c = corrected QT
QT_d = QT dispersion
QT_{c,d} = corrected QT dispersion
ΔQT_d = difference in QT_d
ΔQT_{c,d} = difference in QT_{c,d}

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OBJECTIVE: Our aim was to examine the effect of transient myocardial ischemia on QT interval and QT interval dispersion in patients presenting with unstable angina.

METHODS: We studied 31 patients (mean age 64±10, 22 men, 16 with an old myocardial infarction, 6 with previous coronary bypass surgery) admitted with unstable angina manifestations. Patients with a history of complex ventricular ectopy, malignant ventricular arrhythmias, advanced congestive heart failure or antiarrhythmic drug therapy were excluded. The uncorrected and corrected QT interval and QT dispersion were measured during angina as well as after the relief of pain.

RESULTS: The RR intervals were not significantly changed by the ischemic event (879±121 ms at rest to 877±173 ms during angina). However, both the uncorrected and corrected QT intervals were significantly increased during angina (from 410±45 ms and 440±41 ms at rest to 425±53 ms and 460±42 ms during angina respectively, $p<0.05$ for both). Similarly, both the uncorrected (QT_d) and the corrected (QT_{c,d}) QT dispersion values were significantly prolonged during ischemia (QT_d: 58±23 ms at rest to 83±33 ms during ischemia, $p<0.001$, QT_{c,d}: 63±26 ms at rest to 95±36 ms during ischemia, $p<0.001$). The observed increment in the QT_d and QT_{c,d} provoked by ischemia was not different among the unstable angina patients with and without old myocardial infarction.

CONCLUSION: Transient myocardial ischemia besides an increase in the QT and QT_c intervals provokes an increase in both the corrected and uncorrected QT interval dispersion. Under certain circumstances, this may contribute to the genesis of serious reentry ventricular arrhythmias.

INTRODUCTION

Patients with acute coronary ischemia are at increased risk for sudden cardiac death

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mainly due to ventricular fibrillation.¹ This risk is higher among patients with a previous history of myocardial infarction.² Experimental studies suggest that ventricular repolarization can be unfavorably altered by acute coronary ischemia.^{3,4} In the clinical setting, there is a clear tendency towards increase of QT dispersion in coronary artery disease,⁵ in acute myocardial infarction,⁶ as well as during ischemia induced by balloon inflation during angioplasty,^{7,8} by exercise stress testing or atrial pacing,^{9,10} or during reperfusion following angioplasty.¹¹ Such an increase of the QT dispersion has been associated with a high incidence of malignant ventricular events in most clinical studies.^{5,12-14}

The purpose of this study was to explore the impact of transient myocardial ischemia on QT dispersion among patients presenting with unstable angina.

METHODS

PATIENTS

Our study population consisted from 31 patients with known coronary artery disease (history of previous myocardial infarction and/or coronary artery stenoses >75% involving one or more major vessels in coronary angiography). Patients were admitted at the hospital ward or the Intensive Care Unit with the diagnosis of unstable angina, namely accelerated angina at rest of less than 10 min, associated with transient ischemic ST and T-wave changes, subsiding to the administration of nitroglycerin and not associated with myocardial enzyme elevation. Patients with a QRS duration \geq 120 msec due to underlying bundle branch block or a major intraventricular conduction delay, or patients with atrial fibrillation, excessive sinus tachycardia, an evolving acute myocardial infarction, electrolyte aberrations or frequent premature complexes were excluded. None of these patients was treated with antiarrhythmic drugs or had New York Heart Association congestive heart failure symptoms > class II.

12-LEAD ELECTROCARDIOGRAM

This was performed at a paper speed of 25mm/sec (sensitivity 10mV/cm) during and 15 minutes after the relief of angina using the same lead position while the patient was still in bed. Care was taken to relieve patient's anxiety so the heart rate did not exhibit great fluctuations during the study. Apart from nitroglycerin, no other cardio-active medications were used for the relief of pain.

QT DISPERSION CALCULATION

All electrocardiograms were analyzed manually by two independent and experienced investigators in a blind fashion. The following 3 intervals were calculated for each electrocardiographic lead: RR, QT and corrected QT (QTc) interval.

For the calculation of the latter, Bazett's formula ($QTc = QT / RR^{0.5}$) was used taking into account the RR interval before the measured QT interval. The end of the T-wave was defined as the point of return to the isoelectric TP baseline or in the presence of a well defined U-wave, at the nadir between the T and U waves. In case of flat T-wave changes, where difficulties to define the end of the T-wave were encountered, the measurements were omitted. Care was taken to complete the measurements in at least 10 of the 12 available leads.

The maximum QT interval was considered as QT interval and the maximum QTc interval was taken as QTc interval. As QT dispersion was defined the difference between the maximum and minimum observed QT intervals in any leads. As QTc dispersion was defined the corresponding difference of the corrected QTc intervals. Both the interobserver and intraobserver variability were examined in 10 records.

STATISTICAL ANALYSIS

All of the data were collected and quantitative data were expressed as mean \pm standard deviation. Paired t-tests were used to compare mean values within subjects (pre and post angina) and student's t-tests were used to compare means between independent populations. Data analyses were performed using SPSS (Statistical Package for Social Sciences) version 15 software (Chicago, IL). Values of $P < 0.05$ were considered significant.

RESULTS

PATIENTS

All 31 patients fulfilled the entry criteria. The mean age was 64 ± 10 years (range 42-90 years old) with 22 patients being males. More than half of the studied patients (16/31, 52%) had a previous history of myocardial infarction (anterior in 7, posterior in 8 and non-Q wave in 1) while 6 of the patients (19%) underwent coronary artery bypass surgery in the past. The mean left ventricular ejection fraction was well preserved ($50 \pm 10\%$, range from 30 to 65%). No difference was observed in age, gender, ejection fraction, history of diabetes and hypertension, as well as use of β -blockers and renin-angiotensin-aldosterone blockers between patients with and those without previous myocardial infarction (Table 1).

RR, QT AND QTc CHANGES DURING ISCHEMIA

The mean RR interval was slightly decreased from 879 ± 121 msec at rest to 877 ± 173 msec during angina. The mean maximum QT interval was increased from a value of 410 ± 45 msec at rest to a value of 425 ± 53 msec during angina ($p < 0.05$). Similarly, the mean maximum QTc was increased from 440 ± 41 msec at rest to 460 ± 42 msec during angina ($p < 0.001$) (Table 2, Figure 1).

TABLE 1. Clinical characteristics of the study patients according to the presence or not of previous myocardial infarction.

	Patients with previous myocardial infarction (n=16)	Patients without previous myocardial infarction (n=15)	p
Age (yrs)	64.9±12.3	62.2±7.4	0.49
Males (%)	62.5	80	0.29
CABG (%)	19	7	0.32
Ejection fraction (%)	47.4±8	52.8±4	0.25
History of hypertension (%)	50	47	0.85
History of diabetes (%)	25	20	0.74
RAAS blockers (%)	81	80	0.93
b-blockers (%)	100	100	1
Difference in QT _d (ms)	26.8±25.7	22.0±25.4	0.60
Difference in QTc _d (ms)	32.9±34.3	30.0±26.1	0.79

CABG= coronary artery bypass surgery; RAAS = renin-angiotensin-aldosterone system; QT_d = QT dispersion; QTc_d = corrected QT dispersion

TABLE 2. Electrocardiographic parameters during and 15 minutes after the relief of angina.

	Rest	Angina	p
RR	879.3±121	877.4±174	0.93
QTmax	410±45	425±53	0.012
QTcmax	440±41	460±42	<0.001
QT _d	58±23	83±33	<0.001
QTc _d	63±26	95±35	<0.001

QTcmax=corrected QTmax; QT_d=QT dispersion; QTc_d=corrected QT dispersion

CHANGES IN THE QT DISPERSION PROVOKED BY ISCHEMIA

The mean uncorrected QT dispersion (QT_d) was increased from 58±23 msec at rest to 83±33 msec during ischemia (p<0.001). Similarly, the mean corrected QTc dispersion (QTc_d) value was also increased from 63±26 msec at rest to 95±36 msec during ischemia (p<0.001) (Table 2, Figure

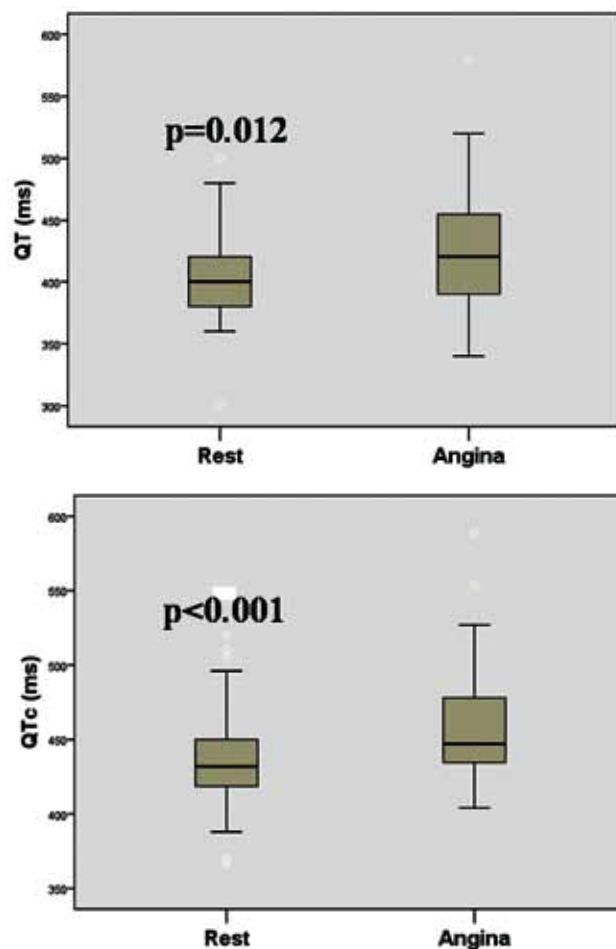


FIGURE 1. Differences in QT and QTc provoked by ischemia in patients with unstable angina.

2). The observed difference in QT_d and QTc_d with ischemia (Δ QT_d and Δ QTc_d) was >20 msec in 21 (68%) and 20 (65.4%) patients respectively. These increments in QT_d were not different between patients with and those without previous history of myocardial infarction. Specifically, the Δ QT_d provoked by ischemia in patients with an old myocardial infarction (n=16) was similar to Δ QT_d observed in patients without a previous myocardial infarction (n=15) (26.8±25.7 vs. 22.0±25.4 msec, p=0.60). Similarly, Δ QTc_d provoked by ischemia was not different between patients with and those without a previous history of myocardial infarction (32.9±34.3 vs. 30.0±26.1 msec, p=0.79) (Table 1).

INTER AND INTRA-OBSERVER VARIABILITY

In 10 re-examined paired-records the observed values were in good agreement both within the same observer (differences of less than 3%) as well as between 2 observers (differences of less than 5%).

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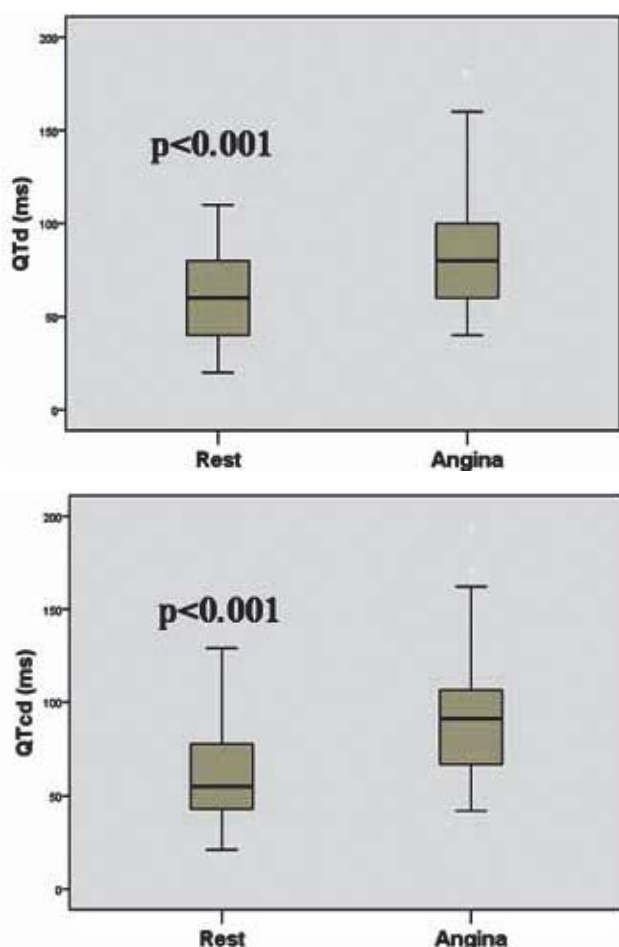


FIGURE 2. Differences in QT_d and QTc_d provoked by ischemia in patients with unstable angina.

DISCUSSION

The results of this study demonstrate that transient myocardial ischemia can induce a temporary increase in the repolarization dispersion among patients presenting with unstable angina. Indeed a significant increase in the QT and corrected QTc dispersion was noted during the angina attack. No difference in the increase of QT dispersion was evident between patients with and those without a history of a previous myocardial infarction.

QT dispersion is increased in the acute phase of myocardial infarction, while there seems to be a trend towards lower or even similar values in the chronic phase of myocardial infarction and in other chronic forms of ischemic artery disease possibly due to the spontaneous dynamicity or to revascularization procedures.^{6,15} Moreover, an increase of QT dispersion has also been demonstrated during ischemia induced during angioplasty,^{7,8} during reperfusion following angioplasty,¹¹ or by exercise stress testing or atrial pacing.^{9,10} Changes of QT

dispersion have also been correlated with improvement of left ventricular contractility after infarction and with the degree of improvement of left ventricular function after revascularization.^{16,17} In parallel, treatment has been shown to decrease QT dispersion, e.g., after successful reperfusion after thrombolysis,¹⁸ revascularization with angioplasty¹⁹ or coronary artery bypass grafting.¹⁷

In the present study, the mean QT and QTc dispersion at rest were slightly prolonged at values commonly observed among patients after a myocardial infarction.^{5,12,20} These indices of a repolarization dispersion abnormality were unfavorably affected by transient myocardial ischemia. Notably, there was no difference in the increase of QT dispersion between patients with and without a history of a previous myocardial infarction. The ischemia induced increment in the QT and QTc dispersion was of rather small magnitude (a mean increase of 25 and 35 msec respectively) not reaching grossly abnormal values such as those observed in patients with long QT syndrome or in patients presenting with an acute myocardial infarction, namely patients at higher risk for the development of polymorphic ventricular tachycardia or/and ventricular fibrillation.^{12,14,21} However, one cannot ignore the potential significance of an unfavorable repolarization pattern induced by transient ischemia among unstable angina patients who are also at risk for sudden cardiac death.^{5,9,13}

This ischemia induced abnormality in the dispersion of the repolarization could be one of the multiple potential pathogenic mechanisms predisposing coronary artery disease patients to reentry ventricular arrhythmia. Previous studies have shown that antiarrhythmic drugs such as type IA agents can also lead to similar increments of QT dispersion when given to coronary artery disease patients.²² It is possible that the combination of an acute ischemic event in the presence of a type I antiarrhythmic agent could lead to marked regional differences in the ventricular repolarization process. This could provide an explanation to the surprisingly increased incidence of sudden cardiac death observed among patients treated with antiarrhythmic medication in the late myocardial infarction period.²³ A number of other transiently altered variables could also operate in the complex process leading to malignant electrical instability. Indeed, changes in the autonomic tone, increased catecholamine levels, electrolyte abnormalities, such as hypokalemia and hypomagnesemia, or acute increases in the afterload could also contribute to a further worsening of an ischemia induced unfavorable repolarization pattern.²⁴⁻²⁶ Revascularization procedures are known to decrease the incidence of sudden cardiac death among specific coronary artery disease populations.²⁷ Successful thrombolytic treatment has also decreased the mortality in both the acute and late myocardial infarction period.^{28,29} Such a treatment has been associated with a decrease in the QT dispersion.¹⁸ Thus one could anticipate that restoration of coronary blood flow can ameliorate the regional ventricular repolarization differences.

Among our patient population, we did not observe any malignant ventricular arrhythmia during the acute ischemia event. This probably reflects the magnitude of the repolarization dispersion induced by ischemia. The mean QT and QTc dispersion observed during ischemia was 88 and 93 msec respectively. All of our patients were promptly treated in a general hospital environment without taking any antiarrhythmic agents and nor demonstrating any significant electrolyte abnormality or hemodynamic aberration. Thus in the absence of any other corroborating factors, the observed increase in the repolarization dispersion was not arrhythmogenic.

The main limitation of the present study is the lack of a control group. Moreover, data regarding structural left ventricular adaptations, that influence QT dispersion and distribution, are also lacking. Manual measurements of the QT interval are not considered as accurate as computer guided measurements even though available automatic methods have not proven their superiority.^{14,30} Furthermore, the definition of the end of T wave may be even more difficult during the ischemia when T wave changes are common, a fact that also bias the blinding process. Nevertheless, both the intraobserver and interobserver variabilities were acceptable. Another point of criticism could be raised from the limitations of using the Bazett's formula for estimating the corrected QT values.^{31,32} However, the mean RR interval during ischemia was not shortened and furthermore both the uncorrected and the corrected were at the same direction. Finally, the 15 minute waiting period for repeating the ECG although guided by ST segment changes resolution may not reflect the real time required for the repolarization changes to be completely resolved.

In this study we observed a temporary increase in the ventricular repolarization dispersion induced by transient myocardial ischemia among patients presenting with unstable angina. This observation may provide a further insight into the mechanism leading to reentry ventricular arrhythmias and should emphasize the important role of restoring coronary blood flow in unstable angina patients.

REFERENCES

1. Lown B. Sudden cardiac death: the major challenge confronting contemporary cardiology. *Am J Cardiol* 1979; 43:313-328.
2. Myerburg RJ, Conde CA, Sung RJ, et al. Clinical, electrophysiologic and hemodynamic profile of patients resuscitated from prehospital cardiac arrest. *Am J Med* 1980; 68:568-576.
3. Kimura S, Bassett AL, Cameron JS, Huikuri H, Kozlovskis PL, Myerburg RJ. Cellular electrophysiological changes during ischemia in isolated, coronary-perfused cat ventricle with healed myocardial infarction. *Circulation* 1988; 78:401-406.
4. Horacek T, Neumann M, von Mutius S, Budden M, Meesmann W. Nonhomogeneous electrophysiological changes and the bimodal distribution of early ventricular arrhythmias during acute coronary artery occlusion. *Basic Res Cardiol* 1984; 79:649-667.
5. Zareba W, Moss AJ, le Cessie S. Dispersion of ventricular repolarization and arrhythmic cardiac death in coronary artery disease. *Am J Cardiol* 1994; 74:550-553.
6. Glancy JM, Garrat CJ, de Bono DP. Dynamics of QT dispersion during myocardial infarction and ischemia. *Int J Cardiol* 1996; 57:55-60.
7. Aytemir K, Bavafa V, Ozer N, Aksoyek S, Oto A, Ozmen F. Effect of balloon inflation-induced acute ischemia on QT dispersion during percutaneous transluminal coronary angioplasty. *Clin Cardiol* 1999; 22:21-24.
8. Tarabey R, Sukenik D, Milnar J, Somberg JC. Effect of intracoronary balloon inflation at percutaneous transluminal coronary angioplasty on QT dispersion. *Am Heart J* 1998; 135:519-522.
9. Yi G, Crook R, Guo H, Staunton A, Camm AJ, Malik M. Exercise-induced changes in the QT interval duration and dispersion in patients with sudden cardiac death after myocardial infarction. *Int J Cardiol* 1998; 63:271-279.
10. Sporton SC, Taggart P, Sutton PM, Walker JM, Hardman SM. Acute ischemia: a dynamic influence on QT dispersion. *Lancet* 1997; 349:306-309.
11. Michelucci A, Padeletti L, Frati M, et al. Effects of ischemia and reperfusion on QT dispersion during coronary angioplasty. *PACE* 1996; 19:1905-1908.
12. Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. *Br Heart J* 1990; 63:342-344.
13. Pye M, Quinn AC, Cobbe SM. QT interval dispersion: a non-invasive marker of susceptibility to arrhythmia in patients with sustained ventricular arrhythmias? *Br Heart J* 1994; 71(6):511-514.
14. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol* 2000; 36(6):1749-1766.
15. Sporton SC, Taggart P, Sutton PM, Walker JM, Hardman SM. Acute ischemia: a dynamic influence on QT dispersion. *Lancet* 1997; 349:306-309.
16. Gabrielli F, Balzotti L, Bandiera A. QT dispersion variability and myocardial viability in acute myocardial infarction. *Int J Cardiol* 1997; 61:61-67.
17. Schneider CA, Voth E, Baer FM, Horst M, Wagner R, Sechtem U. QT dispersion is determined by the extent of viable myocardium in patients with chronic Q-wave myocardial infarction. *Circulation* 1997; 96:3913-3920.
18. Moreno FL, Villanueva T, Karagounis LA, Anderson JL. Reduction of QT interval dispersion by successful thrombolytic therapy in acute myocardial infarction. TEAM-2 study investigators. *Circulation* 1994; 90:94-100.
19. Kelly RF, Parillo JE, Hollenberg SM. Effect of coronary angioplasty on QT dispersion. *Am Heart J* 1997; 134:399-405.
20. Mirvis DM. Spatial variation of QT intervals in normal persons and patients with acute myocardial infarction. *J Am Coll Cardiol* 1985; 5:625-631.
21. De Ambroggi L, Negroni MS, Monza E, Bertoni T, Schwartz PJ. Dispersion of ventricular repolarization in the long QT syn-

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- drome. *Am J Cardiol* 1991; 68:14-20.
22. Hii JT, Wyse DG, Gillis AM, Duff HJ, Solylo MA, Mitchell LB. Preordial QT interval dispersion as a marker of torsade de pointes. Disparate effects of class Ia antiarrhythmic drugs and amiodarone. *Circulation* 1992; 86:1376-1382.
 23. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *N Engl J Med* 1989; 321:406-412.
 24. Schwartz PJ, Stone HL. Left stellectomy in the prevention of ventricular fibrillation caused by acute myocardial ischemia in conscious dogs with anterior myocardial infarction. *Circulation* 1980; 62:1256-1265.
 25. Surawicz B. Ventricular fibrillation. *J Am Coll Cardiol* 1985; 5:43B-54B.
 26. Messerli FH, Ventura HO, Elizardi DJ, Dunn FG, Frohlich ED. Hypertension and sudden death. Increased ventricular ectopic activity in left ventricular hypertrophy. *Am J Med* 1984; 77:18-22.
 27. Passamani E, Davis KB, Gillespie MJ, Killip T. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. *N Engl J Med* 1985; 312:1665-1671.
 28. Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. Gruppo Italiano per lo Studio della Streptochi-nasi nell'Infarto Miocardico (GISSI). *Lancet* 1987; 2:871-874.
 29. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; 2:349-360.
 30. Murray A, McLaughlin NB, Bourke JP, Doig JC, Furniss SS, Campbell RWF. Errors in manual measurement of QT intervals. *Br Heart J* 1994; 71:386-390.
 31. Hodges M. Rate correction of the QT interval. *Cardiac Electrophysiol Rev* 1997; 3:360-363.
 32. Malik M, Camm AJ. Mystery of QTc interval dispersion. *Am J Cardiol* 1997; 79:785-787.