A Comparison of the QT and QTc Dispersion Among Patients with Sustained Ventricular Tachyarrhythmias and Different Etiologies of Heart Disease

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Objectives: To determine if etiology of heart disease is associated with differences in QT and QTc dispersion among patients with ventricular tachyarrhythmias.

Methods: This study was undertaken in 145 patients undergoing electrophysiological testing for sustained ventricular tachycardia or ventricular fibrillation. Patients were divided into groups based on etiology of heart disease determined by history, ECG, coronary angiography, and echocardiography. The groups included patients with: dilated cardiomyopathy (n = 29), myocardial infarction (n = 90), established coronary artery disease without a myocardial infarction (n = 11), or hypertension induced left ventricular hypertrophy (n = 15). The QT intervals on a 12-lead ECG were determined and Bazett's formula was used to derive the QTc intervals. The QT and QTc dispersion were determined by subtracting the shortest QT(c) interval from the longest on each 12-lead recording.

Results: The patients with dilated cardiomyopathy had significantly higher QT and QTc dispersion values as compared to any of the other three groups (P < 0.05 for both). No other differences in electrocardiographic variables were found between groups.

Conclusions: In a group of patients with a history of ventricular tachycardia or ventricular fibrillation, QT and QTc dispersion are significantly greater among patients with dilated cardiomyopathy than for patients with a previous myocardial infarction, established coronary artery disease without a myocardial infarction, or hypertensive left ventricular hypertrophy.

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QT dispersion; dilated cardiomyopathy; myocardial infarction; left ventricular hypertrophy;
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INTRODUCTION

The QT interval is a quantifiable index of ventricular repolarization. The interlead variation of the QT interval provides an index of heterogeneity of repolarization within the ventricles of the heart.¹ The difference between the longest and the short-

est QT interval on a 12-lead ECG (e.g., QT dispersion) is primarily due to changes in the duration of the T waves. From the initiation of the T wave to the peak of the T wave, the epicardium experiences rapid repolarization. While the T wave is descending back towards the isoelectric line, the endocardium repolarizes and the final descending

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portion of the T wave marks repolarization of the M-region. Hence, the changes in QT dispersion reflect a prolongation of repolarization within one region of the heart but not within another region.¹ Enhanced heterogeneity, measured as an increase in QT dispersion, may increase the risk for re-entry and thus ventricular tachyarrhythmias.²

Baseline QT dispersion measurements in normal individuals are approximately 30 to 35 ms.³⁻⁵ Disease or disease sequelae such as hypertension induced left ventricular hypertrophy,⁶⁻⁸ myocardial infarction,^{3,9-11} and dilated cardiomyopathy^{12,13} have been shown to increase QT dispersion significantly. However, whether patients with previous ventricular tachyarrhythmias have higher QT and QTc intervals if they have one of these concomitant problems or if they have established coronary artery disease without a myocardial infarction as compared to the other groups is not currently known. The purpose of this study is to compare the QT and QTc dispersions of patients with ventricular tachycardias grouped on the basis of concomitant structural heart disease.

METHODS

Study Population

The data for the study came from a retrospective review of an electrophysiology study patient database. The study population consisted of patients who had a past medical history of documented ventricular tachyarrhythmias (tachycardia or fibrillation) or syncope with subsequently inducible ventricular tachycardia. All patients were in sinus rhythm without bundle branch block or evidence of other intraventricular conduction abnormalities at the baseline electrophysiology study. The QRS interval had to be less than 100 ms.

History, ECG, coronary angiography, and echocardiography were used to determine the etiology of heart disease. The patients were divided into the following groups: (1) nonischemic dilated cardiomyopathy; (2) left ventricular myocardial infarction; (3) established coronary artery disease without a myocardial infarction; or (4) hypertensive patients with left ventricular hypertrophy but without angina pectoris or a myocardial infarction.

ECG Interval Measurements

All patients had a standard 12-lead electrocardiogram (ECG) recorded at 25 mm/sec at the begin-

ning of the baseline electrophysiology study. A single blinded observer measured the RR, QRS, and QT intervals in each of the 12-leads using a 0.5 mm scale precision ruler (Schaedler Instruments, Parsippany, NJ). This ruler method was previously found to be superior to a caliper and computer method.¹⁴ The QT interval was measured in all leads from the earliest QRS deflection to the end of the T wave. The beginning of the Q wave was identified by visual inspection and the point of T wave offset was defined by return of the terminal part of the T wave to the TP baseline. When a U wave was present and interrupted the T wave, the terminal portion of the visible T wave was extrapolated to the TP baseline to identify the point of T wave offset. When the end of the T wave could not be identified with certainty, that lead was excluded from the analysis. Each interval (RR, QRS, QT) was the average of three consecutive complexes measured from the 12-lead ECG. At least 8 leads were required to be evaluable for the 12-lead ECG to be utilized. QT intervals were also corrected for heart rate using Bazett's formula: $(QTc = QT/RR^{1/2})$.

QT and QTc dispersion was calculated by subtracting the shortest interval from the longest interval measured on the ECG.

Statistical Analysis

Electrocardiographic comparisons between groups were made using ANOVA. Significant differences were then probed with Bonferroni corrected *t*-tests. Data is presented as means $\pm$ SD and a *P* value < 0.05 is considered significant.

RESULTS

The baseline characteristics in each of the study groups were similar except for left ventricular ejection fraction (LVEF) (Table 1). Group comparisons of electrocardiographic variables were similar except for QT and QTc dispersion (Table 2). The QT dispersion was higher in the dilated cardiomyopathy group than the myocardial infarction ($P = 0.0001$), established coronary artery disease without a myocardial infarction ($P = 0.04$), and hypertensive induced left ventricular hypertrophy groups ($P = 0.03$). The QTc was also higher in the dilated cardiomyopathy groups than the others ($P = 0.0001$, $P = 0.019$, $P = 0.028$, respectively).

Table 1. Demographic Comparison

Variable	Dilated Cardiomyopathy	Myocardial Infarction	CAD w/o MI	Hypertensive LV Hypertrophy
Age (years)	56.5 ± 15.2	63.6 ± 9.2	63.7 ± 11.1	65.6 ± 9.7
Gender (Male/Female)	22/7	71/19	11/0	9/6
Number of measurable ECG leads per patient	11.1 ± 1.3	11.6 ± 0.8	11.6 ± 1.0	11.7 ± 0.6
LVEF (%)	28.4 ± 14.6	35.3 ± 14.2	44.1 ± 15.3*	53.2 ± 9.8* ^Δ
Receiving beta-blockers (%)	44.4	52.2	38.2	46.7
History of VF (%)	31.0	17.8	45.5	20.0
History of VT (%)	65.5	53.3	36.4	46.7
Syncope (%)	3.4	29.0	18.2	30.0
Palpitations (%)	0	10.0	0	30.0
Overall inducibility of VT/VF (%)	79.3	63.3	36.4	46.7
Sustained VT (%)	58.6	42.2	27.3	30.0
Nonsustained VT (%)	20.7	21.1	9.1	26.7

CAD w/o MI = Coronary artery disease without myocardial infarction; LVEF = Left ventricular ejection fraction; VT = Ventricular tachycardia, VF = Ventricular fibrillation. ANOVA $P < 0.0001$ for LVEF, nonsignificant for all other comparisons, * denotes $P < 0.05$ vs myocardial infarction and Δ denotes $P < 0.05$ vs dilated cardiomyopathy in LVEF post-hoc tests.

DISCUSSION

In our study of patients previously experiencing an episode of sustained ventricular tachyarrhythmias, the dilated cardiomyopathy group had QT dispersion values that were 50%-65% greater than patients with other etiologies of structural heart disease. However, patients with these other etiologies of heart disease have similar QT dispersion values between 49 and 54 msec; values at least 40% larger than previous data in normal individuals (30 -35 ms).³⁻⁵ This is consistent with previous studies showing that patients with diseases or disease sequelae such as hypertension-induced left ventricular hypertrophy,⁶⁻⁸ myocardial infarction,^{3,9-11} dilated cardiomyopathy,^{12,13} and sustained ventricular tachyarrhythmias have greater degrees of QT dispersion than patients without these disorders. The QT dispersion among non-

myocardial infarction patients with established coronary disease has not, to our knowledge, been evaluated in times without simultaneous ischemia. In this evaluation, the QT dispersion among these patients with established coronary disease and sustained ventricular tachyarrhythmias was not different than those with other types of structural heart disease. Differences in QT and QTc dispersion occurred even though no differences were seen for the QT or QTc intervals between groups.

QT Dispersion Mechanisms

Ventricular myocytes from failing hearts exhibit repolarization delays that are due to the calcium-independent transient outward potassium current (I_{to1}) and the outward component of the inward rectifier potassium current (I_{K1}).¹⁵ I_{to1} is thought to play a role early in repolarization by setting plateau

Table 2. Electrocardiographic Comparison

	Dilated Cardiomyopathy	Myocardial Infarction	CAD w/o MI	Hypertensive LV Hypertrophy
QT (ms)	395 ± 51	389 ± 38	390 ± 31	382 ± 40
RR (ms)	831 ± 204	861 ± 165	853 ± 98	863 ± 161
QTc	438 ± 43	423 ± 29	422 ± 16	413 ± 34
QRS (ms)	89 ± 9	83 ± 9	83 ± 6	77 ± 6
QTd (ms)	81 ± 30*	54 ± 26	49 ± 27	52 ± 28
QTcd (ms)	93 ± 35*	60 ± 30	55 ± 29	59 ± 33

Data presented as means ± SD, QTd = QT dispersion, QTcd = QTc dispersion. $P = 0.026$ for QT dispersion ANOVA, $P = 0.029$ for QTc dispersion ANOVA. * denotes $P < 0.05$ versus all other groups in posthoc between comparisons.

phase potential and in turn affects all currents active during the remainder of the action potential. I_{K1} contributes to the terminal phase of repolarization and establishes a stable resting membrane potential. In pacing derived cardiomyopathic heart failure, canines are predisposed to increases in action potential duration dispersion, early afterdepolarizations, and spontaneous depolarizations. The mid-myocardial cells (m-cells) exhibited greater action potential duration prolongation than epicardial and endocardial cells (thus increased dispersion), an effect accentuated at slow stimulation rates.¹⁵

Clinical Implications

Increased dispersion of repolarization is an important co-factor for torsade de pointes in patients with QT prolongation.¹⁶ Antiarrhythmic agents such as sotalol, ibutilide, quinidine, and dofetilide prolong the QT interval via blockade of the rapid component of the delayed rectifier potassium channel (ibutilide also enhances inward slow sodium channel current [I_{NaS}]).¹⁶⁻¹⁹ In M-cells there are substantially less I_{Ks} channels than in the other regions and hence specific I_{Kr} blockers will prolong repolarization in the M-cells more than the other regions.²⁰ Since the M-cells are already experiencing increased QT dispersion in dilated cardiomyopathy,¹⁵ presumably through I_{to1} and I_{K1} channel effects, the risk of torsade de pointes is enhanced by selective I_{Kr} blockade. In addition, slower heart rates increase the dispersion of repolarization even more in cardiomyopathy, I_{Kr} potassium channel blockers exhibit reverse use dependence, and channel blockade is accentuated at slower heart rates, thus increasing the risk of proarrhythmia even more. This is consistent with studies showing that congestive heart failure substantially increases the risk of torsade de pointes among patients receiving sotalol or ibutilide.^{17,18}

CONCLUSIONS

Among patients with a history of sustained ventricular tachyarrhythmias, QT dispersion is significantly higher among patients with dilated cardiomyopathy than those with other forms of structural heart disease. This may explain the enhanced proarrhythmic potential of I_{Kr} potassium channel blocking agents in this population.

REFERENCES

1. Antzelevitch C, Shimizu W, Yan GX, et al. Cellular basis for QT dispersion. *J Electrocardiol* 1998;30:168-173.
2. Verduyn SC, Vos MA, Zande J, et al. Further observations to elucidate the role of interventricular dispersion of repolarization and early afterdepolarizations in the genesis of acquired torsade de pointes arrhythmias. *J Am Coll Cardiol* 1997;30:1575-1584.
3. Perkiomaki JS, Koistinen J, Yli-Mayry S, et al. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias. *J Am Coll Cardiol* 1995;26:174-179.
4. Yi G, McKenna WJ, Prasad K, et al. QT dispersion and risk factors for sudden cardiac death in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 1998;82:1514-1519.
5. Fei L, Statters DJ, Camm J. QT interval dispersion on 12-lead electrocardiogram in normal subjects: Its reproducibility and relation to the T wave. *Am Heart J* 1994;127:1654-1655.
6. Clarkson PB, Naas AA, McMahon A, et al. QT dispersion in essential hypertension. *Q J Med* 1995;88:327-332.
7. Karpanou EA, Vysoulis GP, Psychogios A, et al. Regression of left ventricular hypertrophy results in improvement of QT dispersion in patients with hypertension. *Am Heart J* 1998;136:765-768.
8. Rials SJ, Wu Y, Xu A, et al. Regression of left ventricular hypertrophy with captopril restores normal ventricular action potential duration, dispersion of refractoriness, and vulnerability to inducible ventricular fibrillation. *Circulation* 1997;96:1330-1336.
9. Higham PD, Furniss SS, Campbell RW. QT dispersion and components of the QT interval in ischemia and infarction. *Br Heart J* 1995;73:32-36.
10. Puljevic D, Smalcelj A, Durakovic Z, et al. Effects of post-myocardial infarction scar size, cardiac function, and severity of coronary artery disease on QT interval dispersion as a risk factor for complex ventricular arrhythmia. *PACE* 1998;21:1508-1516.
11. Schneider CA, Voth E, Baer FM, et al. QT dispersion is determined by the extent of viable myocardium in patients with chronic Q-wave myocardial infarction. *Circulation* 1997;96:3913-3920.
12. Brachmann J, Hilbel T, Grunig E, et al. Ventricular arrhythmias in dilated cardiomyopathy. *PACE* 1997;20(Pt II):2714-2718.
13. Berger RD, Kasper EK, Baughman, et al. Beat to beat variability: Novel evidence of repolarization lability in ischemic and nonischemic dilated cardiomyopathy. *Circulation* 1997;96:1557-1565.
14. Tran HT, Fan C, Tu WQ, et al. QT dispersion: A comparison of three simple methods. *ANE* 1998;3:228-231.
15. Nuss HB, Kaab S, Kass DA, et al. Cellular basis of ventricular arrhythmias and abnormal automaticity in heart failure. *Am J Physiol* 1999;277:H80-91.
16. Hohnloser SH. Proarrhythmia with class III antiarrhythmic drugs: Types, risks and management. *Am J Cardiol* 1997;80:82G-89G.
17. Lehmann MH, Hardy S, Archibald D, et al. Sex differences in risk of torsade de pointes with d,l-sotalol. *Circulation* 1996;94:2534-2541.
18. Kowey PR, Vanderlugt JT, Luderer JR. Safety and risk/benefit analysis of ibutilide for acute conversion of atrial fibrillation/flutter. *Am J Cardiol* 1996;78(Suppl. 8A):46-52.
19. Tsikouris JP. Focus on Dofetilide. *Formulary* 1998;33:1066-1081.
20. Liu DW, Antzelevitch C. Characteristics of the delayed rectifier current (I_{Kr} and I_{Ks}) in canine ventricular myocytes: A weaker I_{Ks} contributes to the longer action potential of the M cell. *Circ Res* 1995;76:351-365.