



ORIGINAL ARTICLE

QTc dispersion and complex ventricular arrhythmias in untreated newly presenting hypertensive patients

AM Saadeh¹, SJ Evans², MA James² and JV Jones²

²Department of Medical Cardiology, Bristol Royal Infirmary, Bristol, BS2 8HW, UK; ¹Department of Internal Medicine, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan

Increased dispersion of ventricular repolarisation (increased QT dispersion) is believed to predispose to arrhythmias associated with sudden death in certain cardiac diseases. Hypertension is also associated with increased risk of sudden death, particularly in those with left ventricular hypertrophy (LVH). Therefore, the first aim of this study is to look into the possible pathogenic role of QT dispersion on the ventricular arrhythmias occurring in a group of never-treated hypertensive patients. The second aim is to look at other possible determinants of QT dispersion (ie, level of blood pressure, hypokalaemia, electrocardiographic LVH and presence or absence of strain pattern) in hypertensive patients, and their relevance to complex ventricular arrhythmias.

QTc (corrected QT) was measured in 70 newly presenting (never-treated) hypertensive patients (47 male, 23 female, mean age 51.9 ± 12.5 years) from a standard 12-lead surface electrocardiogram (ECG). Blood pressure measurements and 24-h ECG holter recordings were performed in all patients. Serum potassium level was measured in 51 of the patients. Ventricular arrhythmias were classified using a modified Lown's scoring system.

Maximum QTc, minimum QTc and QTc dispersion for all patients were 442 ± 30.3 ms, 380 ± 26.7 ms and 61.5 ± 21.6 ms respectively. High grade ventricular

arrhythmias (Lown's score ≥ 3) were found in 43% of the patients. The QTc dispersion was strongly correlated with the Lown's classification of arrhythmia and the age of the patients. Patients with more severe ectopy (Lown's score ≥ 3) were significantly older (57.4 ± 10.3 years) compared to those with score ≤ 2 (48.3 ± 12.6 years) ($P = 0.0067$) and had a significantly greater QTc dispersion (69.9 ± 22.5 ms vs 55.2 ± 18.8 ms; $P = 0.002$). Presence of electrocardiographic strain did not affect the severity of arrhythmia, as 29% of the patients with LVH and strain had grade ≥ 3 Lown's score compared to 39% in the group with LVH but without strain. In the presence of relative hypokalaemia, hypertensive patients with LVH showed more QTc dispersion (85.7 ± 15.5 ms) and a greater tendency for complex ventricular arrhythmias (100% grade ≥ 3 Lown's score) compared to those with LVH and normal serum potassium levels (64.1 ± 22.6 ms and 35%, QTc dispersion and Lown's score ≥ 3 , respectively $P = 0.05$). The level of blood pressure had no effect on either the QTc dispersion or the prevalence of complex ventricular arrhythmias.

Prevalence of complex ventricular arrhythmias in hypertensive patients is strongly correlated with QTc dispersion and age. When hypertensive patients with LVH have low potassium levels the risk of developing complex ventricular arrhythmias is significantly increased.

Keywords: QTc dispersion; arrhythmia; hypertension

Introduction

Hypertension is a major cardiovascular risk factor. Although the incidence of sudden cardiac death is increased in hypertensive patients, particularly in those with left ventricular hypertrophy (LVH),¹⁻³ the exact pathogenesis and mechanisms are not fully clear.

The fact that the majority of such deaths in hypertensive patients occurred in those with LVH has led to the theory that ventricular arrhythmia is the likely responsible cause. While some studies,^{4,5} incriminate diuretic therapy as the primary cause of these

arrhythmias, others⁶ found no correlation between these arrhythmias and diuretic induced hypokalaemia. There have only been three studies on the prevalence of ventricular arrhythmias in newly diagnosed, never treated essential hypertensive subjects. Schillaci *et al*⁷ found a positive correlation between frequent and complex ventricular arrhythmias and LVH. Such a positive correlation was not found by James and Jones⁸ nor by Mayet *et al*.⁹

Inhomogeneous recovery of excitability of cardiac muscle has long been claimed to be responsible for ventricular arrhythmias. As early as 1964 Han and Moe,¹⁰ in studies on animals, demonstrated the link between increased dispersion of repolarisation of the ventricular myocardium and complex ventricular arrhythmias.

Increased dispersion of ventricular recovery time is believed to be the cause of many arrhythmias

associated with certain cardiac diseases including the long QT syndrome,¹¹ dilated cardiomyopathy,¹² chronic heart failure,¹³ post-myocardial infarction¹⁴ and hypertrophic cardiomyopathy.¹⁵

As far as we are aware, there have been no studies on the possible pathogenic role of QT dispersion on ventricular arrhythmias occurring in never-treated hypertensive patients.

However, QT interval dispersion changes have been described in treated hypertensive patients^{16,17} and in one study of LVH in hypertension.¹⁸ Therefore the aim of this study is to look into the different determinants of QTc dispersion in newly presenting, but untreated hypertensive patients and their relevance to development of complex ventricular arrhythmias in these same patients.

Subjects and methods

The study group consisted of 70 consecutive presenting subjects with essential hypertension (47 males and 23 females; mean age 51.9 ± 12.5 years) in whom the high blood pressure was untreated and newly discovered. Patients with a history or evidence on examination of cardiac or systemic diseases were excluded, as were patients with a history of palpitations or 12-lead ECG evidence of arrhythmia, ischaemic changes without accompanying LVH or bundle branch block.

During ECG analysis an additional four patients were excluded. Two because of bundle branch block, one because of ECG evidence of myocardial infarction (absent history of MI) and one because of sinus arrhythmia.

Hypertensive patients were only included in the study if they had never received antihypertensive treatment at the time of presentation and their mean diastolic blood pressure was ≥ 95 mm Hg established from several readings taken during two separate visits.

All patients gave informed consent to participate in the study which was approved by the hospital ethics committee.

Electrocardiography

Standard 12-lead electrocardiograms were recorded on a three-channel ECG recorder at a paper speed of 25 mm/s and standardisation of 1 mV/cm. All leads were recorded simultaneously.

Electrocardiographic measurement of QTc dispersion

QT intervals were measured manually by one blinded observer. For each lead, wherever possible, three consecutive cycles were measured and the mean of the three values was calculated.

The QT interval was taken from the onset of the QRS to the end of the T wave, that is, return to the T-P baseline. When U waves were present the QT interval was measured to the nadir of the curve between the T and U waves. QT measurements were performed only in those leads where the T wave end could be reliably identified. QT intervals were cor-

rected (QTc) according to Bazett's formula ($QTc = \text{measured QT} / \sqrt{R-R}$ intervals).¹⁹ The QTc dispersion was defined as the difference between the maximum and minimum QTc interval occurring in any of the 12 ECG leads.

Fourteen (20%) of the ECGs were randomly selected and measured twice by another observer to study the inter- and within-observer variability of QT measurements. Within and inter-observer variability were 15% and 6% respectively. (Neither were statistically significant).

Electrocardiographic measurement of left ventricular hypertrophy

We have used the precordial leads criteria of Sokolow to measure LVH.²⁰ Left ventricular hypertrophy and strain was defined as being present when there was ST segment depression and T wave inversion in leads I, aVL, V₅ and V₆ in the presence of voltage criteria for LVH.

Twenty-four hours ambulatory electrocardiography

Ambulatory electrocardiography was performed using Reynolds-Tracker recorders and a pathfinder III P₃₁ analyser. Semi-automated, visually assisted analysis was performed by trained cardiology technicians and quality control was maintained by random checking of 24-h tapes by one investigator. Results were analysed by total ectopic counts and by the use of a modified Lown's score.²¹

Serum potassium

Serum potassium was measured by flame emission photometry (chemispeck).

Statistical methods

When two groups of data were compared, the unpaired Student's *t*-test was used for the normally distributed data. One-way analysis of variance (ANOVA) was used to test for overall differences among the groups. Linear regression analysis was used to assess correlations between groups. Values are expressed as means \pm s.d. and a *P* value of ≤ 0.05 was taken as the level of significance.

Results

The mean age of the patients was 51.9 ± 12.5 years with no significant difference between the males (51.3 ± 12.3) and females (53.0 ± 13.0) ($P = 0.299$). A mean of 10.7 ± 1.2 electrocardiographic leads were measured in each patient. Twenty-nine percent of the patients had 12 measurable leads, 41% had 11, 13% had 10, 6% had nine and 11% had eight measurable leads. Maximum QTc intervals were observed mostly in the precordial leads, V₄ and V₅ (40% and 33% respectively) and minimum QTc intervals were seen mostly in the areas in which negative T waves were observed (V₁ 47% and aVR 30%). ECGs with U waves were observed in 12

Table 1 The effect of electrocardiographic LVH (with and without strain) on QTc dispersion and Lown's score in untreated hypertensive patients

	All patients (n = 70)	Patients with no LVH (n = 40)	Patients with LVH (n = 30)	Patients with LVH but without strain (n = 23)	Patients with LVH and strain (n = 7)
Maximum QTc	441.5 ms	436 ms	448.1 ms	441 ms	472.4 ms
Minimum QTc	380 ms	378 ms	383 ms	379 ms	397 ms
QTc dispersion	61.5 ms	58.8 ms	65.1 ms	62.0 ms	75.4 ms
Lown's score ≥ 3	30/70 (43%)	19/40 (48%)	11/30 (37%)	9/23 (39%)	2/7 (29%)

patients (17%) and all were included in the study. U waves were clearly seen in precordial leads (V₂ and V₃ in seven patients, V₃ and V₄ in three, V₄ and V₅ in one, and V₅ alone in one ECG). Hypokalaemia was present in three patients with U waves. The mean QTc dispersion of patients with U waves did not differ from those with no U waves (QTc dispersion; 61.25 ms vs 61.5 ms respectively) ($P=0.33$).

QTc dispersion seen in patients with LVH (65.1 \pm 28.5 ms) was not significantly different compared to those without LVH (58.8 \pm 20.7 ms) ($P=0.116$). When patients with LVH were divided into two groups: patients with LVH and strain (seven patients) and those with LVH but without strain (23 patients, Table 1), patients with LVH and strain had a trend towards greater QTc dispersion (75.4 \pm 28.5 ms) compared to those with LVH and no strain (62.0 \pm 20.1 ms), but this difference was not significant ($P=0.138$). Complex ventricular arrhythmias (Lown's score ≥ 3) were seen in 43% of the patients (Table 1). Patients with LVH did not show a higher Lown's score compared to those with normal ECGs (37% vs 48%). Serum potassium was measured in 51 patients, of whom only eight had hypokalaemia ($K^+ \leq 3.5$ mmol/L). There was no difference in the mean QTc dispersion between patients with and without hypokalaemia (62.8 \pm 21.9 ms vs 61.9 \pm 26.5 ms) ($P=0.46$). Despite this, more patients with hypokalaemia had a higher arrhythmia score (Lown's score ≥ 3) than those with normal potassium level (63% vs 44%). The highest arrhythmia score and greatest QTc dispersion were seen in patients who had LVH and hypokalaemia (5.7 Lown's score and 85.7 \pm 15.5 ms QTc dispersion). Tables 2 and 3 show the relationship between systolic and diastolic BP and each of QTc dispersion and Lown's score. No correlation was found between the severity of either systolic or diastolic BP and QTc dispersion or Lown's score.

Table 2 The relationship between systolic blood pressure, QTc dispersion and Lown's score

	Blood pressure (mm Hg)	QTc dispersion (ms)
Mean systolic BP (all patients, n = 70)	179.4	61.5
Severe systolic BP (≥ 180 mm Hg) (n = 35)	195.6	63.0
Mild-moderate systolic BP (140–179 mm Hg) (n = 35)	163.4	59.9
Lown's score ≥ 3 (n = 30)	176.3	69.9
Lown's score ≤ 2 (n = 40)	181.7	55.2

Table 3 The relationship between diastolic blood pressure, QTc dispersion and Lown's score

	Blood pressure (mm Hg)	QTc dispersion (ms)
Mean diastolic BP (all patients, n = 70)	113.6	61.5
Severe diastolic BP ≥ 115 mm Hg (n = 30)	122.9	58.9
Mild-moderate diastolic BP (95–114 mm Hg) (n = 40)	106.6	63.4
Lown's score ≥ 3 (n = 30)	110.5	69.9
Lown's score ≤ 2 (n = 40)	115.9	55.2

Table 4 The relationship between age, QTc dispersion and complex ventricular arrhythmias in a group of newly presenting patients with essential hypertension

Age (years)	Mean QTc dispersion (milliseconds)	Lown's score ≥ 3
≤ 40 (n = 12)	50.8	3/12 (25%)
41–50 (n = 17)	53.5	4/17 (24%)
51–60 (n = 23)	59.0	9/23 (39%)
61–70 (n = 15)	79.3	12/15 (80%)
71–80 (n = 3)	79.7	2/3 (67%)

More complex ventricular ectopy and greater QTc dispersion were seen in older patients (Table 4). Twenty-four percent of patients who were aged 50 years or less had complex ventricular arrhythmia compared to 56% of patients over 50 years of age. As seen in Figures 1 and 2, the Lown's score of ventricular arrhythmias correlated significantly with

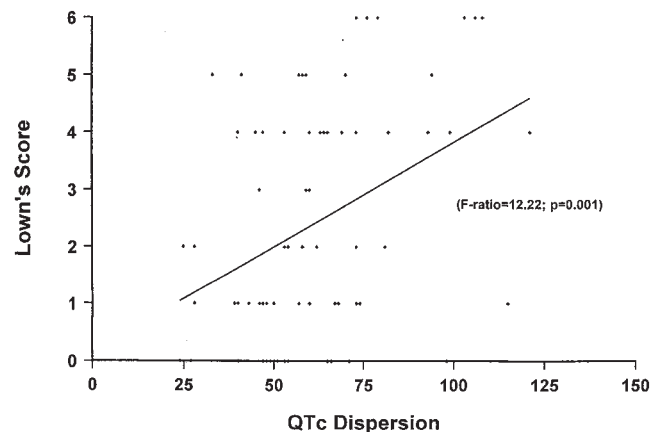


Figure 1 Correlation between QTc dispersion and Lown's score.

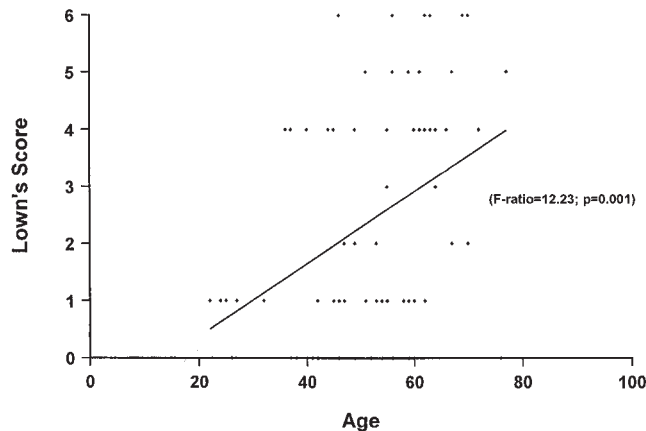


Figure 2 Correlation between age and Lown's score.

QTc dispersion and the age of the patients. Patients who had Lown's scores of ≥ 3 had QTc dispersion of 69.9 ± 22.5 ms compared to those who had ≤ 2 Lown's score (55.2 ± 18.8 ms) ($P = 0.0026$). The QTc dispersion in patients aged 50 years or less was 52.4 ± 14.6 ms compared to those over 50 years (67.9 ± 21.8 ms) ($P = 0.0005$). There was a strong correlation between age and QTc dispersion.

Discussion

Increased QT dispersion of a surface 12-lead electrocardiogram is increasingly recognised to be associated with ventricular arrhythmias and sudden cardiac death in patients with heart disease.^{11–15}

To a lesser extent, patients with hypertension, particularly those with LVH, are also at increased risk of premature cardiac death, much of which is sudden. Although the ventricular arrhythmias in hypertension have previously been correlated with the presence of LVH,^{1,7,22–24} no such positive correlation was found in our patients. However, we used the ECG to determine the presence of LVH and this is much less sensitive than echocardiography – nonetheless, it is still the ECG that is by far the most common method of detecting LVH used in clinical practice. In this study, patients with LVH had no excess ventricular arrhythmia compared to those without LVH. Others,⁹ have also found LVH not to be associated with an excess of arrhythmia in previously untreated patients.

A protective role of LVH against arrhythmia has also been demonstrated in an experimental animal model.²⁵ One possible reason for this discrepancy is that virtually all the studies were carried out on hypertensives who were either on antihypertensive treatment, particularly thiazides, during the study period or the treatment was withdrawn just for a short period of time immediately prior to study. In our results there was no difference in the mean QT dispersion of hypokalaemic patients without LVH from those with normal potassium levels, while it is significantly increased in hypokalaemic patients with associated LVH. Hypokalaemia itself does not seem to lead to increased QTc dispersion but does so only in patients with LVH. Hypokalaemia may lower the threshold towards arrhythmia in hypertro-

phied myocardium by increasing the inhomogeneity of its recovery time or increasing the propensity towards triggered arrhythmias. Again in studies on animal myocytes hypokalaemia alters action potential duration only in hypertrophied cells (from hypertensive rats) and not in non-hypertrophied cells (from normotensive rats).²⁶

Our results suggest a major effect of hypokalaemia, even in the absence of diuretic or other drug treatment, is electrical instability of cardiac cells provided LVH is present. QT dispersion is thought to reflect regional variation in ventricular repolarisation.²⁷ The fact that the greatest QTc dispersion in our patients, although not significant, was found in patients with LVH and strain pattern may possibly reflect a longer duration of the disease in these patients leading to patchy myocardial fibrosis or occult regional ischaemia. In spite of this finding, neither patients with LVH nor those with LVH and strain demonstrated a higher tendency for ventricular arrhythmias. However when hypokalaemia occurred they developed more complex ventricular arrhythmias. In our patients neither the level nor the severity of either systolic or diastolic blood pressures had any effect on the frequency nor on the complexity of ventricular arrhythmias. In contrast to the findings of Clarkson *et al*²⁸ who found that systolic blood pressure was the most significant variable correlating with QT dispersion, we found no correlation to exist between QTc dispersion and the level of blood pressure.

In conclusion, patients with essential hypertension, have a positive correlation between QTc dispersion and Lown score. When patients with LVH are hypokalaemic they demonstrate a significant increase in QTc dispersion and increased tendency towards complex ventricular arrhythmias. The role of potassium replacement therapy in correcting QT dispersion and preventing ventricular arrhythmias in hypertensive patients with LVH needs to be studied further, as does the long term significance of these arrhythmias in relation to sudden cardiac death.

References

- Messerli FH *et al*. Hypertension and sudden death: increased ventricular ectopic activity in left ventricular hypertrophy. *Am J Med* 1984; **77**: 18–22.
- Kannel WB, Schatzkin A. Sudden death: lessons from subsets in population studies. *J Am Coll Cardiol* 1985; **5**: 141B–149B.
- Le Henzy JY, Guize L. Cardiac prognosis in hypertensive patients: incidence of sudden death and ventricular arrhythmias. *Am J Med* 1988; **84** (Suppl 1B): 65–68.
- Multiple Risk Factor Intervention Trial Research Group. Baseline rest electrocardiographic abnormalities, antihypertensive treatment and mortality in the multiple risk factor intervention trial. *Am J Cardiol* 1985; **55**: 1–15.
- Holland OB, Nixon JV, Kuhnert la Von. Diuretic induced ventricular ectopic activity. *Am J Med* 1981; **70**: 762–768.
- Madias JE, Madias NE, Gavras HP. Non-arrhythmogeneity of diuretic induced hypokalaemia. *Arch Intern Med* 1984; **144**: 2171–2176.
- Schillaci G *et al*. Association between persistent press-

- ure overload and ventricular arrhythmias in essential hypertension. *Hypertension* 1996; **28**: 284–289.
- 8 James MA, Jones JV. Ventricular arrhythmias in untreated newly presenting hypertensive patients compared with a matched normal population. *J Hypertens* 1989; **7**: 409–415.
 - 9 Mayet J et al. Ventricular arrhythmias in hypertension: in which patients do they occur? *J Hypertens* 1995; **13**: 269–276.
 - 10 Han J, Moe GK. Non-uniform recovery of excitability in ventricular muscle. *Circ Res* 1964; **14**: 44–60.
 - 11 De Ambroggi L et al. Dispersion of ventricular repolarisation in the long QT syndrome. *Am J Cardiol* 1991; **68**: 614–620.
 - 12 Pye M, Quinn AC, Cobbe SM. QT Interval dispersion: a non-invasive marker of susceptibility to arrhythmias in patients with sustained ventricular arrhythmias. *Br Heart J* 1994; **71**: 511–514.
 - 13 Barr CS et al. QT dispersion and sudden unexpected death in chronic heart failure. *Lancet* 1994; **343**: 327–329.
 - 14 Potratz J et al. Prognostic significance of QT dispersion in patients with acute myocardial infarction. *Eur Heart J* 1993; **14**: 254.
 - 15 Buja G et al. Comparison of QT dispersion in hypertrophic cardiomyopathy between patients with and without ventricular arrhythmias and sudden death. *Am J Cardiol* 1993; **72**: 973–976.
 - 16 Perkiomaki JS et al. Dispersion of the QT interval and autonomic modulation of heart rate in hypertensive men with and without left ventricular hypertrophy. *Hypertension* 1996; **28**: 16–21.
 - 17 Balanescu S et al. Correlation entre la dispersion de l'intervalle QT et les arythmies ventriculaures dans l'hypertension arterielle. *Arch Mal Coeur* 1996; **89**: 987–990.
 - 18 Mayet J et al. Left ventricular hypertrophy and QT dispersion in hypertension. *Hypertension* 1996; **28**: 791–796.
 - 19 Bazett HC. An analysis of the time-relationship of electrocardiograms. *Heart* 1920; **7**: 353–370.
 - 20 Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J* 1949; **37**: 161–186.
 - 21 Calvert A, Lown B, Gorlin R. Ventricular premature beats and anatomically defined coronary heart disease. *Am J Cardiol* 1977; **39**: 627–634.
 - 22 Schmieder RE, Messerli FH. Determinants of ventricular ectopy in hypertensive cardiac hypertrophy. *Am Heart J* 1992; **123**: 89–95.
 - 23 McLenachon JM, Henderson E, Morris KI, Dargie HJ. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. *N Engl J Med* 1987; **317**: 787–792.
 - 24 Luque-Oterom, Casar-Perez F, Alcazar J. Increased ventricular arrhythmias in hypertensives with left ventricular hypertrophy. *J Hypertens* 1986; **4** (Suppl 6): 66–67.
 - 25 James MA, Jones JV. The paradoxical role of left ventricular hypertrophy in wall-stress related arrhythmias. *J Hypertens* 1992; **10**: 167–172.
 - 26 Evans SJ, Levi AJ, Jones JV. Reduction of external potassium causes increased action potential shortening in ventricular myocytes from the spontaneously hypertensive rat. *J Hypertens* 1997; **16**: 659–666.
 - 27 Higham PD et al. QT dispersion: a measure of underlying dispersion of ventricular recovery? *Eur Heart J* 1993; **14**: 86 (abstract).
 - 28 Clarkson P et al. QT dispersion in essential hypertension. *Q J Med* 1995; **88**: 327–332.