QT dispersion in patients with arrhythmogenic right ventricular dysplasia

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Aims Arrhythmogenic right ventricular dysplasia is a rarely diagnosed cardiomyopathy, but a frequent cause of ventricular arrhythmia and sudden cardiac death. QT interval dispersion, measured as an interlead variability of QT, is a marker of dispersion of ventricular repolarization and, hence, of electrical instability. The present study was conducted to assess the occurrence of QT dispersion and its modulation during treatment with sotalol.

Methods Twenty-five patients with the diagnosis of arrhythmogenic right ventricular dysplasia were studied retrospectively. Fourteen patients were considered low risk for malignant ventricular arrhythmia and sudden cardiac death, and 11 high risk due to documented sustained ventricular arrhythmia, cardiac arrest, or sudden cardiac death. Twenty five healthy volunteers served as control subjects.

Results Dispersion of repolarization was significantly higher in patients than in control subjects (QTd and JTd: P<0.05). Dispersion of repolarization was equal in patients both with and without malignant arrhythmias. There was no significant change in dispersion after treatment with sotalol. Adjacent QT dispersion between leads V3–V4, V4–V5 and V5–V6, respectively, was higher in patients than in control subjects (P<0.05), while no differences were seen in leads V1–V2 and V2–V3.

Conclusion QT interval dispersion is increased in patients with arrhythmogenic right ventricular dysplasia. However, the degree of dispersion is not related to the severity of symptoms, nor is it influenced by treatment with sotalol.

Key Words: Arrhythmogenic right ventricular cardiomyopathy, cardiomyopathy, electrocardiography, sudden death, sotalol.

See page 703 for the Editorial comment on this article

Introduction

Arrhythmogenic right ventricular dysplasia is a rarely diagnosed cardiomyopathy but a frequent cause of ventricular arrhythmia and sudden cardiac death among young and otherwise healthy individuals[1].

Recently, major and minor criteria for a positive diagnosis have been proposed. These are based on the identification of structural abnormalities, fatty or fibro-fatty replacement of the right ventricular myocardium, electrocardiographic changes (repolarization abnormalities, identified as inverted T waves in right precordial leads, and depolarization, repolarization, and/or conduction abnormalities, identified as epsilon waves or localized prolongation of the QRS complex in right precordial leads of the electrocardiogram), arrhythmias of right ventricular origin, and familial disease[2]. Right ventricular abnormalities are progressive, but the evolution and behaviour of the arrhythmias are highly variable and cannot be predicted in the individual patient[3].

QT interval dispersion, measured as an interlead variability of QT, has been proposed as a marker of heterogeneous repolarization and, hence, of electrical instability. The underlying rationale is that QT dispersion is likely to reflect heterogeneities in recovery of excitability, which is known to increase the propensity for ventricular arrhythmia[4–11].

Previous studies have evaluated the usefulness of QT interval dispersion as a predictor of ventricular arrhythmia and sudden death in patients with the long QT syndrome[5,12], hypertrophic cardiomyopathy[13], idiopathic dilated cardiomyopathy[14], myocardial infarction[15,16], and chronic heart failure[17].

To assess the occurrence of QT dispersion, its modulation during treatment with sotalol (a beta-blocking agent with a class III effect) and to estimate the value of


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QT dispersion as a possible diagnostic or prognostic marker, we analysed the initial electrocardiographic presentation and follow-up changes in patients with arrhythmogenic right ventricular dysplasia.

**Method**

**Study population**

We retrospectively identified 25 patients with arrhythmogenic right ventricular dysplasia according to the diagnostic criteria proposed by the arrhythmogenic right ventricular dysplasia Task Force in 1994[2]. Four patients were members of the same family, the others were unrelated. Only patients with a follow-up after diagnosis of at least 1 year were included. A group of 25 healthy volunteers, matched in age and sex with the study group, served as control subjects to provide information on dispersion of repolarization in normal individuals.

Patients were allocated to two subgroups: subgroup one included patients who were considered low risk for sudden cardiac death, and consisted of those patients who had previously experienced non-sustained ventricular arrhythmia, but never sustained ventricular arrhythmia or cardiac arrest. Subgroup two included patients who were considered high risk for sudden cardiac death and consisted of those who had experienced sustained ventricular arrhythmia, and had been resuscitated from cardiac arrest or had suffered sudden cardiac death.

Twenty five healthy subjects, with no history of heart disease, a normal clinical examination, ECG and echocardiogram of the heart, served as controls. To study the effects of sotalol treatment on dispersion of recovery, electrocardiograms were obtained before and during treatment with d,l-sotalol, 160 to 320 mg per day. D,l-sotalol has an antiarrhythmic class III effect and was prescribed to prevent arrhythmias.

**Evaluation of dispersion of repolarization**

The standard 12-lead ECG recorded during sinus rhythm, with the patient at rest in a supine position, was analysed. Two blinded observers measured the different intervals manually, directly from the original ECG. Measurements were obtained with a minimal detection level of 20 ms. ECGs were recorded at 25 and 50 mm·s⁻¹. QT intervals were measured from the onset of the QRS to the end of the T wave, defined as the intersection between the tangent and the baseline. When U waves were present, the QT interval was measured to the nadir of the curve between the T and U wave. When diphasic T waves were present, measurements were excluded. For each lead, wherever possible, three consecutive cycles were measured and an average QT and JT calculated. QT measurements could not be made when T waves were isoelectric or of a very low amplitude. The J point was defined as the intersection of the isoelectric part of the ST segment and the tangent of the S wave upstroke. QT and JT dispersion were defined as the differences between the maximum and minimum QT and JT. The adjacent QT dispersion was defined as the difference between two adjacent precordial leads. The intra- and inter-observer variation coefficient for QT measurements were determined, to 5·6% and 10·0%, respectively. Electrocardiograms obtained at the diagnosis of arrhythmogenic right ventricular dysplasia were used to measure baseline values. The ECG recording obtained at the last follow-up visit was used in patients receiving sotalol.

**Statistical analysis**

Data are presented as means ± standard deviations, and, when appropriate, the median value and range are given, hence data are not normally distributed. Differences among groups were assessed by the Mann–Whitney U test. The differences between values before and during antiarrhythmic treatment were assessed by Wilcoxon signed rank tests. A two-tailed value of P<0.05 was accepted as significant.

**Results**

**Study population**

Patient characteristics are summarized in Table 1. Subgroup 1 comprised 14 patients considered low risk for sudden cardiac death, and subgroup 2 comprised 11 patients considered high risk; two of them had been resuscitated from cardiac arrest, and five had died suddenly. The study population consisted of 18 males and seven females, with a mean age at onset of 30·1 years (±12·0 years). The mean follow-up time was 7·2 years (±3·6 years). Two patients had intermittent atrial fibrillation and eight incomplete right bundle branch block.

The average number of analysable leads was 10·7 with a minimum of five leads. Five and six leads were analysable in 2% of the ECGs, eight and nine leads in 4% and ten leads in 12% of ECGs, respectively.

**Comparison between patient group and control subjects**

Baseline values are shown in Table 2. The arrhythmogenic right ventricular dysplasia patients presented significantly longer baseline QT and JT intervals than the control group. The degree of QT and JT dispersion in the patient group was significantly higher than that in the control subjects. The QRS duration tended to be longer in arrhythmogenic right ventricular dysplasia patients, but the difference was not significant.
<table>
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<th>Dysfunction and structural alterations</th>
<th>Endomyocardial biopsy</th>
<th>Inverted T waves</th>
<th>Epsilon waves or QRS &gt;110 ms in V1–3</th>
<th>Late potentials</th>
<th>Ventricular tachycardia or ventricular extrasystoles &gt;1000/24 h</th>
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Arrhythmogenic right ventricular dysplasia patients characterized according to criteria for arrhythmogenic right ventricular dysplasia diagnosis. ++ = major findings; + = minor findings; 0 = abnormalities not present; na = not available.
**Table 2** Electrocardiographic values at baseline

<table>
<thead>
<tr>
<th>Control subjects (n=25)</th>
<th>ARVD patients (n=25)</th>
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<tbody>
<tr>
<td>Heart rate (beats (\text{min}^{-1}))</td>
<td>70 (± 14.0)</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>96 (± 16.0)</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>350 (± 33.4)</td>
</tr>
<tr>
<td>JT (ms)</td>
<td>267 (± 26.3)</td>
</tr>
<tr>
<td>QT dispersion</td>
<td>52 (± 22.6)</td>
</tr>
<tr>
<td>JT dispersion</td>
<td>52 (± 22.3)</td>
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</tbody>
</table>

*P<0.05, control subjects vs arrhythmic right ventricular dysplasia patients.

**Table 3** Electrocardiographic values at baseline and at follow-up in untreated patients

<table>
<thead>
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<th>Baseline (n=11)</th>
<th>Follow-up</th>
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<td>Heart rate (beats (\text{min}^{-1}))</td>
<td>70 (± 7.5)</td>
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<tr>
<td>QRS (ms)</td>
<td>92 (± 12.5)</td>
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<tr>
<td>QT (ms)</td>
<td>382 (± 40.5)</td>
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<tr>
<td>JT (ms)</td>
<td>295 (± 49.1)</td>
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<tr>
<td>QT dispersion</td>
<td>92 (± 30.1)</td>
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<tr>
<td>JT dispersion</td>
<td>80 (± 38.3)</td>
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</table>

*P<0.12 baseline vs follow-up. †P<0.05 baseline vs follow-up.

Adjacent QT dispersion between leads \(V_3-V_4\), \(V_4-V_5\), and \(V_5-V_6\) were significantly higher in patients than in control subjects (\(V_3-V_4\): 28 (± 24.5) vs 9 (± 9.5) ms, \(V_4-V_5\): 33 (± 51.2) vs 6 (± 6.5) ms and \(V_5-V_6\): 15 (± 13.8) vs 6 (± 7.5) ms, \(P<0.05\) respectively). Adjacent dispersion between leads \(V_1-V_3\) and \(V_2-V_3\) were similar in patients and control subjects.

**Comparison of values obtained at baseline and at follow-up without medical treatment**

The data are shown in Table 3. The mean follow-up time of patients who did not receive medical treatment was 7.0 years (3.0–12.1 years). JT dispersion had increased significantly at follow-up (\(P<0.05\)), but there was no significant changes in heart rate, the QT and JT intervals or QT dispersion.

**Comparison between patient subgroups**

The results are shown in Table 4. There were no differences in terms of mean QRS, QT and JT intervals and heart rate between subgroups 1 and 2. The same was true for QT and JT dispersion. A comparison of values between patients who suffered sudden cardiac death (five patients) and the rest of the patients, revealed no differences or even a tendency towards higher dispersion, but numbers in the subgroups are small.

**Comparison of values obtained before and during sotalol therapy**

The results are shown in Table 5. The heart rates of 10 patients treated with sotalol were significantly lower during this treatment than at baseline (\(P<0.05\)). There was a significant change in the mean QT and JT values (\(P<0.05\)) during treatment with sotalol, but no significant change was seen in the degree of QT and JT dispersion during treatment compared with that at baseline.

**Study limitations**

A limitation of QT and JT interval assessment is that they are not always measurable in every lead or may be difficult to measure with sufficient precision in certain leads\(^{[18]}\). Hence the intra- and inter-observer variation coefficients in our study were acceptable. Another limitation is that although the variability of QT duration is low (6%) the variability of QT dispersion is high (28–33%)\(^{[19,20]}\), with the possibility of a similar high risk of a type II error, i.e. erroneously overlooking a difference in dispersion between groups.

Values in the two patients with intermittent atrial fibrillation were measured from recordings obtained during sinus rhythm, hence the QT interval can be...
prolonged during atrial fibrillation. Incomplete right bundle branch block did not affect the QT interval measurement, but in some cases made assessment of the J point difficult.

The study was conducted as an observational study with all its pitfalls. A prospective study, including estimation of the predictive value of dispersion of repolarization in family screening, would be of interest.

**Discussion**

The salient findings of the present study are that QT dispersion is increased in patients with arrhythmogenic right ventricular dysplasia in comparison with matched healthy controls, but is not changed in response to treatment with sotalol. The degree of QT dispersion, however, failed to be useful as a marker for risk of life threatening arrhythmias in patients with arrhythmogenic right ventricular dysplasia.

The finding of increased QT dispersion in patients with arrhythmogenic right ventricular dysplasia is similar to that found in studies of patients with other cardiac diseases and partly in accordance with a previous lar to that found in studies of patients with other cardiac diseases and partly in accordance with a previous [correlated](#) study of patients with other cardiac diseases [21]. In the latter study, abnormal QRST integral body surface maps were consistent with delayed repolarization in regions of the myocardium, whereas this could not be confirmed by the QT dispersion on standard electrocardiograms. Another study of body-surface potentials in arrhythmogenic right ventricular dysplasia patients also revealed delayed repolarization of the right ventricle, but failed to show a relationship with the occurrence of ventricular arrhythmia in the study population.

The finding that the degree of QT dispersion failed to be useful as a marker for risk of arrhythmia in patients with arrhythmogenic right ventricular dysplasia in our study is in conflict with that of Corrado et al. [23] who showed significantly higher QT dispersion in arrhythmogenic right ventricular dysplasia patients suffering sudden cardiac death compared to patients with uncomplicated arrhythmogenic right ventricular dysplasia. This discrepancy between the two studies could be due to differences in risk stratification, phenotypes of arrhythmogenic right ventricular dysplasia patients or the small numbers in our subgroups.

Treatment with sotalol did not reduce QT dispersion in patients with arrhythmogenic right ventricular dysplasia in our study. This is consistent with the findings in one study of patients with myocardial infarction [24], but not with the results of Day et al., who demonstrated a significant reduction in dispersion during successful sotalol treatment in similar patients [25]. D,L-sotalol has been shown to be an effective and safe treatment in patients with arrhythmogenic right ventricular dysplasia, although evaluation of programmed stimulation before and during treatment has been shown to be of limited value in predicting risk of sudden cardiac death [26,27].

The finding of an increased degree of JT dispersion during long-term follow-up could be due to progression of the disease; however, it is not known if dispersion changes during ageing. This finding is in accordance with the finding that the degree of dispersion is a dynamic phenomenon in hypertensive patients and is dependent on the degree of left ventricular hypertrophy [28,29].

Different hypotheses on the pathophysiological mechanisms leading to QT dispersion could include:

1. **Modulation of repolarization due to structural changes in the heart.**

   Gross anatomical changes, as seen in left ventricular dilatation or hypertrophy, can lead to spatial extension of the repolarising tissue and hence alter the geometry of repolarization. Structural changes in some of the cardiac myocytes could prolong their repolarization and lead to repolarization dispersion in the whole myocardium. This hypothesis is supported by the finding of increased QT dispersion in patients with left ventricular dilatation and the subsequent reduction in dilatation and dispersion after 6 weeks of ACE inhibition [28]. Further support is lent to this argument by the finding of prolonged repolarization in isolated hypertrophied cardiac myocytes from the rabbit after in vivo induced hypertension, and subsequent normalization in parallel with a reduction in size after 3 months of ACE inhibition [28]. The increased QT dispersion in arrhythmogenic right ventricular dysplasia patients and the lack of modulation during sotalol treatment is consistent with dispersion secondary to structural changes. However, it is striking that differences between patients and control subjects in adjacent QT dispersion are found in the left precordial leads and not in the right, when the anatomical changes are confined to, or are most pronounced, in the right ventricle.

2. **Modulation of repolarization due to differences in ionic currents.**

   Differing distribution and activity in cellular ionic channels between adjacent areas could lead to changes in action potential morphology, and, hence to QT dispersion. This theory is supported by the normalization of dispersion during potassium treatment in patients with the long QT syndrome due to mutations in the HERG gene, encoding a cardiac potassium channel that is modulated by extracellular potassium [31].

3. **Modulation of ventricular repolarization by the autonomic nervous system.**

   It has been proposed by several authors that the autonomic nervous system has an effect on dispersion of repolarization [32–37]. Normal QT dispersion has been found in patients with primary autonomic failure [38,39], but in a study in diabetic patients with autonomic dysfunction the QT dispersion was increased [34]. This apparent discrepancy may be due to the fact that primary autonomic failure mainly involves the sympathetic nervous system, whereas
diabetics also invariably have defects of the vagal innervation of the heart\textsuperscript{40}. The results of these studies may lead to the hypothesis that vagal disinnervation could result in QT dispersion, whereas the effect of the sympathetic nervous system is questionable. MIGB scintigraphies of arrhythmogenic right ventricular dysplasia patients have revealed reduced re-uptake of noradrenaline in the left ventricular myocardium, a finding that has been interpreted as an affected sympathetic innervation of the myocardium\textsuperscript{41}. Whether this is a primary change or secondary to a disease process in the myocardium is not known.

**Conclusion**

QT interval dispersion is significantly increased in patients with arrhythmogenic right ventricular dysplasia; however, the degree of QT dispersion is not related to the severity of symptoms, nor is it influenced by treatment with sotalol.

The results of the present study partly support the theories of dispersion as a consequence of structural changes in the myocardium, or alterations in cardiomyocyte membrane ionic currents, rather than being due to alterations in autonomic innervation.

This study was supported by grants from The Danish Heart Foundation.

**References**


