QT dispersion, daily variations, QT interval adaptation and late potentials as risk markers for ventricular tachycardia

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Aims The aim of the study was to determine the value and correlation between QT dispersion, daily variations in the QT interval and late potentials as risk markers for ventricular tachycardia.

Methods and results QT dispersion was defined as the difference between the longest and the shortest QT interval in 12 electrocardiographic leads, QTc variability as the difference between the maximal and minimal QTc interval during 24-h Holter monitoring and QT interval adaptation as the regression line between heart rate and the uncorrected QT interval. One hundred and forty-five patients, 3 months after myocardial infarction were included in the study. QT dispersion significantly increased with the severity of arrhythmia (modified Lown's classification; P<0.001). The level of 80 ms was associated with ventricular tachycardia with a sensitivity of 72.7% and a specificity of 86.4%. The greater daily variability of the QTc interval in patients with ventricular tachycardia was insignificant (P>0.05). QT interval adaptation did not discriminate between patients with ventricular tachycardia from those in other groups. Late potentials were associated with ventricular tachycardia with a sensitivity of 50% and a specificity of 90.3%.

Conclusion Large QT dispersion and late potentials were risk markers for ventricular tachycardia, but there was no correlation between QT dispersion, daily variations in the QT interval and late potentials in patients 3 months after myocardial infarction.

Key Words: QT dispersion, adaptation, late potentials, arrhythmia.

Introduction
Reentry arrhythmias depend on regionally different electrophysiological characteristics of the myocardium (conduction speed duration of refractory period or electrically inert tissue)1. All these conditions can be found as a consequence of myocardial infarction2. Correlation between infarction size and ventricular arrhythmia was established years ago, but the arrhythmogenic substrate has not been defined3. Also, it is known that the autonomic nervous system modulates the electrophysiological characteristics of the myocardium4-3. QT dispersion is an indicator of regional differences in action potential duration (recovery of excitability) and in some conditions it represents a risk for malignant arrhythmia5-8. Data regarding the prolonged QT interval, as a risk marker for malignant arrhythmia in the post-infarction period, are contradictory9,10. Heart rate and the autonomic nervous system (along with sex, age, circadian variations) independently influence the QT interval11, hence a single measurement during the day has no major significance. A better risk predictor could be the maximal daily value of the QTc interval or QT interval behaviour during heart rate changes (QT interval adaptation), which is an indicator of autonomic nervous system influence12,13. It is suggested that late potentials (fragmented activity of low amplitude) are indicators of delayed impulse conduction through non-homogeneous scar, and it has been shown that late potentials in the post-infarction period are often present in patients with ventricular tachycardia14,15. This suggests that these three methods, in different ways, might estimate the same disorder, i.e. the basis for reentry arrhythmia.

The aim of this study was to establish the value and correlation between these methods (QT dispersion, QTc variability, QT adaptation, late potentials) in estimating the risk for ventricular tachycardia after myocardial infarction, as well as the relationship between these parameters and infarction size.
Methods

Three hundred and forty consecutive patients without cardiac failure who 3 months after myocardial infarction, and between 1994 and 1995 attended a 3-month programme of outpatient cardiac rehabilitation, were eligible. Those who satisfied the criteria, were included. Those included were receiving no antiarrhythmic or other medication which could influence heart rate or QT interval; they had no electrocardiographic (ECG) alterations which would interfere with QT or infarction size measurements using the QRS scoring system (bundle branch blocks, ventricular hypertrophy, preexcitation, fascicular blocks), and the QT interval was measurable in a minimum of 10 out of 12 ECG leads. One hundred and forty five patients met all these criteria (among 195 excluded patients 124 were receiving enalapril, 31 propranolol, 17 amiodarone and 13 diltiazem or verapamil).

Twenty-one examinees without any cardiovascular disease (estimated by clinical examination, exercise stress testing and echocardiography) constituted a separate age-matched control group.

In the morning of the first day the patients underwent 12-lead ECG recording, echocardiographic examination and exercise stress testing. On the second and third days, they underwent telemetry monitoring during a rehabilitation exercise programme. Twenty-four hour Holter recording followed by a signal-averaged ECG were carried out on the 4th day. During the 3 months, the patients were clinically followed-up daily (heart rate and blood pressure before and after exercise, history of symptoms). In the case of symptoms, we repeated Holter or telemetry monitoring. On the last day, exercise stress testing was performed again.

Measurements

The QT interval was measured in 12 ECG lead (2 x 6 simultaneously recorded leads, paper speed 25 mm. s⁻¹, Marquette MAC 15) after the strip was enlarged 100%. All measurements were done manually, using a magnifying glass and a caliper, by a single observer blinded to other study data. The QT interval was measured from the onset of the Q wave to the end of the T wave in two to three consecutive cycles, and the average value was taken for each lead. The duration of the T wave was defined as a return to the isoelectric P-T-P baseline, but if the end of the T wave could not be determined, the tangential method was applied (12% ECG strips). The end of the T wave is formed by the intersection of the isoelectric line and the tangent trough of the peak of the T wave and the point of maximum T wave slope[16]. In the presence of the U wave, the end of the T wave was defined as the nadir between the T and the U wave if it was in isoelectric level, otherwise we applied the tangential method. The corrected QT interval was calculated by Bazett's formula (QTc=QT/√RR). QT interval dispersion was defined as the difference between the longest and the shortest QT interval in a minimum of 10 ECG leads. From the same ECG, infarction size was calculated by Selvester's QRS scoring system (Wagner's and Hindman's modification)[17].

Daily QTc interval variability was estimated from 24-h Holter recordings (Oxford Medilog-Excel ECG Analysis System). The QT interval was measured manually, by the same observer, in the modified V5 lead when the rhythm was stable (without premature ventricular complex) in eight time points (at 8, 11, 14, 17, 20, 23, 2, 5 h) and at maximal and minimal heart rate. In each time point we used the average of three consecutive cycles. The daily QTc interval variability was defined as the difference between the maximal and minimal QTc interval measured in the same lead during a 24-h recording. QT interval adaptation was estimated on the basis of regression line parameters between the uncorrected QT interval and the corresponding heart rate (slope, intercept with the Y axis).

During a signal-averaged ECG recording (Marquette MAC 15) 25 and 40 Hz filters were used and 256 cycles were averaged. Late potentials were present if two out of three criteria were positive in either filter: ventricular activation time >114 ms, voltage <20 uV in the last 40 ms of the filtered QRS complex, and duration lower than 40 µV for more than 38 ms in the terminal part of the QRS complex[18].

The echocardiographic examination was performed by two observers blinded to other study data. This comprised the ejection fraction in 2-D mode using the automatic counting method according to Simpson's rule, left ventricular diastolic diameter, interventricular septum and posterior wall thickness. Treadmill exercise stress testing was performed using the Bruce protocol. Ventricular arrhythmia was registered by 24-h Holter recording, repeated exercise stress testing or telemetry monitoring during training. Arrhythmia was graded by partly modified (for greater precision) Lown's classification in which O =<450 monomorphic premature ventricular complexes, I = 50-700 (<30 . h⁻¹), II = >700 (>30 . h⁻¹), III = multiform premature ventricular complexes, IV = premature ventricular complex pairs (R-R interval lower than 550 ms), V = ventricular tachycardia with at least three consecutive premature ventricular complexes with an R-R interval less than 550 ms.

Reproducibility

All QT measurements were performed by one observer. Fifteen (10%) randomly chosen ECG strips were measured again by the same observer. The mean difference in QT dispersion between the two measurements was 8.9 (5.8) ms.

Statistical analysis

The results are presented as arithmetic means and standard deviation. For statistical analysis we used, in parallel, analysis of variance and the Kruskall-Wallis
test, linear and range correlation, Fisher’s exact test for frequencies, and multiple regression analysis (stepwise method). Statistical package SPSS 5.0 was used for the analysis.

**Results**

All patients were without heart failure (New York Heart Association classes I (79.2%) and II (20.8%), 68 (46.9%) suffered from hypertension, 30 (21%) had mild left ventricular hypertrophy on echocardiographic examination (interventricular septum or posterior wall thickness >12 mm) but none had ECG signs of left ventricular hypertrophy. All with ECG signs of hypertrophy were excluded from the study.

There were no significant differences between the control and the study group regarding age and sex (age 52.8 (5-1) vs 53.8 (8-9) males/females 93/7% vs 86/9/ 13-1%). QT interval dispersion significantly increased with the severity of arrhythmia (P<0.001; Table 1). This was also noted when the whole group, regardless of therapy, was examined (n=340). Dispersion greater than 80 ms was associated with ventricular tachycardia with a sensitivity of 72-7%, a specificity of 86.4%, a positive predictive accuracy of 30-7%, a negative predictive accuracy of 97.4% and a relative risk of 15.7. This was the best ratio because with the increase in borderline value to 90 ms, specificity and positive predictive accuracy increases, but sensitivity significantly decreases. At the same time, the corrected QT interval was not a good marker of ventricular tachycardia because a significant proportion of patients without serious arrhythmia also had a significantly prolonged QTc interval, indicating a low positive predictive value.

For QTc >480 ms, sensitivity was 27-2%, specificity 96-2%, relative risk 5.0. Patients with post-infarction scar of the left ventricular myocardium ≤12% had significantly lower QT interval dispersion than those with a scar of 24-30% (and in particular ≥33%) of the left ventricular myocardium (62.4 (15-1) vs 70.3 (16-4) vs 78.8 (13-9) ms P<0.01). The QTc interval was also significantly longer in the group with massive scar (43.3 (25) vs 449 (18) ms P<0.05).

Patients with ventricular tachycardia had the greatest daily QTc variability, but the difference between the groups was not significant in any test (P>0.05; Table 1). A similar result was noted when the whole group, regardless of therapy, was examined (n=340). The daily variations in the QTc interval in the group with ventricular tachycardia was approximately the same as in the group without ventricular tachycardia (Fig. 1). Consequently, the greater variability in the group with ventricular tachycardia was due to the extreme values of the QTc interval; the maximal QTc was longer and the minimal shorter in relation to other groups. The maximal daily QTc interval was also insignificantly higher in the group with ventricular tachycardia (P>0.05). In the post-infarction group, regression line parameters were not significantly different between the patients with ventricular tachycardia and those without it, which means that QT interval adaptation was approximately equal regardless of arrhythmia. In the group with ventricular tachycardia vs the group without ventricular tachycardia; the line slope was -1.81 vs -1.93, the intercept with the Y axis was 534.91 vs 537.68; Fig. 2. In patients after myocardial infarction the QT interval adaptation was significantly different from the control group. There was a tendency to a longer QT interval with higher frequency (control vs non-Q infarction vs Q infarction; line slope -1.85 vs -1.92 vs -2.03; intercept with the Y axis 529.03 vs 542.66 vs 546.11; Fig. 3). However, in the group with healed infarction, post-infarction scar size had no significant influence either on daily variations or on QT interval adaptation.

**Table 1** Values of dispersion, variations and QTc interval in the control and arrhythmia groups

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 21)</th>
<th>Postinfarction groups</th>
<th>n*</th>
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<tr>
<td></td>
<td>(n = 74)</td>
<td>(n = 36)</td>
<td></td>
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<tr>
<td>Heart rate (ECG)</td>
<td>75.3 (14.3)</td>
<td>68.3 (11.5)</td>
<td></td>
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<tr>
<td>Longest QTc (ECG)</td>
<td>420 (20)</td>
<td>428 (23)</td>
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<tr>
<td>QTc dispersion</td>
<td>48.2 (9.5)</td>
<td>62.0 (11.8)</td>
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<tr>
<td>95% CI</td>
<td>43.9–52.4</td>
<td>59–62.4</td>
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<tr>
<td>QT dispersion</td>
<td>42.8 (8.0)</td>
<td>57.9 (9.8)</td>
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<tr>
<td>95% CI</td>
<td>39.3–46.4</td>
<td>55.6–60.2</td>
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<tr>
<td>Maximum heart rate</td>
<td>136 (12)</td>
<td>120 (17)</td>
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<tr>
<td>(Holter)</td>
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<tr>
<td>Maximum QTc (Holter)</td>
<td>458 (19)</td>
<td>468 (26)</td>
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<tr>
<td>Daily QTc variability</td>
<td>61.5 (14.9)</td>
<td>73.2 (26.0)</td>
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<tr>
<td>95% CI</td>
<td>54.7–68.3</td>
<td>67.1–79.2</td>
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*Analysis of variance (without control group); differences only in post-infarction groups. ECG=electrocardiogram; ns=non significant; CI=confidence interval; PVC=premature ventricular complex; VT=ventricular tachycardia: 3–6 PVCs in a row (n=5), unsustainable VT (n=6), sustained VT (n=0); dispersion 0.0 (10.3), 0.1 (14.5), -.
Figure 1 Corrected QT interval according to time of day. □ = <50 premature ventricular complexes; ● = ventricular tachycardia.

Figure 2 Correlation between heart rate and QT interval according to severity of arrhythmia. □ = <50 premature ventricular complexes; ● = ventricular tachycardia.

Figure 3 Correlation between heart rate and QT interval according to Q wave. ● = control; ——— = linear control; ▲ = non-Q myocardial infarction; ——— = linear non-Q myocardial infarction; □ = Q myocardial infarction; ——— = linear Q myocardial infarction.

(Scar size <12% vs ≥33% of left ventricular myocardium; QTc variability 70.6 (24.6) vs 71.8 (26.5) ms P>0.05; Fig. 4). Patients with massive scar (≥33% of left ventricular myocardium) had an insignificantly longer QTc during the entire Holter recording period. The ejection fraction was not significantly different regardless of arrhythmia group (non-ventricular tachycardia group vs ventricular tachycardia group; 63 (8) vs 61 (9.5)). At the same time a significant inverse correlation existed between ejection fraction and QT interval dispersion (r = −0.332 P<0.001).

Late potentials were positive in 8.9% of patients but significantly more frequent in those with pairs of premature ventricular complexes or ventricular
tachycardia ($P<0.05$). In this study, sensitivity, specificity, positive predictive accuracy, negative predictive accuracy and the relative risk of this method in relation to ventricular tachycardia were 50%, 90.3%, 33.3%, 94.9% and 5%, respectively. There was no significant difference in any ECG parameter regarding the positive late potentials ($P>0.05$; Table 2). Also, there was no correlation between daily variability and QTc interval dispersion among 12 ECG leads ($r=0.108 \ P>0.05$), but there was a significant correlation between QTc dispersion and the longest QTc interval in the ECG ($r=0.497 \ P<0.001$) as well as between daily variations and the maximal QTc interval in the Holter strip ($r=0.305 \ P<0.001$).

Multivariate regression analysis showed that the significant risk markers for ventricular tachycardia in the post-infarction period were QT interval dispersion ($P<0.001$) and positive late potentials ($P<0.05$) ($R^2=0.40 \ P<0.001$). Daily variations and maximal QTc interval were not shown to be associated with ventricular tachycardia.

**Discussion**

Greater QT dispersion, as an arrhythmia risk factor, has been established in patients with hereditary QT interval prolongation and hypertrophic cardiomyopathy in the acute phase of myocardial infarction. This study shows that significant correlation between QT interval dispersion and complex ventricular arrhythmia also persists in the chronic phase of myocardial infarction. The value of 80 ms is associated with ventricular tachycardia of the same sensitivity and specificity as in other studies. Previous research has shown that ventricular arrhythmia is significantly more often present in patients with larger infarctions (>15% of left ventricular myocardium). It is supposed that large infarctions result in larger areas with delayed or blocked impulse propagation and non-homogeneous repolarization. Correlation between infarction size and QT dispersion in this study suggests that QT dispersion can be an arrhythmogenic substrate which predisposes to arrhythmia in larger infarctions.

A single measurement of the QTc interval is not a good risk marker of arrhythmia in the post-infarction period. Previous controversial data possibly relate to significant, but not complete, correlation between dispersion and the QTc interval. Autonomic nervous system imbalance and non-homogeneous distribution of alpha-adrenergic receptors (which prolong the QT interval) and beta-adrenergic receptors (which shorten the QT interval) described in a canine model could also be a consequence of regional denervation after myocardial infarction. It could be
the reason for disarranged QT interval adaptation. Patients in the post-infarction period had significantly different adaptation compared to the healthy group, but in the post-infarction group scar size did not significantly influence QT interval adaptations. This is in accordance with the data of Gill et al.\textsuperscript{[13]} where patients with ventricular tachycardia due to ischaemic heart disease had a lower regression line (tendency to longer QT with higher heart rate) compared to subjects without structural heart disease. On the other hand, patients with ventricular tachycardia without structural heart disease had a steeper line (shorter QT interval with higher heart rate) compared to patients without ventricular tachycardia\textsuperscript{[13]}. It has been shown that QT adaptation in healthy subjects also significantly changes depending on the time of day\textsuperscript{[29]}. This means that multiple daily measurements and QT interval adaptation in one lead are not important risk indicators for ventricular tachycardia in the post-infarction period. Insignificantly greater daily QT variability in patients with ventricular tachycardia can be explained by certain hysteresis in QT interval adaptation to heart rate changes, which sometimes lasts up to 3 min, and by the well-known shortcomings of Bazett’s formula at extreme heart rates (hypercorrection with high and hypocorrection with low heart rate)\textsuperscript{[28]}. Although early research showed a high prevalence of late potentials only in patients with acute infarction, recent papers show that late potentials can also be relatively frequent in the absence of overt structural heart disease\textsuperscript{[14,29]}. In this study there was no correlation between scar size and late potentials which some authors found earlier\textsuperscript{[15]}. In view of the fact that fibrous tissue is electrically inert, an inhomogeneous scar with more viable tissue provides better conditions for fragmented activity, as can be found in non-transmural infarction. This infarction mainly has a lower QRS score\textsuperscript{[29]}. The sensitivity and specificity of late potentials in predicting ventricular arrhythmias was high in some studies (78-92 and 63-99)\textsuperscript{[14,13]}, while in others sensitivity was remarkably low with the relative risk of 4-4, which is in accordance with our data\textsuperscript{[13,129]}. In multivariate analysis, late potentials were, along with QT interval dispersion, independent markers of ventricular tachycardia. Since there is no correlation between these methods, the arrhythmogenic substrates which they show are different. Late potentials show delayed conduction or disorder of depolarization, while QT interval dispersion shows differences in action potential duration. Although action potential duration also includes depolarization time, it mainly depends on repolarization time. The overall value of late potentials as risk markers of ventricular arrhythmia seems somewhat lower compared to QT dispersion, not only because of lower sensitivity but also due to the fact, although not yet proven, that pharmacologically induced reduction of QT dispersion could be predictive of antiarrhythmic efficacy\textsuperscript{[15]–36}, while late potentials mostly deteriorate with antiarrhythmic therapy\textsuperscript{[18,37]}.}

### Conclusion

Large QT interval dispersion is a risk factor for ventricular tachycardia in the post-infarction period. It significantly depends on the post-infarction scar size. Daily variations and QT interval adaptation are changed after myocardial infarction but they do not depend on the scar size and do not represent a risk factor for arrhythmia. Late potentials are, as well as QT interval dispersion, risk factors for ventricular tachycardia, but there is no correlation between them. A possible reason is that they show different electrophysiological disorders in the background of the same reentry ventricular arrhythmia.

### References

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NOTICE OF MEETING

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European Cardiology Congress Stockholm

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J. W. Goethe University, Frankfurt

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