Increased QT Dispersion in Patients With Vasospastic Angina

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Background—The risk factors for ventricular arrhythmias in patients with coronary vasospasm have not been identified. We evaluated QT dispersion in patients with vasospastic angina and its relation to susceptibility to ventricular arrhythmias during myocardial ischemia and reperfusion.

Methods and Results—We assessed the corrected QT (QTc) dispersion before induction of coronary artery spasm by intracoronary injection of acetylcholine (baseline) and 30 minutes after administration of isosorbide dinitrate in 50 patients with vasospastic angina and 50 patients with atypical chest pain. The baseline QTc dispersion was significantly greater in patients with vasospastic angina than in patients with atypical chest pain (mean SD: 69±24 versus 44±19 ms, 95% confidence interval of mean difference [CI]: 16 to 33 ms; P<0.001). QTc dispersion decreased significantly, to 48±15 ms (CI: 15 to 26 ms; P<0.001 versus baseline), after administration of isosorbide dinitrate in patients with vasospastic angina but did not change significantly in patients with atypical chest pain (mean SD: 41±17 ms, CI: −3 to 9 ms). During the provocation test, 24 of 50 patients with vasospastic angina experienced ventricular arrhythmias. The baseline QTc dispersion was significantly greater in patients with than without ventricular arrhythmias (mean SD: 77±23 versus 61±19 ms, CI: 4 to 26 ms; P<0.05).

Conclusions—Patients with vasospastic angina exhibited an increased baseline QTc dispersion compared with patients with atypical chest pain, which suggests that inhomogeneity of repolarization and susceptibility to ventricular arrhythmias are increased in patients with vasospastic angina, even when asymptomatic. The association between increased QTc dispersion and ventricular arrhythmias during the provocation test suggests that measurement of QT dispersion may help predict which patients with vasospastic angina are at high risk for ventricular arrhythmias during ischemia. (Circulation. 1998;98:435-440.)

Key Words: angina ▪ vasospasm ▪ intervals ▪ arrhythmia ▪ death, sudden

Life-threatening ventricular arrhythmias occur in 5% to 15% of patients with vasospastic angina.1–7 These arrhythmias are associated with an increased incidence of cardiac events, including sudden death.1–7 However, the factors that increase the risk for malignant ventricular arrhythmias have not been identified in patients with vasospastic angina.

Measurement of the variability in the duration of the QT interval among different leads of a standard 12-lead ECG has been proposed as a noninvasive method to detect inhomogeneity of ventricular recovery times and arrhythmogenic potential.8–11 Prolonged QT dispersion is associated with an increased risk of serious ventricular arrhythmias in patients with the long QT syndrome,12–14 hypertrophic cardiomyopathy,15 chronic heart failure,16 and myocardial infarction.17–19 However, no previous studies have examined QT dispersion in patients with vasospastic angina and its relation to susceptibility to arrhythmias.

We recently reported that patients with vasospastic angina exhibit increased ventricular vulnerability, even during an asymptomatic phase. This increased vulnerability may predispose them to the development of malignant ventricular arrhythmias aggravated by vasospastic events.20 This study was designed to test the hypotheses that patients with vasospastic angina exhibit an increase in QT dispersion and that QT dispersion is related to the susceptibility to ventricular arrhythmias in these patients.

Methods

Study Patients

We studied 50 consecutive patients with vasospastic angina (29 men and 21 women; mean age 58 years, range 44 to 71 years) evaluated...
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The QT interval and QRS duration were measured in all leads of a 12-lead ECG recorded at a speed of 50 mm/s for 2 consecutive cycles. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, which was defined as the percent decrease in the luminal diameter, and the organic coronary artery lesion was evaluated. Coronary arteriography was performed again 30 minutes after the relief of vasospasm to confirm the absence of significant stenosis.

QT Interval and QT Dispersion of a 12-Lead Surface ECG

TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>VSA (+) Group</th>
<th>VSA (−) Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>58±15</td>
<td>57±14</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>29/21</td>
<td>28/22</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.7±2.9</td>
<td>24.4±2.7</td>
</tr>
<tr>
<td>Pulse rate, bpm</td>
<td>70±14</td>
<td>71±14</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>125±22</td>
<td>124±21</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>83±22</td>
<td>79±20</td>
</tr>
<tr>
<td>Smoking, yes/no</td>
<td>12/38</td>
<td>7/23</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L</td>
<td>5.4±1.4</td>
<td>4.8±0.9</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>11.7±2.3</td>
<td>10.9±2.6</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>7.1±2.1</td>
<td>6.6±1.5</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>2.4±1.2</td>
<td>2.7±0.9</td>
</tr>
</tbody>
</table>
| VSA (+) Group indicates patients with vasospastic angina; VSA (−) Group, patients with atypical chest pain; BP, blood pressure; and HDL-C, HDL cholesterol. Values are expressed as mean±SD or number of patients.

None of the patients with atypical chest pain showed significant vasospasm (>50%) or ischemic ST-segment changes at baseline or after intracoronary injection of acetycholine. The total coronary vasomotor response to acetylcholine, defined as the percent decrease in the luminal diameter, ranged from −10% to 50% (31.1±3.0%) in patients with atypical chest pain.

In patients with vasospastic angina, no chest pain or myocardial ischemic ECG changes were observed at baseline. A spontaneous 25% vasoconstriction of the right coronary artery was observed in 4 patients and 25% vasoconstriction of the left anterior descending artery was observed in 4 patients. One patient showed 50% vasoconstriction of the right coro-

Results

There were no significant differences in baseline characteristics between groups (Table 1). None of the patients with atypical chest pain showed significant vasospasm (>50%) or ischemic ST-segment changes at baseline or after intracoronary injection of acetycholine. The total coronary vasomotor response to acetylcholine, defined as the percent decrease in the luminal diameter, ranged from −10% to 50% (31.1±3.0%) in patients with atypical chest pain.

In patients with vasospastic angina, no chest pain or myocardial ischemic ECG changes were observed at baseline. A spontaneous 25% vasoconstriction of the right coronary artery was observed in 4 patients and 25% vasoconstriction of the left anterior descending artery was observed in 4 patients. One patient showed 50% vasoconstriction of the right coronary artery was observed in 4 patients.
The mean difference between observers in the measurement of baseline QT dispersion (n=50) was 0±4 ms and 95% CI was between -1 and 1 ms. After the relief of vasospasm, the mean difference between observers was 0±5 ms and 95% CI was between -1 and 1 ms (Figure 1).

Reproducibility of QT Dispersion Measurements

The mean heart rate increased significantly after the relief of coronary vasospasm compared with the baseline value in both groups (vasospastic angina, mean ± SD: 70±14 versus 76±15 bpm, MD: -6.0±15 bpm, CI: -10 to -2 bpm, P<0.01; atypical chest pain, mean ± SD: 71±14 versus 76±14 bpm, MD: -5±13 bpm, CI: -8 to -1 bpm, P<0.01). Systemic arterial pressure did not change significantly after the relief of vasospasm in either group (vasospastic angina, mean ± SD: 125±22 versus 120±20 mm Hg, MD: 5±22 mm Hg, CI: -2 to 10 mm Hg; atypical chest pain, mean ± SD: 124±21 versus 119±20 mm Hg, MD: 5±29 mm Hg, CI: -3 to 13 mm Hg). There was no significant difference in the mean QTc interval between patients with vasospastic angina and patients with atypical chest pain. In patients with vasospastic angina, the QTc interval was significantly smaller at baseline than that after the relief of coronary vasospasm in patients with vasospastic angina (Table 2). The baseline QTc dispersion was significantly greater in patients with vasospastic angina than in patients with atypical chest pain (mean ± SD: 69±24 ms versus 44±19 ms, MD: 25±30 ms, CI: 16 to 33 ms; P<0.001) (Figure 2). QTc dispersion decreased significantly, to 48±15 ms (MD: 21±20 ms, CI: 15 to 26 ms; P<0.001 versus baseline) after administration of isosorbide dinitrate in patients with vasospastic angina, but did not change significantly in patients with atypical chest pain (mean ± SD: 41±17 ms, MD: 3±22 ms, CI: -3 to 9 ms) (Figure 2).

Ventricular Arrhythmias in Patients With Vasaospastic Angina

Ventricular arrhythmias occurred in 24 of 50 patients with vasospastic angina only during the provocation test. Polymorphic nonsustained ventricular tachycardias lasting at least 3 consecutive beats were observed in 5 of 24 patients. The remaining 19 patients had less serious ventricular arrhyth-

![Figure 1. Reproducibility of measurements of QTc dispersion at baseline (A) and after the relief of vasospasm (B) in 50 patients with vasospastic angina by 2 observers using the Bland-Altman method. There are fewer than 50 points because of data overlap.](http://circ.ahajournals.org/lookup/doi/10.1161/01.CIR.98.3.437)
mias, including isolated premature ventricular contractions, bigemini, and couplets. All ventricular arrhythmias were observed when the patients had ischemic symptoms after the administration of acetylcholine and no ventricular arrhythmias were observed immediately after intracoronary injection of isosorbide dinitrate.

At baseline, QTc dispersion was significantly greater in patients with than without ventricular arrhythmias (mean±SD: 77±23 ms versus 61±19 ms, MD: 16±26 ms, CI: 4 to 26 ms; P<0.05) (Figure 3). QTc dispersion did not differ significantly between these subgroups after the relief of isosorbide dinitrate.

There were no significant differences in baseline patient characteristics or the severity of vasospasm between patients with vasospastic angina with and without ventricular arrhythmias. No patients with atypical chest pain showed ventricular arrhythmias during the provocation test.

**Discussion**

In the present study, patients with vasospastic angina exhibited greater baseline QTc dispersion than patients with atypical chest pain. Increased QTc dispersion in asymptomatic patients with vasospastic angina was associated with increased vulnerability to ventricular arrhythmias related to ischemic events. These findings suggest that patients with vasospastic angina have increased dispersion of ventricular repolarization, which may increase the risk of sudden death caused by malignant arrhythmias.1–7 The present findings support previous reports demonstrating that subsets of patients with increased QT dispersion are at increased risk of sudden cardiac death.8–19

**QT Dispersion in Patients With Vasospastic Angina**

To the best of our knowledge, this study is the first to evaluate QT dispersion in patients with vasospastic angina. QT dispersion reflects the regional variation in ventricular repolarization, which is an electrophysiologic substrate for the genesis of arrhythmias. QT dispersion has been proposed as a marker of arrhythmogenic potential.8–19 In this study, the baseline QTc dispersion was significantly increased in patients with vasospastic angina without evidence of myocardial ischemia or angiographically detectable coronary artery spasm. After the relief of vasospasm by isosorbide dinitrate, QTc dispersion decreased significantly to the level similar to that in patients with atypical chest pain. These data suggest that patients with vasospastic angina have greater inhomogeneity of repolarization, independent of the presence or absence of ischemic symptoms.

**Sudden Death in Patients With Vasospastic Angina**

Fatal ventricular arrhythmias have frequently been documented in patients with ischemic heart diseases, including vasospastic angina, exertional angina, and myocardial infarction.5–7 Previous studies have shown that the occurrence of ventricular arrhythmias depends on the magnitude of the dispersion in the refractory period. Inhomogeneity and increased dispersion of repolarization may promote polymorphic ventricular tachycardia and ventricular fibrillation.20,26–31

The development of ventricular arrhythmias in patients with vasospastic angina is thought to be caused not only by reentry associated with myocardial ischemia during vasospasm but also by reentry and/or triggered activity associated with reperfusion after the relief of spasm.5–10,20,32–34

In this study, 24 of 50 patients with vasospastic angina experienced ventricular arrhythmias, including ventricular tachycardia. Arrhythmias were observed during induced ischemia but not immediately after the relief of spasm by the
administration of isosorbide dinitrate (assumed to be a reperfusion period). This may partly be due to the very short period of myocardial ischemia induced by the provocation test. QTc dispersion at baseline was significantly greater in patients with than without ventricular arrhythmias. There was no difference in the degree or severity of coronary vasospasm between patients with and without ventricular arrhythmias. The greater QTc dispersion in patients with vasospastic angina who developed ventricular arrhythmias during induced ischemia may indicate that the dispersion of ventricular refractoriness was increased in the asymptomatic state, due to abnormal microcirculation or autonomic dysfunction. These findings suggest that evaluation of QTc dispersion may provide useful information about baseline abnormalities of ventricular repolarization and susceptibility to ventricular arrhythmias caused by ischemia in patients with vasospastic angina.

We recently reported that the effective refractory period for right ventricular sites is short and that electrophysiological instability is present in patients with vasospastic angina, even when asymptomatic. The results of the present study support these previous findings. Thus the measurement of QTc dispersion obtained in the nonmedicated, asymptomatic state appears to be a simple, noninvasive method of obtaining information about the susceptibility of patients with vasospastic angina to ventricular arrhythmias.

Study Limitations
The relation between the incidence of ventricular arrhythmias during the ischemic state and the prognosis of these patients remains to be determined. This study did not directly demonstrate a higher risk of sudden death in these patients. However, in a previous study from our laboratory, patients with ventricular arrhythmias during induced myocardial ischemia had a higher incidence of ventricular tachycardia induced by programmed stimulation, suggesting that the risk of lethal cardiac events was increased in these patients.

Conclusions
QTc dispersion was increased in asymptomatic patients with vasospastic angina compared with patients with atypical chest pain, indicating that patients with vasospastic angina had greater inhomogeneity of ventricular refractoriness, which may predispose them to life-threatening arrhythmias, even in the absence of signs of ischemia. The relation between increased QT dispersion and the incidence of ventricular arrhythmias during myocardial ischemia in patients with vasospastic angina suggests that the simple, noninvasive measurement of QT dispersion may help identify patients at an increased risk of malignant arrhythmias. The prognostic implications should be evaluated in prospective follow-up studies.

References


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