Opening of K<sub>ATP</sub> Channel Attenuates the Increase in QT Dispersion Produced by the First Balloon Inflation During Coronary Angioplasty

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Increased QT dispersion predicts the occurrence of lethal ventricular arrhythmias complicating percutaneous transluminal coronary angioplasty (PTCA). Moreover, these arrhythmias occur more frequently at the first balloon inflation. Activation of the K<sub>ATP</sub> channel may influence QT dispersion and ventricular arrhythmias during coronary angioplasty, so 40 consecutive patients with stable angina were randomized to receive 3 mg/h of nicorandil infusion or placebo and QT dispersion and the incidence of ventricular ectopy were investigated before and throughout PTCA. There were no significant differences in QT dispersion at baseline between the nicorandil group (42±8 ms) and placebo (42±12 ms). At the first balloon inflation, the QT dispersion in the nicorandil group (51±13 ms) was significantly less than that observed with placebo (76±16 ms, p<0.001). However, the QT dispersion at the second inflation was similar in both groups (nicorandil: 45±12 ms; placebo: 52±14 ms). Ventricular ectopy was observed in 1 patient receiving nicorandil and 5 patients in the placebo group during the first inflation, and none in the nicorandil and 1 patient in the placebo group during the second balloon inflation. Activation of the K<sub>ATP</sub> channel may inhibit the development of ventricular arrhythmias during PTCA, particularly at the first balloon inflation.  

Key Words: Angioplasty; K<sub>ATP</sub> channel; QT dispersion

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Methods

Patient Population
We studied 40 consecutive patients (27 men, 13 women; mean age: 68 years, range: 47–80 years) who underwent balloon inflation at least twice during PTCA. All 40 patients had 1-vessel coronary artery disease (>90% diameter stenosis) of the proximal two-thirds of the LAD. PTCA was successfully performed with standard equipment and techniques. None of the patients had an acute myocardial infarction or a history of sustained ventricular tachycardia or ventricular fibrillation and none was receiving any antiarrhythmic agent or other type of therapy that could affect the QT interval. None of the patients had evidence of left ventricular hypertrophy or wall motion abnormalities on the echocardiogram or conduction defects on the electrocardiogram (ECG). All patients gave informed consent and the study protocol was approved by the Ethics Committee of the institution.

Study Protocol
This was a single-blind, placebo-controlled, randomized recovery after ischemia and reperfusion, whereas opening the K<sub>ATP</sub> channel with pinacidil enhanced it.
study. All patients were randomly assigned to 2 groups: nicorandil or placebo. Standard medications, including long-acting nitrates and calcium channel blockers, were continued on the day of the procedure. Twenty patients (13 men, 7 women; mean age: 69 years, range: 47–80 years) in the nicorandil group received nicorandil (3 mg/h iv) 1 h before PTCA, while the 20 patients (14 men, 6 women; mean age: 65 years, range: 50–80 years) in the placebo group received an intravenous infusion of saline solution. PTCA was performed in both groups with a balloon catheter (2.5–3.75 mm diameter) that was passed over a 0.014 mm guide wire. After baseline angiography, the guide wire was placed across the stenotic lesion, the balloon catheter was placed within the stenosis and the balloon was inflated for 1 min. After balloon deflation and withdrawal of the catheter proximal to the lesion, leaving the guide wire across the lesion, the second balloon inflation, using the same balloon and the same pressure, was performed for 1 min after the 5-min recovery time.

Electrocardiography
Standard 12-lead ECG were obtained 1 h before angioplasty, just before angioplasty and 1 min after balloon inflation. The ECG from each patient at each time point was printed at a gain of 10 mm/mV and paper speed of 50 mm/s. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, defined as a return to the TP baseline (between the end of the T wave and the following P wave) while excluding the U wave. Analysis was performed blindly by 2 independent observers who were unaware of the clinical data. Linear regression analysis yielded minimal intraobserver (r=0.94, p<0.0001) and interobserver (r=0.93, p<0.0001) variation. QT dispersion, defined as the difference between the maximum (QTmax) and minimum QT (QTmin) intervals, was determined as previously described.12,13

Ventricular Ectopy
After visual inspection of the RR interval tachograms, all ECG recordings were scanned manually by an experienced observer. Ventricular extrasystoles were identified on the basis of prematurity and the width of the QRS complex.

Statistical Analysis
All data are expressed as means ± SD. Statistical analyses were performed using analysis of variance for repeated measurements. QT dispersion in patients with and without nicorandil was compared by paired or unpaired t-test. Fisher’s exact test was used for discrete data. These analyses were performed using the StatView 4.51J program (SAS Institute, Cary, NC, USA). A p value less than 0.05 was considered significant.

Results

Clinical Characteristics
PTCA was successfully performed in all patients. There were no significant differences in baseline characteristics between the groups with respect to age, sex, smoking history, diabetes mellitus, balloon size and ejection fraction (Table 1). The 1 patient with diabetes mellitus was not on

Table 1 Characteristics (n or Mean ± SD) in the Nicorandil and Placebo Groups

<table>
<thead>
<tr>
<th></th>
<th>Nicorandil (n=20)</th>
<th>Placebo (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69±9</td>
<td>65±8</td>
</tr>
<tr>
<td>Male sex</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Smokers</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Balloon diameter (mm)</td>
<td>3.0±0.3</td>
<td>3.0±0.3</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>68±8</td>
<td>71±7</td>
</tr>
</tbody>
</table>

Table 2 Hemodynamic Variables (Mean ± SD) in the Nicorandil and Placebo Groups

<table>
<thead>
<tr>
<th></th>
<th>Nicorandil (n=20)</th>
<th>Placebo (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>76±12</td>
<td>72±11</td>
</tr>
<tr>
<td>Just before angioplasty</td>
<td>75±14</td>
<td>75±10</td>
</tr>
<tr>
<td>First balloon inflation</td>
<td>76±12</td>
<td>76±11</td>
</tr>
<tr>
<td>Second balloon inflation</td>
<td>77±13</td>
<td>75±9</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>133±20</td>
<td>137±20</td>
</tr>
<tr>
<td>Just before angioplasty</td>
<td>133±17</td>
<td>136±21</td>
</tr>
<tr>
<td>First balloon inflation</td>
<td>136±21</td>
<td>132±21</td>
</tr>
<tr>
<td>Second balloon inflation</td>
<td>131±17</td>
<td>138±21</td>
</tr>
</tbody>
</table>

Fig 1. QTmax (closed bars) and QTmin (open bars) in the nicorandil and placebo groups. Data are means ± SD. B, baseline; 1A, after first coronary angioplasty; 2B, after second coronary angioplasty. *p<0.05, †p<0.01, ‡p<0.0001 (vs baseline).

Fig 2. QT dispersion in the nicorandil (open bars) and placebo (closed bars) groups before and after the first and second balloon inflation. Data are means ± SD. B, baseline; 1A, after first coronary angioplasty; 2B, after second coronary angioplasty. *Significant differences in comparison with nicorandil group; *p<0.001.
medication. Intravenous administration of nicorandil alone resulted in no significant changes in heart rate or blood pressure before and during the procedure in either group (Table 2). At the first balloon inflation, ventricular ectopy was observed in 1 patient with the nicorandil group and in 5 with the placebo group. At the second balloon inflation, ventricular ectopy was only observed in 1 patient with the placebo group.

**QT Interval and QT Dispersion**

Before the drug administration, the QTmax, QTmin and QT dispersion in the nicorandil group (424±25 ms, 382±24 ms, 42±8 ms, respectively) were similar to those in the placebo group (435±24 ms, 393±22 ms, 42±12 ms, respectively) (Figs 1, 2). The QT dispersion showed a tendency to shorten, but not significantly, after nicorandil administration (39±10 ms). At the first balloon inflation, the change in QTmin in the nicorandil group (38±21 ms) was similar to that in the placebo group (386±27 ms). However, a significant difference in the QTmax was observed between the 2 groups: QTmax in the placebo group increased significantly (461±52 ms, p<0.0001 vs baseline), but showed little increase in the nicorandil group (435±26 ms, p=0.01 vs baseline) and the increase was attenuated compared with the placebo. The QT dispersion in the placebo group (76±16 ms, p=0.001) was significantly larger than in the nicorandil group (53±13 ms) (Fig 2). At the second balloon inflation, the QTmin in the nicorandil group was unaffected (384±23 ms) and the QTmax increased (429±27 ms, p=0.01 vs baseline). The QTmax in the placebo group was unaffected (441±27 ms) and the QTmin decreased slightly (389±28 ms, p=0.05 vs baseline). The QT dispersion (45±12 ms [nicorandil] vs 52±14 ms [placebo]) was similar in both groups (Fig 2).

**Discussion**

There are 2 major findings from this study. First, intravenous nicorandil reduced the increase in QT dispersion at the first balloon inflation compared with the placebo group. Second, there were no significant changes in QT dispersion in the 2 groups at the second balloon inflation. These findings suggest that nicorandil mimics ischemic preconditioning in patients undergoing PTCA and may prevent ventricular arrhythmias at the first balloon inflation. The incidence of ventricular ectopy showed a tendency to decrease in the nicorandil group, but the difference was not significant because of the small number of incidences.

QT dispersion may be a measure of variability in ventricular recovery time and thus identify patients with coronary artery disease at risk for lethal ventricular arrhythmias and sudden death. However, the mechanism of increased QT dispersion is multifactorial and there are no reports on the changes in QT intervals and QT dispersion in patients with coronary artery disease.

Aizawa et al showed that nicorandil shortened QT interval in patients with congenital long QT syndrome, possibly through activation of the KATP channel. Nicorandil mimics ischemic preconditioning, which reduce chest pain and ST elevation during PTCA and reduces the infarct size in acute myocardial infarction. In the present study, long-acting isosorbide dinitrate was given to patients in both groups to minimize the effect of nitrate and nicorandil alone did not reduce the QT dispersion at baseline. Activation of the KATP channel may cause the change in QT dispersion during balloon inflation. Sato et al showed in an isolated rat and rabbit model that nicorandil is a fairly selective mitochondrial KATP channel opener that improves functional recovery after ischemia but the physiological role of mitochondrial KATP channels in human cardiac myocytes remains uncertain and further study is needed to determine the effect of nicorandil in humans. Matsubara et al demonstrated that 3 min, but not 1 min, of ischemia with balloon inflation had a preconditioning effect at the ST segment level but Okishige et al reported that 1–2 min of ischemia had a preconditioning effect with regard to QT dispersion. Our data showed that 1 min only of ischemia with balloon inflation is enough for ischemic preconditioning and, in addition, that nicorandil attenuated the QT dispersion when the drug was given before and throughout the occlusive episode at a low, clinically relevant, nonhypotensive dose.

In the present study, the response of QTmin was similar in both groups, but QTmax was quite different at the first balloon inflation and nicorandil significantly attenuated the increase in QTmax. In patients with diabetes mellitus, there is a relation between QTmax and autonomic dysfunction, but the mechanism of increased QTmax in patients with angina pectoris is still unknown. Although we can not rule out an effect on the microcirculation by nicorandil, these data suggest that activation of the KATP channel by nicorandil is involved in the attenuation of QTmax change, which may be linked to an imbalance in sympathetic nervous activity caused by regional cardiac denervation in the ischemic area.

In the clinical setting, ventricular arrhythmias occur more frequently at the first balloon inflation than at the second balloon inflation. It has been suggested that ischemic preconditioning might reduce the inhomogeneity in ventricular repolarization and QT dispersion. Kajiyama et al showed that QT dispersion correlates with ventricular arrhythmias, although they did not demonstrate either the mechanism or the prevention of the arrhythmias. We found that nicorandil reduced the increase in QT dispersion, particularly at the first balloon inflation, with some decrease in the incidence of ventricular ectopy. But because of the small number of arrhythmic events, the reduction in the incidence of ventricular arrhythmias did not reach statistical significance. Further study is required in a large population.

In conclusion, opening the KATP channel attenuates the increase in QT dispersion during PTCA, particularly at the first balloon inflation, and may reduce the incidence of lethal ventricular arrhythmias associated with the procedure. QT dispersion has been used to characterize myocardial repolarization, but recent studies showed that QT dispersion is unrelated so further study will be required to identify the clinical importance and electrophysiological role of QT dispersion.

**Acknowledgments**

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**References**