Nicorandil, a Hybrid Between Nitrate and ATP-Sensitive Potassium Channel Opener, Preconditions Human Heart to Ischemia During Percutaneous Transluminal Coronary Angioplasty

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The heart progressively becomes more tolerant to ischemia after repeated balloon inflations during percutaneous transluminal coronary angioplasty (PTCA). The present study investigated whether nicorandil, a hybrid between nitrate and an ATP-sensitive potassium channel opener, affects this ischemic preconditioning. Sixteen patients with stable angina pectoris caused by left anterior descending artery lesions were subjected to 2 balloon inflations of 2-min duration with a 3-min reperfusion period. Seven of these patients served as the control group and in the remaining 9 patients, nicorandil was administered intravenously (6 mg/h) throughout the PTCA procedure (nicorandil group). The lactate extraction ratio (LER) was obtained at 30 s after each ischemic event (LERpost-1 and LERpost-2) in both groups. In the control group, LERpost-1 was more negative than LERpost-2 (–185.7±74.2 vs –98.0±37.3%, p<0.01). The ratio of the sum of the ST elevation in the precordial leads during the second inflation (ΣST-2, 0.94±0.66 mV) to that during the first inflation (ΣST-1, 1.43±1.17 mV) was 0.72±0.16 in the control group, which was less than the ratio in the nicorandil group (1.06±0.13, p<0.01). Nicorandil abolished the difference between the 2 ischemic events (LERpost-1, –45.1±41.6 vs LERpost-2, –43.5±51.1%; ΣST-1, 1.38±0.80 vs ΣST-2, 1.46±0.90 mV). LER was less negative in the nicorandil group than that in the control group (LERpost-1, –45.1±41.6 vs –185.7±74.2%, p<0.01; LERpost-2, –43.5±51.1 vs –98.0±37.3%, p<0.05). Thus, nicorandil improved lactate metabolism during PTCA without significantly influencing ST-elevation. In conclusion, intravenous pre-administration of nicorandil appears to precondition the human heart during PTCA. (Jpn Circ J 2001; 65: 526–530)

Key Words: ATP-sensitive potassium channel; Ischemic preconditioning; Nicorandil; Percutaneous transluminal coronary angioplasty

Ischemic preconditioning was first described in animal experiments as an infarct-size limiting effect in which brief repetitive episodes of ischemia diminished the size of the myocardial infarction caused by subsequent long-lasting ischemia. Many molecules have been proposed as candidates for the key role in this intriguing phenomenon, including adenosine, an endogenous cardioprotective substance, protein kinase C, manganese-superoxide dismutase, heat shock proteins and ATP-sensitive potassium channel.

It has been suggested that ischemic preconditioning occurs in human myocardium. A similar phenomenon has been observed in the process of repetitive balloon inflations during percutaneous transluminal coronary angioplasty (PTCA); that is, the degree of ischemia caused by the first balloon inflation was more severe than that caused by subsequent inflations. This cardioprotection was abolished by glibenclamide, an ATP-sensitive potassium channel inhibitor. In an ex vivo experiment using human atrial trabeculae, chronic oral intake of sulfonylurea also abolished the ischemic preconditioning effect. Thus it would appear that the ATP-sensitive potassium channel plays a crucial role in ischemic preconditioning of human myocardium.

Nicorandil, a hybrid between the nitrates and ATP-sensitive potassium channel activators has been widely used as an anti-anginal agent and is an only pharmacological tool that opens the ATP-sensitive potassium channels in the clinical setting. Its cardioprotective action has been reported in various animal models and in humans. The present study investigated whether or not nicorandil affects ischemic preconditioning during PTCA.

Methods

Seventeen consecutive patients with stable angina caused by a significant stenosis of the left anterior descending (LAD) artery, who admitted into Ishinkai Yao General Hospital from April 1995 to August 1997 and underwent PTCA, were enrolled. Written informed consent was obtained from each patient.

The first 9 patients served as the nicorandil group and the remainder became the control group. Exclusion criteria were: (1) history of myocardial infarction; (2) abnormal left ventriculography (eg, dyskinesis); (3) angiographical delay along the LAD artery prior to PTCA; and (4) presence of collateral vessels to the anteroseptal region before
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PTCA. The stenotic sites were successfully dilated to less than 50% stenosis without angiographical delay, except in 1 patient of the control group who was subsequently excluded from the analysis (Table 1). Diabetes mellitus was present in patients 6, 7, 9, and 13. Two patients (Nos. 6 and 7) used insulin to control the disease. All medications were discontinued at least for 15 h prior to the PTCA except long-acting nitrate, calcium channel blockers, and aspirin. Gliclazide for patient 9 and acetohexamide for patient 13 were suspended at least for 24 h prior to PTCA.

A PTCA balloon was inflated twice, to at least 8 atm, for 2-min each time with a 3-min reperfusion period, as described previously, because previous reports considered these time periods to be sufficient for the ischemic preconditioning effect. During the inflation, contrast medium was injected into a left coronary artery to observe if antegrade flow occurred. Angiographical delay was not detected after either of the 2 inflations. For the nicorandil group (n=9), an intravenous bolus injection of 2 mg nicorandil (Chugai Pharmaceutical Co, Tokyo, Japan) was followed by at least 1 h of continuous infusion (6 mg/h) so that 8 mg of nicorandil was injected prior to PTCA, which was considered to be the amount necessary to observe its cardioprotective effect.

ΣST, the sum of the ST elevation in the precordial leads, other than V1, and the lactate extraction ratio (LER) were used to evaluate the severity of ischemia. The degree of ST elevation was measured at 80 ms from the J-point immediately before each deflation. For the lactate measurement, blood was sampled immediately before and 30 s after each ischemic event, simultaneously from the great cardiac vein (through a 5Fr NIH catheter) and from the ascending aorta. LER was calculated according to the following equation:

\[
LER = 100 \times \left( \frac{\text{arterial lactate concentration (mg/dl)} - \text{coronary venous lactate concentration (mg/dl)}}{\text{arterial lactate concentration (mg/dl)}} \right)
\]

All data were reported as mean ± standard deviation (SD). One-way ANOVA followed by the Fisher’s test was used for intragroup comparison. Unpaired t-test was used for comparison between groups. When p<0.05, the difference was considered statistically significant.

Results

Effects of Nicorandil on Conditions Prior to PTCA

To rule out any effects of nicorandil on the systemic circulation, the systolic blood pressure and heart rate were recorded non-invasively at the left brachial artery immediately before PTCA. Rate–pressure product, systolic arterial pressure × heart rate, as an indicator of the cardiac oxygen consumption.

Table 1 Patient Characteristics

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Sex</th>
<th>Site of lesion</th>
<th>% stenosis</th>
<th>Medications*</th>
<th>Systolic BP (mmHg)</th>
<th>Heart rate (beats/min)</th>
<th>Rate–pressure product (mmHg/min)</th>
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<td></td>
<td>21</td>
<td>14</td>
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</tbody>
</table>

Nicorandil group

| 8        | 60   | M   | Mid            | 90         | C, N         | 167               | 56                    | 9,352                          |
| 9        | 80   | F   | Mid            | 75         | C, G, N, NC  | 136               | 74                    | 10,064                         |
| 10       | 65   | M   | Mid            | 90         | C, N         | 163               | 82                    | 13,366                         |
| 11       | 71   | F   | Prox           | 90         | C, N         | 158               | 65                    | 10,270                         |
| 12       | 80   | M   | Mid            | 90         | C, N         | 131               | 65                    | 8,515                          |
| 13       | 54   | M   | Mid            | 90         | A, C, N      | 106               | 68                    | 7,208                          |
| 14       | 62   | M   | Prox           | 90         | C, N         | 144               | 54                    | 7,776                          |
| 15       | 47   | M   | Mid            | 90         | N            | 106               | 60                    | 6,360                          |
| 16       | 61   | M   | Mid            | 90         | D, N         | 111               | 66                    | 7,326                          |
| Mean     | 68.3 | 10.6|                |             |              | 136               | 66                    | 8,915                          |
| SD       | 24   | 9   |                |             |              | 24                | 9                     | 2,138                          |

*Long-term oral medications prior to PTCA: A, acetohexamide; C, calcium channel blocking agents; D, dipyridamole; G, gliclazide; N, long-acting nitrates; NC, nicorandil (15 mg/day). Systolic blood pressure (BP) and heart rate were measured non-invasively at the left brachial artery immediately before PTCA. Rate–pressure product, systolic arterial pressure × heart rate, as an indicator of the cardiac oxygen consumption.
first inflation (0.94±0.66 vs 1.43±1.17 mV), which indicates that the second ischemia was milder than the first one, confirming the occurrence of ischemic preconditioning during PTCA.

For the nicorandil group, LERpost-1 was similar to LERpost-2 (–45.1±41.6 vs –43.5±51.1%) and ΣST during the first inflation was also similar to that during the second inflation (1.38±0.80 vs 1.46±0.90 mV). The ratio of ΣST during the second to that of the first ischemia (ΣST-2/ΣST-1) was 1.06±0.13 in the nicorandil group, which was greater than the result in the control group (0.72±0.16, p<0.01). These results indicate that nicorandil abolishes the ischemic preconditioning that occurs during PTCA. LERpost-1 was less negative in the nicorandil group than that in the control group (–45.1±41.6 vs –185.7±74.2%, p<0.01), as was LERpost-2 (–43.5±51.1 vs –98.0±37.3%, p<0.05), which indicates that nicorandil attenuated the severity of ischemia during PTCA, especially during the first balloon inflation.

**Discussion**

The pharmacological action of nicorandil was originally thought to be on vascular smooth muscle because, like classical nitrates, it elevates the intracellular level of cGMP to cause relaxation of vascular smooth muscle. Later, its action on the ATP-sensitive potassium channel was discovered and consistent with the important role of this channel in ischemic preconditioning. There were reports of cardioprotection by nicorandil in unstable angina and acute myocardial infarction. The most important finding in the present study is that intravenous administration of nicorandil improved lactate metabolism during PTCA, more prominently during the first ischemic period than in the second one, which is an apparent preconditioning effect (Table 2).

What is the subcellular mechanism underlying the ischemic preconditioning that occurs during PTCA? Adenosine, an endogenous cardioprotective substance released from the ischemic heart, is proposed as the mediator because one of the subcellular signal transduction pathways of the adenosine receptor is opening of the ATP-sensitive potassium channels localized on the sarcolemma and mitochondrial inner membranes. Recent experiments using selective channel inhibitors or activators have suggested that mitochondrial ATP-sensitive potassium channels play a key role in the signal transduction of ischemic preconditioning especially in the rabbit heart and at least partially in the canine heart. In rabbit cardiomyocytes, nicorandil exerted its cardioprotective action through selective opening of the mitochondrial ATP-sensitive potassium channels. This hypothesis is compatible with the present results because nicorandil affected mainly lactate metabolism without a significant influence on ST-segment shift (Table 2), which depends on sarcolemmal but not mitochondrial ATP-sensitive potassium channels.

We used 2 parameters to evaluate severity of ischemia: LER after inflation (LERpost) and ΣST. Linear regression analyses of the relation between LERpost and ΣST showed that these 2 parameters correlated well in the control group (r²=0.421, p=0.012, n=14), but not in the nicorandil group (r²=0.154, p=0.017, n=18), which indicates that the 2 parameters represent the severity of ischemia only in the control group. Dissociation of the 2 parameters in the nicorandil group is compatible with the pharmacology of nicorandil; that is to say, its selectivity for mitochondrial ATP-sensitive potassium channels.

Nicorandil affected cardiac lactate metabolism not only during the balloon inflations (LERpost-1 and LERpost-2), but also under the baseline conditions (LERpre-1 and LERpre-2).
Both LER\textsuperscript{pre-1} and LER\textsuperscript{pre-2} were more positive in the nicorandil group than in the control group (Table 2). Under the baseline conditions, there was no significant difference in arterial lactate concentrations between the control and nicorandil groups (data not shown), suggesting that the nicorandil-perfused heart extracted more lactate from the coronary circulation. One possible explanation is that intravenous infusion of nicorandil increases coronary blood flow at the level of the microcirculation.\textsuperscript{27}

**Study Limitations**

First, differences in the individual ischemic areas was unavoidable because of the clinical setting. To minimize this difference, we used patients with stenosis of the middle or proximal portion of the left anterior descending artery and those with collateral vessels to the anteroseptal region were excluded. The second limitation is with the study design (2-min inflation and 3-min reperfusion). Because we administered intravenous nicorandil before the first inflation, no basal (nicorandil-free) data were available in the nicorandil group, which differs from a study by Saito et al\textsuperscript{22} who administered intravenous nicorandil between the first and second balloon inflations (30 s each with a 5-min reperfusion period) to compare the 2 ischemic events, nicorandil-free and nicorandil-treated, in the one individual. What they found was a lesser ST-segment shift during the second ischemia than during the first one. However, it can be argued that the second ischemia might have been affected not only by nicorandil but also by the first ischemia (ie, an ischemic preconditioning effect). Matsubara et al used a protocol of 3-min inflation and 5-min reperfusion and found that the 3-min ischemic event produced less ST elevation throughout the subsequent 2-min ischemia, and that with pre-administration of nicorandil, this attenuation of ST elevation continued only during the first half of the 2-min ischemia (ie, at 2 min after the inflation the degree of ST elevation was equivalent to that of the control).\textsuperscript{23} Their data suggest that the ischemic preconditioning was somehow different from the pharmacological preconditioning induced by nicorandil, which concurs with our results.

Although the techniques of coronary intervention have progressed rapidly, adjunctive medication to reduce the severity of the ischemia produced during the procedure has not yet been established. The present study provides a rational basis for the use of intravenous nicorandil during coronary interventions, rather than intracoronary adenosine, which frequently causes chest pain and bradycardia.\textsuperscript{31,33}

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**References**


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