Clinical Studies

Coronary Dilating Effects of Intracoronary Nicorandil
Comparison with Isosorbide Dinitrate

Jun-ichi Ejima, M.D., Koji Kaneda, M.D.,* Hidetoshi Moriyama, M.D.,* Ichiro Ohmura, M.D.,* Toru Maruyama, M.D., Yoshiakzu Kaji, M.D., Yasuo Tsuda, M.D., Shozo Kanaya, M.D., Takehiko Fujino, M.D., and Yoshiyuki Niho, M.D.

Summary
Although nicorandil, N-(2-hydroxyethyl) nicotinamide dinitrate, is a nitrate ester, its cardiovascular action differs from that of nitrate compounds in several aspects. In this quantitative angiographic study, the acute coronary dilating effect of intracoronary nicorandil (0.25, 0.50, 1.0 mg) was compared with that of isosorbide dinitrate (ISDN; 1.0 mg) in 46 patients with or without ischemic heart disease (IHD). Dose-dependent right coronary dilating action was observed by intracoronary administration of nicorandil without any adverse effects. The same degree of right coronary dilation was achieved by the intracoronary application of equivalent doses of ISDN. We conclude that intracoronary administration of nicorandil is beneficial for the supportive treatment of IHD during coronary artery investigation and intervention without the risk of severe systemic hypotension. (Jpn Heart J 36: 699–707, 1995)

Key words: Nicorandil Isosorbide dinitrate Coronary dilating effect

Different types of angina require different types of drugs, including β-adrenergic receptor blocking agents for effort angina with fixed coronary stenosis, calcium antagonists for vasospastic angina, and nitrates for both types.1–6) Unfortunately, the use of β-blocking agents introduces complications such as bradycardia and depression of mechanical cardiac function. Likewise, the use of calcium antagonists tends to be associated with reduced myocardial contractility and conduction disturbance.7) Nitrates have the disadvantage of causing hypotension and resultant tachycardia.
Although intracoronary administration of nicorandil and nitrate compounds has become increasingly common, particularly in conjunction with reperfusion therapy and percutaneous coronary angioplasty, the optimal clinical intracoronary dose of nicorandil remains to be established.\(^8\) Isosorbide dinitrate (ISDN) and nicorandil have significant coronary vasodilatory actions.\(^9\) However, the relative potency of these two agents when given in equivalent doses by the intracoronary route is not known. Furthermore, potential synergistic actions between nicorandil and ISDN on the coronary circulation are expected because the vasodilating mechanisms of these two drugs are considerably different. In the present study, we compared the coronary vasodilatory effects of these two drugs, attempted to establish the routine intracoronary dosage of nicorandil, and confirmed the beneficial effects of combination therapy on normal and stenotic vessel segments.

**Patients and Methods**

**Patient selection:** Informed consent for the study was obtained from 46 hospitalized patients with various heart diseases (27 men and 19 women), none of whom showed signs of congestive heart failure. The heart diseases included the following: angina pectoris (31 cases), recent or old myocardial infarction (10 cases), hypertrophic cardiomyopathy (2 cases), dilated cardiomyopathy (1 case), sick sinus syndrome (1 case), and atrial fibrillation (1 case). The study vessel was the right coronary artery, and patients with a fixed narrowing of more than 50\% of the luminal diameter of the right coronary artery or a fixed narrowing of more than 75\% of the luminal diameter of the left coronary artery were excluded.

**Method:** All antianginal drugs were withdrawn at least 12 hours before the angiographic study. All patients were premedicated with hydroxyzine pamoate, 50 mg, one hour before the procedure. The standard 12-lead electrocardiogram was monitored using radiolucent carbon electrodes throughout the study.

In the first protocol using 46 consecutive patients, induction of coronary spasm was attempted by injecting ergometrin maleate (Ergonovine\textsuperscript{®}, Fuji Co. Ltd., Tokyo, Japan, 4 µg/min for 3 min) into the right coronary artery. Patients were then assigned randomly to four groups to investigate the dose-dependent effect of intracoronary nicorandil administration. The three groups of patients received intracoronary nicorandil, 0.25, 0.5 and 1.0 mg, respectively, and those in the last group received intracoronary ISDN (Nitrol\textsuperscript{®}, Eisai Co. Ltd., Tokyo, Japan), 1.0 mg. Right coronary arteriogram was then performed. In the second protocol the same patients were randomly assigned to receive intracoronary nicorandil (0.25 or 1.0 mg) or ISDN (1.0 mg), after observation of the right coronary spasm as in the first protocol. Thereafter, the patient group assigned
nicorandil received intracoronary nicorandil (1.0 mg) or ISDN (1.0 mg) (i.e., 1.0 mg ISDN in addition to 0.25 mg nicorandil administration, and repetitive 1.0 mg nicorandil administrations). Likewise, the patients administered ISDN received an intracoronary injection of 1.0 mg of ISDN or nicorandil. Right coronary arteriographies were performed 1 min after the 1st drug administration and 2 min after the 2nd drug administration. Therefore, the second protocol was designed to investigate the relative potency of coronary dilation between ISDN and nicorandil. Nicorandil solution was prepared by dissolving nicorandil powder (2 mg per vial) in sterile saline. Sones’ technique from the right brachial artery was employed and left ventriculography was postponed until the study had been completed in order to avoid the vasodilatory effects of the large amount of contrast media (Iopamiron, Nippon Schering Co. Ltd., Tokyo Japan).

Identical projections were used for each injection of the study, i.e., left anterior oblique view at 60° projection for right coronary artery opacification. Care was taken to ensure that the x-ray tube was placed at the same distance from the patient’s chest wall throughout the study, and that identical contrast media was used for all injections. The right coronary artery luminal diameter of the three normal portions (segments 2, 3 and 4) was measured before and after nicorandil administration in the same phase of the cardiac cycle. Coronary artery luminal diameter was determined on the 35 mm cinefilms using the outer diameter of an 8F catheter as the standard. The alteration in coronary arterial diameter following the administration of each drug was converted into a percentage. Hence the coronary artery dilating ratio in the case of nicorandil or ISDN application was calculated and shown (in percentage) as the coronary artery luminal diameter after the intracoronary drug administration divided by the luminal diameter before the administration. All evaluations were conducted by the same cardiologist who was unaware of the study protocol.

Statistical analyses: All data are expressed as means ± S.D. Symbols and vertical bars indicate means and S.D., respectively. The statistical comparison was performed by Wilcoxon’s t-test. P values of 0.05 or less were considered to be statistically significant.

RESULTS

For all groups, ergometrin maleate caused a significant (p < 0.05) reduction in coronary arterial diameter compared to the control. Nicorandil increased the coronary arterial diameter in a dose-dependent manner. Nicorandil 1.0 mg and ISDN 1.0 mg exhibited almost equivalent coronary dilating effects (Figure 1). Angiographies following administration of the first and second drugs revealed a greater increase for the second drug when compared with that for the first drug.
Figure 1. Dose response curve for nicorandil after vasoconstriction induced by ergometrin maleate (Ergonovine®, Fuji Co. Ltd., Japan). Ergometrin maleate (0.012 mg/3 min) was administered to the right coronary artery selectively. Thereafter, confirming that vasoconstriction was evoked, various doses of nicorandil (0.25, 0.5, and 1.0 mg) were applied selectively. The diameter of the right coronary artery was measured before and after drug administration. Each patient received only one concentration of nicorandil. The open circles represent ISDN, closed circles represent nicorandil and vertical bars indicate the relative coronary diameter with the diameter measured before ergometrin maleate administration as a control (mean ± S.D.).

Table. Effects of Nicorandil and ISDN on Right Coronary Artery Dilation

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Ergonovine</th>
<th>1st drug</th>
<th>2nd drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA (2)</td>
<td>I</td>
<td>3.3 ± 0.6</td>
<td>2.6 ± 0.6**</td>
<td>3.6 ± 0.9**</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>3.4 ± 0.5</td>
<td>2.3 ± 0.5**</td>
<td>3.8 ± 0.4*</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>3.6 ± 0.6</td>
<td>2.6 ± 0.8*</td>
<td>3.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>3.8 ± 0.9</td>
<td>2.8 ± 0.7**</td>
<td>3.8 ± 0.8</td>
</tr>
<tr>
<td>RCA (3)</td>
<td>I</td>
<td>2.8 ± 0.4</td>
<td>2.3 ± 0.5**</td>
<td>3.2 ± 0.4*</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>2.9 ± 0.4</td>
<td>2.0 ± 0.6**</td>
<td>3.3 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>3.2 ± 0.3</td>
<td>2.1 ± 0.6**</td>
<td>3.1 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>3.4 ± 0.7</td>
<td>2.5 ± 0.8**</td>
<td>3.6 ± 1.1</td>
</tr>
<tr>
<td>RCA (4PL)</td>
<td>I</td>
<td>2.1 ± 0.5</td>
<td>1.7 ± 0.5**</td>
<td>2.4 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>2.0 ± 0.5</td>
<td>1.4 ± 0.6*</td>
<td>2.1 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>2.3 ± 0.3</td>
<td>1.6 ± 0.3**</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>2.4 ± 0.6</td>
<td>2.0 ± 0.7*</td>
<td>2.7 ± 0.8</td>
</tr>
</tbody>
</table>

*, p < 0.05, **, p < 0.01

In the protocol using 46 consecutive patients, induction of coronary spasm was attempted by injecting ergometrin maleate into the right coronary artery. Patients were then assigned randomly to four groups to investigate the coronary dilating effect of intracoronary (ic) ISDN and nicorandil administration. Group I patients received ic ISDN 1.0 mg, followed by ic nicorandil 1.0 mg. Group II patients received ic nicorandil 1.0 mg followed by ic ISDN 1.0 mg. Group III patients received ic nicorandil 1.0 mg, then ic nicorandil 1.0 mg. Group IV patients received ic ISDN 1.0 mg, then ic ISDN 1.0 mg. The right coronary artery luminal diameter of three normal portions (segments 2,3,4PL) were measured before and after drug administration in the same phase of the cardiac cycle.
Figure 2. The open circles, closed circles, open triangles and closed triangles represent groups I, II, III and IV, respectively, and vertical bars indicate the absolute right coronary diameter (mean ± S.D.). Control angiography revealed no significant difference in actual value, while angiography following ergometrin maleate loading revealed significant differences between groups II and IV ($p < 0.05$). For all groups, angiography following ergometrin maleate loading revealed significant reductions in segment (2) of right coronary arterial diameter compared with control angiography ($p < 0.05$). Both angiographies following administration of the first and second drugs revealed no significant differences among any groups or segments. Angiographies following administration of the first and second drugs revealed a significant increase in coronary diameter.

Figure 3. Similar changes were observed on segment (3) of the right coronary artery. Angiographies following administration of the first and the second drugs revealed significant increases in coronary diameter. The symbols are the same as in Figure 2.

This suggests that a further increase in the coronary diameter by the second drug relative to the first is attributable to the additive effects of two drugs with mutually different pharmacological actions in combined administration (Table, Figures 2, 3 and 4).

For all groups, control angiography revealed no significant intergroup dif-
Figure 4. The changes in diameter on segment (4PL) of the right coronary artery as in segments (2) and (3). The symbols are the same as in Figure 2.

Differences in the basal coronary tonus, while angiography following ergometrin maleate loading revealed significant differences in the segment 2 diameter between groups II and IV. However, both angiographies following administration of the first and second drugs revealed no significant differences among any groups or segments. Between the nicorandil-treated group and the ISDN-treated group, no significant difference was noted in the rate of magnification of the coronary arterial diameter following administration of each drug.

Administration of either nicorandil or ISDN as the 1st drug yielded no differences in the luminal diameters. The same was noted with the 2nd drug, suggesting an equivalent coronary dilating effect for the two drugs. Intracoronary injection of nicorandil and ISDN caused neither arrhythmia nor hypotension, at least at the dosage employed in the present study.

**DISCUSSION**

Nicorandil is a recently developed nicotinamide derivative antianginal drug which has profound dilating and cardioprotective activity following oral administration. The pharmacological properties differ from those of conventional antianginal drugs. Although this drug is a nitrate ester, its cardiovascular action differs from that of nitrate compounds in several respects. Nicorandil markedly increases coronary blood flow in a dose-dependent manner without any significant hemodynamic influences. This agent has little effect on cardiac output, arterial pressure and pulse pressure, and does not decrease myocardial contractility or oxygen consumption.

There have been few studies investigating the dose-dependent acute effects of intracoronary nicorandil on intact or stenotic human coronary arteries. A spasmolytic effect of intracoronary nicorandil administration has been reported...
in ten patients with vasospastic angina evoked spontaneously or by administration of ergometrin malate. In light of the dose dependency, another report compared low- and high-dose nicorandil therapy, however, only patients with chronic stable angina were examined. Likewise, several studies have looked at the vasodilating potency of nicorandil in comparison with that of nitrate, calcium antagonists and β-blocking agents. In the present quantitative angiographic study designed as a crossover investigation using the same patients as their own control, nicorandil demonstrated dose-dependent acute coronary dilating effects as potent as those of equivalent doses of ISDN, at least following ergometrin-induced vasoconstriction. These results are quantitatively compatible with another report from the view point of coronary circulation. However, the coronary dilating effect of nicorandil is reported to be less potent than that of nitroglycerin. The present results are not necessarily contradictory to this report, since our study aimed to compare the coronary dilating effect of nicorandil with that of ISDN and not nitroglycerin. Moreover, the difference in drug administration (i.e., intracoronary nicorandil and ISDN vs. oral nicorandil followed by sublingual nitroglycerin) may have influenced the results quantitatively. On the other hand, nicorandil is reported to exert a beneficial effect on exercise tolerance in patients with chronic stable angina pectoris to the same extent as calcium antagonist and β-blocking agents. The results of the exercise study imply that some additional mechanisms of action of nicorandil contribute to the improved exercise capacity, which is equivalent to other antianginal agents, in spite of reports of less potent coronary dilation of nicorandil relative to that of nitrates.

Nicorandil increases coronary blood flow when administered to mammals and humans, and has a potent antispastic activity. The coronary dilating mechanisms of nicorandil are ascribed to both a nitrate action which increases intracellular cyclic guanosine-3′,5′-monophosphate (cyclic GMP) and prostacyclin in vascular smooth muscle and potassium (K) channel activation that increases K conductance. The former is beneficial for the vasodilation of angiographically visible epicardial large coronary arteries, whereas the latter induces the vasodilation of resistant small coronary arteries (i.e., coronary arterioles), which are invisible angiographically. Therefore, the less potent coronary dilating effect of nicorandil compared to nitrate, if any, would be supplemented by the improved coronary microcirculation which could not be evaluated angiographically.

With recent progress in coronary investigation and intervention, a proper therapeutic strategy for the various types of angina pectoris must be determined. One is to reduce myocardial oxygen consumption under the limited oxygen delivery caused by the fixed coronary stenosis. The representative agent suitable for this pathophysiology is a β-blocking agent. The other is to relieve the dynamic...
coronary obstruction causing interruption of blood supply to the myocardium. A calcium antagonist is preferentially effective in this situation. However, there exist problems such as systemic hypotension, subsequent tachycardia and inhibition of cardiac functions associated with calcium antagonists. Unlike conventional calcium blockers, nicorandil does not inhibit calcium currents, but rather inhibits calcium release from intracellular organelles. It is reported that no significant hemodynamic changes were observed after administering nicorandil, except for a slight decrease in venous return. Moreover, nicorandil has no influence on the conduction system or on myocardial compliance and contractility.

Nicorandil, as a K channel activator, actually causes hyperpolarization, accelerates membrane repolarization and may shorten the effective refractory period (ERP) in cardiac muscle. This tendency is beneficial in the treatment of arrhythmia based on partial depolarization or a long and dispersed refractory period. This agent is also reported to suppress abnormal automaticity. Proarrhythmic effects of nicorandil which shorten the absolute value of ERP have actually been reported. However, this agent is reported to cause a relative prolongation of ERP compared with the action potential duration (APD), and the important index governing the reentrant arrhythmogenicity is the ratio of ERP/APD. In any case, neither arrhythmogenic accident nor conduction disturbance was observed in this study under the obvious coronary dilation induced by nicorandil at this dose range.

As a limitation, we admit that serial intracoronary drug delivery is not the best way to compare the vasodilatory ability of each drug or investigate the dose-responsiveness. However, this problem is irrelevant because there was no change in the effect when we changed the sequence of drug application. At present, nitrate compounds are used to improve coronary blood flow and to relieve coronary spasm, but intracoronary administration of nicorandil (1.0 mg as the minimum effective dose) is also concluded to be an effective and safe strategy for the same purposes. In conclusion, nicorandil has a coronary vasodilating effect, which is almost equivalent to that of ISDN. This agent may be useful for the treatment of IHD, and as a supportive agent during percutaneous transluminal coronary recanalization and angioplasty.

ACKNOWLEDGEMENTS

We wish to thank Chugai Pharmaceutical Company for providing the nicorandil since this agent was not yet commercialized when this study was conducted.
REFERENCES