**Angiographic Response to a Vasodilating
Drug, Nicorandil, in Patients with
Coronary Artery Disease**

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SUMMARY

To investigate the usefulness of nicorandil as an antianginal drug, we compared the coronary vasodilatory response in nonstenotic coronary artery segments and the hemodynamic response in 26 coronary artery disease patients. Both responses were studied prior to sublingual administration of 10 mg of this drug and 10, 30 and 60 min afterward. The plasma nicorandil concentration was determined up to 120 min after administration. The mean coronary dilating ratio of nicorandil was 117% 30 min after administration ($p < 0.01$) and showed a good correlation to the plasma nicorandil concentration. The mean maximum dilating ratio of each patient was 125%. There was no difference between individual coronary arteries or between proximal and distal segments in terms of the coronary artery dilating ratio. The plasma nicorandil concentration required for 120% dilation of the coronary arteries was 26 ng/ml, 89 ng/ml and 142 ng/ml for those cases with variant angina, exertional angina and postinfarction angina, respectively. Hemodynamic changes due to administration of this drug included a decrease in blood pressure, and a reduction in total peripheral resistance, rate-pressure product, pulmonary capillary pressure and stroke-work index. These results indicate that the antianginal effects of nicorandil are derived from its coronary vasodilatory action and an inhibitory effect on myocardial oxygen consumption.

Additional Indexing Words:

Nicorandil Coronary artery disease Variant angina Coronary
vasodilatory response

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NICORANDIL has noncategorical coronary vasodilatory activity.¹⁾⁻³⁾ It is known to be effective in patients with exertional angina and variant angina.⁴⁾⁻⁶⁾ There have recently been indications that coronary tonus plays a role in the mechanism which causes angina pectoris.⁷⁾ Nicorandil, with its coronary vasodilatory activity, appears to be effective as a therapeutic agent for angina. To determine the difference in the coronary vasodilatory response to nicorandil, we investigated the correlation between coronary artery dilatory response and plasma concentration of the drug in patients with exertional angina, variant angina and postinfarction angina. We also studied the antianginal activity of the drug in these angina pectoris cases as reflected by coronary vasodilatory response and hemodynamic response.

PATIENTS AND METHODS

1. Patients

Informed consent for the study was obtained from the study population consisting of 26 patients with coronary artery disease (21 men and 5 women) none of whom showed signs of congestive heart failure. The mean age was 55.3 ± 6.9 years (ranging from 40 to 65). The types of coronary artery disease included the following: variant angina (5 cases), exertional angina (6), postinfarction angina (5) and myocardial infarction without postinfarction angina (10).

A fixed narrowing of more than 75% of the luminal diameter was defined as significant coronary artery stenosis. Of the population, 6 patients had no significant coronary artery lesions, 16 patients single-vessel disease and 4 patients multi-vessel disease. Of the 26 patients, 16 had lesions in the left anterior descending coronary artery, 3 in the left circumflex artery and 6 in the right coronary artery.

2. Protocol

Antianginal drugs were discontinued the day before the study. Coronary arteriograms were taken and hemodynamic response determined prior to sublingual administration of 10 mg of nicorandil, the latter after 10 min rest. Coronary arteriograms were taken 10, 30 and 60 min after sublingual treatment with hemodynamic responses determined concurrently. Blood samples were taken 10, 20, 30, 40, 50, 60, 90 and 120 min after sublingual treatment to determine nicorandil plasma concentrations.

3. Determination of coronary artery luminal diameter

Coronary arteriograms were taken of the left and right coronary arteries each in one projection (right anterior oblique and left anterior oblique), using 4 to 7 ml of 76% urografin under the above-mentioned time conditions. Subsequent to the arteriograms, the coronary artery luminal diameter was determined before and after nicorandil administration in the same cardiac cycle for the normal portion of a total of 6 segments: the distal and proximal segments of the left anterior descending branch, the left circumflex branch and the right coronary artery. Changes in luminal diameter before and after administration were investigated by type of coronary artery disease.

Coronary artery luminal diameter was determined by enlarging the image by 1.6 times on a 35 mm cinefilm using an angiogram projection system and a picture analyzer model E-5 (Medical Systems Research Co., Ltd.). Luminal diameter was calculated from the following equation using the outer diameter of a 7F catheter (7/3 mm) as the standard: coronary artery luminal diameter (mm) = $7/3 \times \text{measured coronary artery luminal diameter} / \text{measured 7F catheter outer diameter}$. The coronary artery dilating ratio was calculated from the following equation based on the coronary artery luminal diameter before and after nicorandil administration: coronary artery dilating ratio = $\text{coronary artery luminal diameter after nicorandil administration} / \text{diameter at baseline} \times 100(\%)$. All determinations were done by the same physician. The error per 10 determinations performed on the same part was 1% or less.

4. Determination of hemodynamic response

Blood pressure was determined by placing a 7F catheter used for coronary arteriograms in the ascending aorta and the pulmonary capillary wedge pressure, pulmonary artery pressure and central venous pressure were determined by the Swan-Ganz catheter method. Cardiac output was determined by the thermodilution technique. The rate-pressure product, stroke-work index and total peripheral resistance were also determined.

5. Determination of plasma nicorandil concentration

Blood was collected a total of 72 times from 26 patients. Blood samples were centrifuged and the plasma was separated and frozen. The plasma samples were assayed for nicorandil by high pressure liquid chromatography according to Kinoshita et al.⁵⁾ The maximum plasma concentration ($C_{\max}$), time of $C_{\max}$ ($T_{\max}$) and biological half-life ($T_{1/2}$) were calculated. The regression curve was determined from the coronary vasodilating ratio and the plasma concentration at each determination time after nicorandil ad-

ministration. The plasma concentration of nicorandil required to obtain a coronary vasodilating ratio of 120% was calculated for each type of coronary artery disease.

6. Statistical analysis

All averages are expressed as mean $\pm$ standard deviation. The results were considered significant when the p value was <0.05 . The results were evaluated statistically using 2-way analysis of variance for multiple comparisons within the same group.

RESULTS

1. Coronary artery dilatory response to nicorandil

Table I shows the time course of changes in the coronary artery luminal diameter before and after nicorandil administration. The mean coronary artery luminal diameter dilating ratios were 103.4, 116.9 and 114.0% 10, 30 and 60 min, respectively, after administration when compared to the preadministration ratio. In all cases, luminal diameter became larger than that prior to administration, reaching significant values 30 and 60 min after administration ($p<0.01$ in both cases). The maximum coronary artery dilating ratio after nicorandil administration for each case was 125.2%.

Table I. Comparison of Coronary Vasodilatory Responses Before and After Nicorandil Administration (N=26)

	Before administration	After administration			Maximal dilatory response
		10 min	30 min	60 min	
RCA-proximal	2.9 $\pm$ 0.6	3.2 $\pm$ 0.7 (108.3 $\pm$ 13.5)**	3.4 $\pm$ 0.6 (119.6 $\pm$ 17.3)**	3.6 $\pm$ 0.7 (123.4 $\pm$ 19.9)**	3.7 $\pm$ 0.7 (129.8 $\pm$ 18.8)**
RCA-distal	1.3 $\pm$ 0.4	1.4 $\pm$ 0.4 (108.1 $\pm$ 21.6)	1.5 $\pm$ 0.6 (115.3 $\pm$ 34.9)*	1.5 $\pm$ 0.5 (113.2 $\pm$ 22.0)**	1.6 $\pm$ 0.5 (127.7 $\pm$ 29.4)**
LAD-proximal	2.6 $\pm$ 0.7	2.6 $\pm$ 0.5 (101.1 $\pm$ 14.6)	2.9 $\pm$ 0.6 (115.1 $\pm$ 23.0)*	2.8 $\pm$ 0.7 (108.4 $\pm$ 17.8)*	3.0 $\pm$ 0.6 (120.2 $\pm$ 21.6)**
LAD-distal	1.8 $\pm$ 0.6	1.8 $\pm$ 0.5 (100.6 $\pm$ 22.6)	2.0 $\pm$ 0.4 (115.0 $\pm$ 26.1)	2.0 $\pm$ 0.6 (110.3 $\pm$ 23.6)	2.1 $\pm$ 0.5 (123.1 $\pm$ 25.5)**
CX-proximal	2.6 $\pm$ 0.9	2.5 $\pm$ 0.7 (100.4 $\pm$ 21.2)	2.9 $\pm$ 0.8 (119.2 $\pm$ 24.8)**	2.8 $\pm$ 0.7 (116.9 $\pm$ 25.6)*	3.1 $\pm$ 0.8 (124.7 $\pm$ 23.8)**
CX-distal	1.4 $\pm$ 0.4	1.4 $\pm$ 0.5 (101.7 $\pm$ 22.0)	1.5 $\pm$ 0.4 (116.9 $\pm$ 26.3)*	1.5 $\pm$ 0.5 (111.5 $\pm$ 24.7)	1.7 $\pm$ 0.5 (126.2 $\pm$ 23.9)**
Total	2.1 $\pm$ 0.9	2.1 $\pm$ 0.9 (103.4 $\pm$ 19.5)	2.4 $\pm$ 0.9 (116.9 $\pm$ 25.4)**	2.4 $\pm$ 1.0 (114.0 $\pm$ 22.6)**	2.6 $\pm$ 1.0 (125.2 $\pm$ 23.8)**

CX=left circumflex artery; LAD=left anterior descending coronary artery; RCA=right coronary artery. Values are expressed as mean $\pm$ standard deviation. Values in parentheses were calculated as a ratio to coronary artery luminal diameter before nicorandil administration.

* $p<0.05$ (vs Before), ** $p<0.01$ (vs Before).

The coronary artery dilating ratio following nicorandil revealed dilation of all of the coronary arteries. Of these, a significant increase was noted in both the proximal and distal segments of the right coronary artery regardless of time. Significant dilation of the proximal parts of the left coronary artery and the left circumflex branch was also observed. However, there was no significant dilation of distal segments, with the exception of the left circumflex branch 30 min after administration.

The maximum dilating ratio of each part of the coronary arteries by type of coronary artery disease was 132.3, 125.3, 123.6 and 121.9% in the cases of variant angina, exertional angina, myocardial infarction without angina and postinfarction angina, respectively. The dilating ratio was largest in the variant angina cases and smallest in the postinfarction angina cases.

2. Cardiac hemodynamic response

Hemodynamic responses before and after nicorandil administration are shown in Table II.

Table II. Hemodynamic Responses to 10 mg of Nicorandil (N=26)

	Before administration	After administration		
		10 min	30 min	60 min
SP (mmHg)	116±21	117±20 (100.6±4.8)	107±17 (92.8±6.1)**	101±19 (88.4±5.1)**
DP (mmHg)	66±11	67±11 (100.5±5.3)	63±9 (96.3±7.6)**	63±10 (95.4±7.0)**
HR (beats/min)	70±10	71±10 (102.1±8.2)	74±11 (106.7±9.3)**	72±11 (103.8±10.4)
PRP (mmHg·beats/min)	8133±2079	8302±2060 (102.9±11.3)	7962±1826 (99.2±12.7)	7368±1666 (91.8±11.5)**
PCWP (mmHg)	6.2±2.7	5.9±2.7 (99.4±24.6)	5.4±2.4 (91.1±25.9)*	4.5±2.1 (79.8±26.1)**
CVP (mmHg)	5.2±2.5	4.9±2.5 (95.5±17.9)	4.9±2.4 (98.3±25.9)	4.5±2.0 (96.1±32.6)
CI (L/min/m ²)	3.1±0.4	3.2±0.5 (101.8±8.4)	3.2±0.4 (101.6±9.0)	3.1±0.5 (99.3±10.3)
SWI (L·mmHg/min/m ²)	49.0±10.6	48.8±10.6 (100.4±11.8)	44.5±10.5 (91.3±12.3)**	44.4±8.9 (90.6±14.9)**
PVR (dyne/sec/cm ⁻⁵)	1284±296	1269±274 (99.7±10.8)	1191±264 (94.0±11.5)**	1191±287 (93.6±11.5)**

CI=cardiac index; CVP=central venous pressure; DP=diastolic pressure; HR=heart rate; PCWP=pulmonary capillary wedge pressure; PRP=pressure-rate product; PVR=total peripheral resistance; SP=systolic pressure; SWI=stroke-work index. Values are expressed as mean ± standard deviation. Values in parentheses were calculated as a ratio to hemodynamic response before nicorandil administration.

* p<0.05 (vs Before), ** p<0.01 (vs Before).

Systolic and diastolic pressure, rate-pressure product, pulmonary capillary wedge pressure, stroke-work index and total peripheral resistance showed a tendency to decrease either to some extent or significantly 30 min and 60 min after administration compared to the pretreatment values. Heart rate increased significantly from the pretreatment level 30 min after administration ($p < 0.01$). Therefore, although there were some changes 10 min

Fig. 1. Plasma nicorandil concentration after sublingual administration of 10 mg nicorandil. Values are expressed as mean $\pm$ standard deviation. $C_{max} = 118.3 \pm 61.3$ ng/ml, $T_{max} = 45.4 \pm 17.5$ min, $T_{1/2} = 60.8 \pm 57.8$ min.

Fig. 2. Relationship between dilatory response of right coronary artery (proximal segment) and plasma nicorandil concentration in each type of angina pectoris.

- : VA; Variant angina $r = 0.8105$ $p < 0.001$, $y = 0.4710x + 107.5334$
- : EA; Exertional angina $r = 0.5791$ $p < 0.05$, $y = 0.2035x + 101.8013$
- ▲: PIA; Postinfarction angina $r = 0.5971$ $p < 0.05$, $y = 0.1211x + 102.8241$
- ×: MI; Myocardial infarction without angina $r = 0.2783$, $y = 0.0739x + 106.2200$
- Total (dotted line): All cases $r = 0.4589$ $p < 0.001$, $y = 0.1543x + 106.5361$

after sublingual administration of nicorandil, significant changes in hemodynamic response were observed 30 min afterward and the response persisted until 60 min after administration.

3. Coronary vasodilating ratio and nicorandil plasma concentration

Changes in plasma concentration by sublingual administration of 10 mg of nicorandil are shown in Fig. 1. T_{max} was 45.4 ± 17.5 min, C_{max} 118.3 ± 61.3 ng/ml and $T_{1/2}$ 60.8 ± 57.8 min.

Figure 2 shows the relations between the coronary artery dilating ratios for the proximal segments of the right coronary artery, which demonstrated a marked dilating response, and nicorandil plasma concentration by type of disease. Though a significant positive correlation was noted between the ratio and the plasma concentration for all types of coronary artery disease, the strongest correlation was observed with variant angina. The plasma concentrations required to dilate coronary arteries to 120% are 26 ng/ml, 89 ng/ml, 102 ng/ml and 142 ng/ml for variant angina, exertional angina, myocardial infarction without angina and postinfarction angina, respectively. In one postinfarction angina case which involved progression from variant angina to myocardial infarction, a marked dilation was observed at a low plasma concentration.

DISCUSSION

Coronary artery dilatory response to nicorandil:

The coronary artery maximum dilating ratio was reached 30 to 60 min after sublingual administration of nicorandil in the present study. A positive correlation was observed between this dilatory response and the nicorandil plasma concentration. A comparison between the dilatory responses of coronary artery segments indicated that the response was somewhat greater in the proximal part of the right coronary artery than in other segments. However, a significant difference was not observed.

According to Suryapranata et al,⁸⁾ the dilating ratio 30 min after sublingual administration of 20 mg of nicorandil is +9% at the proximal part of the left anterior descending coronary artery, +10% at the midportion, and +15% at the distal part. It is +13% at the proximal part of the circumflex artery and +10% at the distal part. All of these values are low compared to our findings. Suryapranata et al⁸⁾ used a dose of 20 mg instead of 10 mg administered in the present study. Their dilating ratio was lower, regardless of the high dose. This may be due to the fact that the T_{max} of the plasma concentration for this drug is 45.4 min. The ratio might have

been higher had they performed the determination 45 min after nicorandil administration. However, the correlation with the plasma concentration alone cannot account for our higher dilating ratio 30 min afterward.

Differences in determination methods, determination sites, and the types of coronary artery disease are also likely to affect the results. However, the first two factors do not account for differences in our results, because our determination methods and sites are the same as those of Suryapranata et al.⁸⁾

The patients of the present study included those with variant angina, exertional angina, and myocardial infarction. Of these, the dilating ratio of the variant angina cases was higher than those in other types of coronary artery disease. Inclusion of variant angina cases among our subjects may have been responsible for any differences between the dilatory responses we have reported and those by Suryapranata et al.⁸⁾

According to reports presented so far, the diameter of the large coronary arteries in coronary artery disease patients increased 12% to 29% after intracoronary or sublingual treatment with nitroglycerin or isosorbide dinitrate.⁹⁾⁻¹¹⁾ These ratios are comparable to the nicorandil dilating ratio in the present study. It has been recently suggested^{9),10),12)-14)} that nitroglycerin dilates both normal and stenotic coronary arteries in patients. In the present study we did not investigate the dilatory response of stenotic coronary arteries to nicorandil treatment and therefore, we do not deal with this point.

Antianginal effect of nicorandil:

The dilatory response was greatest in the cases with variant angina followed by exertional angina and postinfarction angina, in that order. There was a positive correlation between the coronary artery dilatory response and nicorandil plasma concentration. This correlation varied with the type of coronary artery disease. These findings may be helpful in describing the mechanism causing each type of coronary artery disease and the effects of nicorandil.

On the other hand, the hemodynamics of nicorandil are connected to a drop in blood pressure, and a reduction in total peripheral resistance, rate-pressure product, pulmonary capillary wedge pressure and stroke-work index. There are reports of an increase in venous return in response to this drug¹⁵⁾ as well as reports of a reduction in venous return.¹⁶⁾ Although it is unclear whether the results are based on preload or afterload changes, the present study demonstrated an inhibitory effect on myocardial oxygen consumption based on a reduction in left ventricular wall tension. The study

therefore indicated a possibility of nicorandil having antianginal effects against exertional angina and postinfarction angina.

As described above, nicorandil showed both vasodilatory action and inhibitory effects against myocardial oxygen consumption. Therefore, it is likely that each type of angina has a different coronary vascular tone and that the antianginal effects of nicorandil are also different depending upon the type of angina pectoris.

REFERENCES

1. Uchida Y, Yoshimoto N, Murao S: Effect of 2-nicotinamidoethyl nitrate (SG-75) on coronary circulation. *Jpn Heart J* **19**: 112, 1978
2. Sakai K, Shiraki Y, Nabata H: Cardiovascular effects of a new coronary vasodilator N-(2-hydroxyethyl) nicotinamide nitrate (SG-75): comparison with nitroglycerin and diltiazem. *J Cardiovasc Pharmacol* **3**: 139, 1981
3. Furukawa K, Itoh T, Kajiwara M: Vasodilating actions of 2 nicotinamidoethyl nitrate on porcine and guinea pig coronary arteries. *J Pharmacol Exp Ther* **218**: 246, 1981
4. Murao S, Kimura E: Clinical effect of nicorandil on angina pectoris: a double-blind trial in comparison with propranolol. *Jpn J Clin Pharmacol Ther* **13**: 311, 1982
5. Kinoshita M, Nishikawa S, Sawamura M, Yamaguchi S, Mitsunami K, Itoh M, Motomura M, Bito K, Mashiro I, Kawakita S: Comparative efficacy of high-dose versus low-dose nicorandil therapy for chronic stable angina pectoris. *Am J Cardiol* **58**: 733, 1986
6. Kishida H, Murao S: Effect of a new coronary vasodilator, nicorandil, on variant angina pectoris. *Clin Pharmacol Ther* **42**: 166, 1987
7. Gould KL: Dynamic coronary stenosis. *Am J Cardiol* **45**: 286, 1980
8. Suryapranata H, Serruys PW, Feyter PJ, Verdouw PD, Hugenholtz PG: Coronary vasodilatory action after a single dose of nicorandil. *Am J Cardiol* **61**: 292, 1988
9. Schulz W, Anderten WV, Rieber JHC, Bernauer R, Kaltenbach M, Kober G: Active and passive coronary vasodilation after intracoronary and sublingual nitroglycerin. *Z Kardiol* **72** (suppl 3): 82, 1983
10. Feldman RL, Pepine CJ, Curry RC, Conti CR: Coronary arterial responses to graded doses of nitroglycerin. *Am J Cardiol* **43**: 91, 1979
11. Rafflenbeul W, Urthaler F, Russell RO, Lichtlen P, James TN: Dilation of coronary artery stenoses after isosorbide dinitrate in man. *Br Heart J* **43**: 546, 1980
12. Brown BG, Bolson E, Peterson RB, Pierce CD, Dodge HT: The mechanisms of nitroglycerin action: stenosis vasodilation as a major component of the drug response. *Circulation* **64**: 1089, 1981
13. Rafflenbeul W, Lichtlen PR: Quantitative coronary angiography: evidence of a sustained increase in vascular smooth muscle tone in coronary stenoses. *Z Kardiol* **72** (suppl 3): 87, 1983
14. Brown BG: Response of normal and diseased epicardial coronary arteries to vasoactive drugs: quantitative arteriographic studies. *Am J Cardiol* **56**: 23E, 1985
15. Taira N, Satoh K, Yanagisawa T, Imai Y, Hiwatari M: Pharmacological profile of a new coronary vasodilator drug, 2-nicotinamidoethyl nitrate (SG-75). *Clin Exp Pharmacol Physiol* **6**: 301, 1969
16. Nakagawa Y, Takeda K, Katano Y, Tsukada T, Kitagawa T, Otorii T, Imai S: Effects of 2-nicotinamidoethyl nitrate on the cardiovascular system. *Jpn Heart J* **20**: 881, 1979