Cardiovascular Drugs and Therapy 1995;9:755–761

Effect of Nicorandil on Abnormal Coronary Flow Reserve Assessed by Exercise ^{201}Tl Scintigraphy in Patients with Angina Pectoris and Nearly Normal Coronary Arteriograms

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Summary. **The purpose of the present study is to assess the effect of nicorandil, a coronary vasodilator with a mechanism of potassium channel opening, on the abnormal myocardial ^{201}Tl perfusion evoked by exercise. Eleven patients who had a history of typical angina, positive exercise electrocardiograms, positive ^{201}Tl scintigraphy, nearly normal coronary arteriograms, and negative coronary vasospasm underwent exercise ^{201}Tl scintigraphies under no medication (baseline test) and administration of nicorandil (nicorandil test). ^{201}Tl was injected at a matched workload in both tests. Nicorandil did not alter heart rate, blood pressure, or the rate-pressure product at the end of the exercise, but it significantly improved the extent score from 0.37 ± 0.22 to 0.20 ± 0.15 ($p < 0.05$) and the severity score from 33.9 ± 32.2 to 13.5 ± 16.4 ($p < 0.05$), and also significantly hastened the ^{201}Tl mean washout rate from 30.5 ± 14.8% to 37.4 ± 13.1% ($p < 0.05$). Anginal symptoms disappeared in 3 of 5 cases and ST depression improved in 5 of 7 cases after nicorandil. We conclude that nicorandil augments coronary flow reserve, possibly due to a reduction of vasotone in the small coronary arteries.**

Cardiovasc Drugs Ther 1995;9:755–761

Key Words. **angina pectoris and normal coronary arteriograms, exercise test, ^{201}Tl scintigraphy, nicorandil, small coronary arteries**

Patients with angina pectoris and normal coronary arteriograms have reduced coronary flow in response to metabolic and pharmacologic vasodilating stimuli [1–3]. Small coronary arteries, including prearterioles and arterioles, are postulated as sites of the coronary flow limitation [4,5]. The impaired coronary flow may be reversible because calcium antagonists have been reported to improve myocardial ischemia [6–8]. However, the benefits of other antianginal drugs are not in agreement [6,9–12]. Nicorandil is a coronary vasodilator affecting both small arteries and large conductance arteries by activation of potassium conductance as well as guanosine monophosphate (GMP) cyclase [12–14]. Our hypothesis is that nicorandil can improve coronary flow reserve in patients with angina pectoris and normal coronary arteriograms. In the present study we assessed quantitative indices of myocardial thallium-201 (^{201}Tl) perfusion during exercise and determined the effect of the agent on coronary flow.

Methods

Subjects

Eleven patients (8 males and 3 females; mean age 56 ± 11 years, range 35–69 years) were studied. The entry criteria of the subjects for this study were as follows: patients who had a history of typical anginal chest symptoms on effort or at rest, a normal resting electrocardiogram (ECG), a positive exercise ECG response (ST depression ≥1.0 mm with horizontal or downslope shape, at least twice but not always reproducible), angiographically normal or nearly normal coronary arteries, a negative provocation for epicardial coronary spasm, and a positive perfusion defect in exercise ^{201}Tl scintigraphy. From November 1990 to March 1992, we performed coronary arteriograms for diagnosis of angina pectoris in 125 cases who had not had previous percutaneous transluminal angioplasty, previous myocardial infarction, myocarditis, cardiomyopathy, or valvular heart disease, including mitral valve prolapse and congenital heart disease. Fifty-three out of these 125 cases had normal or nearly normal angiographic findings. Forty-nine cases

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Received 15 July 1994; receipt/review time 10 months; accepted in revised form 12 May 1995

underwent a vasospasm provocation test with intracoronary acetylcholine or ergonovine malate, and 26 cases showed a positive vasospasm, 7 cases showed an equivocal response, and 16 cases showed a negative vasospasm. Thirteen out of these 16 cases revealed the perfusion defect in the exercise ^{201}Tl scintigraphy. Thus, 13 cases were candidates for this study. Finally, 11 cases agreed to enter into the present study.

Echocardiographic left ventricular hypertrophy was not found in any subjects. Antianginal medications were discontinued at least 1 week prior to the study in all patients. The protocol was approved by the Institutional Research Committee of the Kobe University School of Medicine. The risks of the study were fully explained to all patients, and written informed consent was obtained.

Study design

Patients repeated exercise ^{201}Tl scintigraphy twice on separate days. The first test was performed without medication (baseline test), and the second was done after administration of nicorandil (nicorandil test). The interval was 7 ± 6 days (3–14 days). A 4 mg bolus of intravenous nicorandil was administered 5 minutes before exercise. Patients exercised to the maximal symptomatic point in the baseline test and to the same workload in the nicorandil test. The coronary flow reserve was assessed by quantitative indices of ^{201}Tl myocardial perfusion, as described later.

Exercise ^{201}Tl scintigraphy

All patients underwent symptom-limited ergometer exercise testing until they felt chest pain or leg fatigue. Heart rate (HR), blood pressure (BP), and electrocardiography were recorded serially. The rate-pressure product (RPP) was calculated as HR × systolic BP. After bolus injection of 111 MBq ^{201}Tl, patients continued exercise for 1 more minute. Five minutes later, the initial ^{201}Tl single photon emission computed tomography (SPECT) image was collected by a rotating gamma camera (ZLC75ECT, Siemens Medical Systems) interfaced with a computer (Scintipac 2400, Shimazu Medical System). Delayed images were also taken 3 hours later. The image was constructed into transaxial sections with a Butterworth and Wiener–type filter. The images were reconstructed along the horizontal axis, vertical axis, and coronal axis. The perfusion defect and redistribution phenomenon were identified visually by three skilled investigators without any information from the coronary arteriograms.

The ^{201}Tl SPECT images were quantified by means of a computerized two-dimensional polar map of the coronal section. Circumferential profile curves of each slice were drawn and compared with those obtained from the normal control subjects. An extent map and severity map were determined by subtracting the patient's polar map from the normal map. The ratio of the number of the pixels below normal limits to total pixels was defined as the extent score, which expresses the area of ischemia. The severity score was calculated as the sum of abnormal pixels below two standard deviations from the normal mean values. This expresses the severity of ischemia. The normal range was based on the accumulated data of control subjects in our laboratory. It is below 0.1 for the extent score and below 5.0 for the severity score. In the same manner, the mean washout rate (%) was calculated as the total counts of the initial polar map minus the counts of the delayed polar map divided by the counts of the initial polar map. The normal range was set above 40%. The above-mentioned indices were compared for the baseline and nicorandil tests.

Cardiac catheterization

All patients underwent a selective coronary arteriogram without pretreatment with nitroglycerin. If the baseline arteriogam was normal or nearly normal, a vasospasm provocation test with intracoronary administration of acetylcholine or ergonovine was performed. Then, intracoronary nitroglycerin was administered. Luminal reduction was judged by a comparison between the nitroglycerin and provocative arteriograms. In this study, *negative vasospasm* was defined as the coronary luminal diameter not being reduced by more than 50% by provocative test. *Luminal stenosis* was based on the American Heart Association classification.

Statistical analysis

The comparison between the baseline and nicorandil tests was analyzed by the paired t test. The comparison between subgroups was done by the Wilcoxon signed rank test. Statistical significance was defined as a p value less than 0.05. The results were expressed as the mean ± standard deviation.

Results

Patient features

Anginal symptoms had been present for 15 ± 19 months (2 months to 5 years) at the start of the study. Patients complained of typical anginal chest symptoms at rest in five cases, on effort in one case, and both at rest and on effort in five cases. Nine patients also complained of atypical chest symptoms. Seven of 11 patients had at least one of the following characteristics: hypertension (two cases), hypercholesterolemia (three cases), smoking (four cases), and diabetes (one case). Resting electrocardiography was normal in all patients, and echocardiographic abnormalities, including left ventricular hypertrophy, were not found in any patient. Coronary arteriograms revealed smooth walls in seven cases and nonsignificant stenoses in four cases. Intracoronary administration of acetylcholine or ergonovine did not cause excessive vasoconstriction in any of the patients, although it provoked

mild vasoconstriction, with 50% luminal stenosis, in three cases.

Results of baseline exercise test and ^{201}Tl SPECT

Table 1 provides a summary of the results. In the baseline exercise test, the workload was 78 ± 29 watts. Typical anginal symptoms were provoked in five cases; the remaining six cases stopped exercise because of leg fatigue. Ischemic ST depression was noted in seven cases. Four cases showed both typical anginal symptoms and ST-segment depression. Four cases showed either anginal symptom or ST-segment depression. Three cases did not show either.

The initial ^{201}Tl SPECT images revealed perfusion defects in all cases, and the delayed images confirmed the redistribution in all cases. The quantitative indices of ^{201}Tl SPECT also showed abnormalities. The mean washout rate was abnormal in nine cases (30.5 ± 14.8%, range 4–51%). The extent score was abnormal in all cases (0.37 ± 0.22, range 0.10–0.83). The severity score was abnormal in 10 cases (33.9 ± 32.2, range 2.1–108.6). These indices were not significantly different between patient subgroups characterized by the presence or absence of exercise-induced angina in the baseline test, ischemic ST-segment depression in the baseline test, coronary risk factors, nonsignificant coronary wall stenosis, or the provoked vasoconstriction with 50% stenosis.

Effects of Nicorandil

In the resting state just before exercise, hemodynamic parameters (HR, BP, and RPP) did not differ significantly between the baseline and nicorandil tests. Hemodynamic data at the peak workload also did not differ significantly between the two tests; that is, HR was 132 ± 21 beats/min in the baseline test versus 131 ± 21 beats/min in the nicorandil test (ns), systolic BP was 198 ± 21 mmHg versus 194 ± 29 mmHg (ns), and RPP was 26,300 ± 6100 mmHg · beats/min versus 25,800 ± 6800 mmHg · beats/min (ns). However, angina symptoms disappeared after administration of nicorandil in 3 out of the 5 patients who had complained of angina in the baseline test. The ST-segment depression also improved after nicorandil in 5 out of 7 cases (in 4 cases it disappeared); however, the degree of ST-segment depression deteriorated in one case after nicorandil.

Nicorandil hastened the ^{201}Tl mean washout rate in seven cases, and the average value was significantly improved from 30.5 ± 14.8% to 37.4 ± 13.1% ($p < 0.05$), as shown in Figure 1. The extent score was reduced in 8 of 11 cases, and the average value was significantly improved from 0.37 ± 0.22 to 0.20 ± 0.15 ($p < 0.05$) after nicorandil (Figure 2A). The severity score was also decreased in 8 of 11 cases, and the average value was significantly improved from 33.9 ± 32.2 to 13.5 ± 16.4 ($p < 0.05$) after nicorandil (Figure 2B). The presence or absence of coronary risk factors, nonsignificant coronary stenosis, and 50% luminal reduction in the provocative arteriogram did not relate to the effect of nicorandil. Figure 3 shows representative ^{201}Tl SPECT images of a case. Details are described in the legend.

Discussion

The present study demonstrates that the administration of nicorandil improves exercise-induced angina,

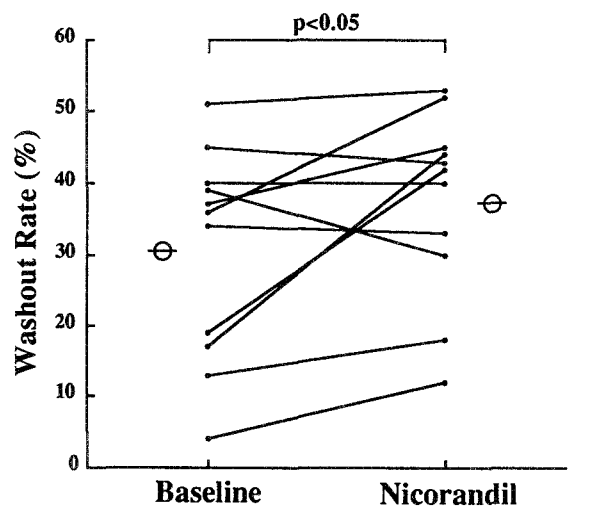

Fig. 1. *Comparison of washout rate between the baseline and nicorandil tests. The mean washout rate of ^{201}Tl was significantly hastened from 30.5 ± 14.8% to 37.4 ± 13.1% ($p < 0.05$) by nicorandil.*

Table 1. *Summary of results of exercise thallium-201 scintigraphy*

	Workload (watt)	Rest HR (bpm)	Peak HR (bpm)	Rest BP (mmHg)	Peak BP (mmHg)	Rest RPP (mmHg · bpm)	Peak RPP (mmHg · bpm)	ST change (cases)	Angina (cases)	Washout rate (%)	Extent score	Severity score
Baseline test	78 ± 28	79 ± 15	132 ± 21	146 ± 21	198 ± 21	11500 ± 3000	26300 ± 6100	7 out of 11	5 out of 11	30.4 ± 14.8	0.37 ± .022	33.9 ± 32.2
Nicorandil test	78 ± 28	79 ± 7	131 ± 21	138 ± 24	194 ± 29	10800 ± 2300	25800 ± 6800	3 out of 11	3 out of 11	37.4 ± 13.1	0.20 ± 0.15	13.5 ± 16.4
p value	ns	ns	ns	ns	ns	ns	ns	ns	ns	<0.05	<0.05	<0.05

HR = heart rate; BP = blood pressure; RPP = rate pressure product.
p value compares the baseline test versus the nicorandil test.

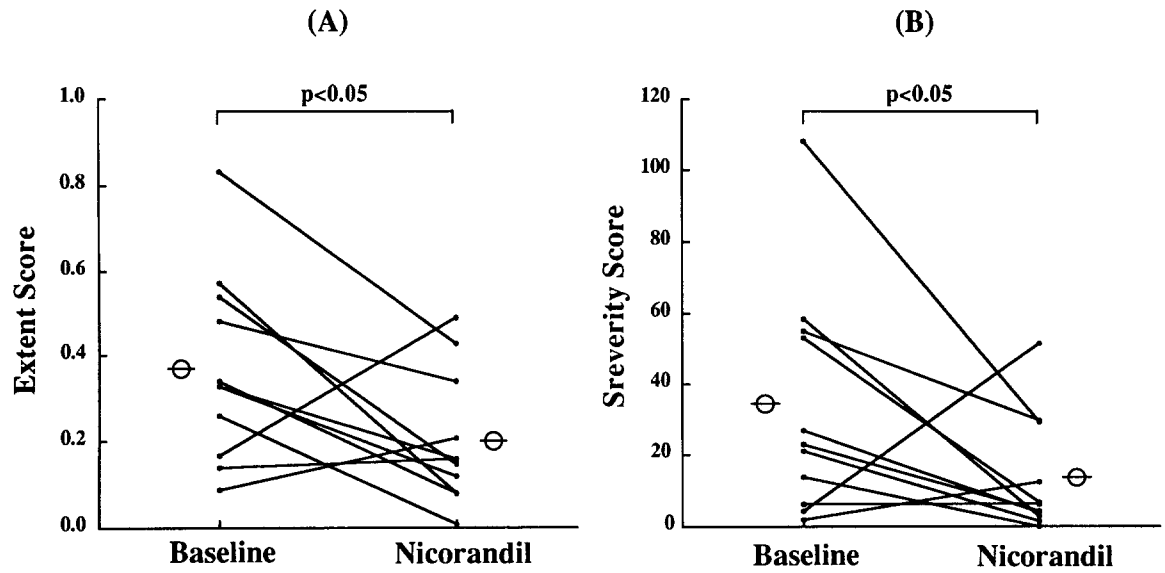

*Fig. 2. Comparison of extent score and severity score between baseline and the nicorandil tests. The extent score was significantly improved from 0.37 ± 0.22 to 0.20 ± 0.15 ($p < 0.05$; **A**), and the severity score was also significantly improved from 33.9 ± 32.2 to 13.5 ± 16.4 ($p < 0.05$; **B**) by nicorandil.*

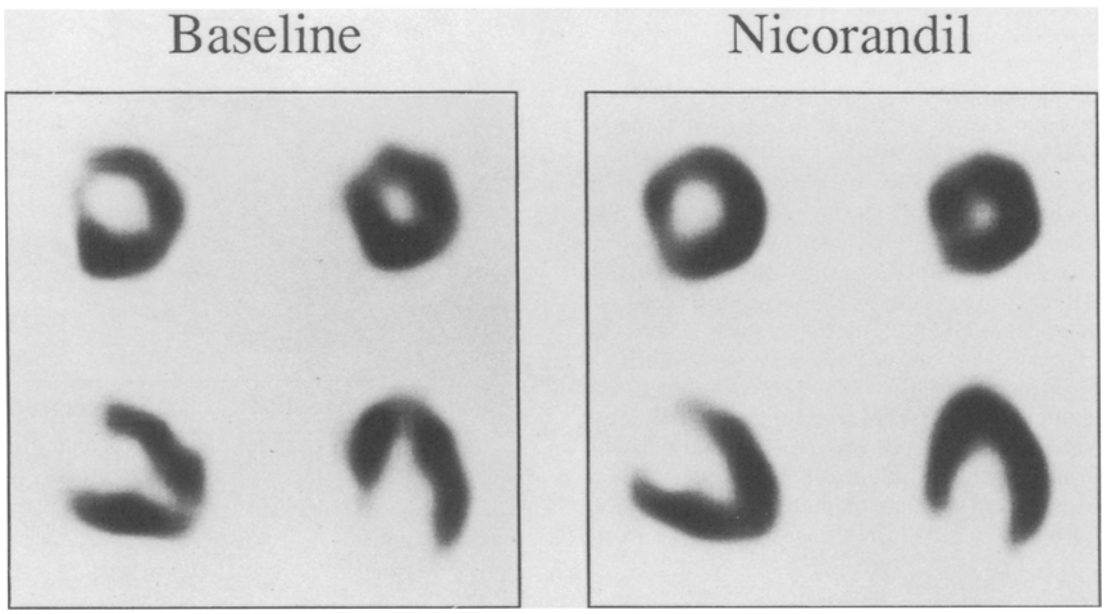

Fig. 3. A representative ^{201}Tl image. A ^{201}Tl image of a 43-year-old female, whose exercise test caused ischemic ST-segment depression but not angina. The baseline initial image (left panel) showed hypoperfusion in the apex, septum, anterior wall, and lateral wall; however, ^{201}Tl perfusion improved in all the areas after the administration of nicorandil. The mean washout rate was hastened from 17% to 44%, the extent score decreased from 0.33 to 0.12, and the severity score also decreased from 23.1 to 4.3.

ST-segment depression, ^{201}Tl perfusion, and the mean washout rate in patients with angina pectoris and nearly normal coronary arteriograms. Angina pectoris with normal coronary arteriograms is a syndrome with various clinical signs [5,15,16]. The patients in our study were selected using standard criteria. However, our criteria were not very strict in several areas; namely, exercise stress did not always cause angina or ST-segment depression, and some patients had coronary risk factors, minimal coronary lesions, or mild vasoconstriction. Recently a new disease entity, the *insulin resistance syndrome* [17] (metabolic syndrome X), has been proposed as a high risk factor for coronary atherosclerosis associated with microvascular angina [18]. These characteristics fit our subjects, although we did not verify this by performing an insulin resistance test. We consider such a profile to be rather common in patients with angina pectoris and normal coronary arteriograms [19]. The most important criterion in our study was confirmation of impaired coronary flow by exercise ^{201}Tl scintigraphy. This may be essential to evaluate the effect of antiischemic drugs.

There has been controversy with regard to angina pectoris in patients with normal coronary arteries over the presence of myocardial ischemia [2,15,20–26] and histologic lesion of the small coronary arteries [23,27]. However, numerous investigations have shown abnormal coronary flow reserve and/or abnormal coronary resistance [1–3,28,29]. Tweddel et al. showed that the ^{201}Tl scan was very sensitive in detecting abnormal coronary flow in syndrome X (98 out of 100 patients) [30], although positron emission tomography was reported to be more sensitive for diagnosing heterogeneous perfusion [31]. We analyzed quantitative indices of ^{201}Tl perfusion. The extent score and severity score were useful for avoiding bias in visual inspection. The mean washout rate has the additional advantage of detecting generalized homogeneous hypoperfusion, and increased coronary flow hastens ^{201}Tl washout. In the baseline exercise test, anginal symptoms and ST-segment depression were negative in six and four patients, respectively. This is not surprising because ST-segment depression is a less sensitive sign in microvascular angina [32], and chest pain is not always provoked by effort in syndrome X [5]. The relatively high incidence of resting angina in our subjects may indicate that the functional abnormality in small arteries [33–37] in addition to the anatomical lesion, is important for interpreting intermittently positive findings in exercise-induced angina.

The therapeutic strategy for patients with angina pectoris and normal coronary arteriograms has yet to be established. It seems reasonable to expect benefits from vasodilating drugs that affect small coronary arteries. The present study focused on nicorandil, which dilates vessels via a nitrate-like action and potassium channel opening [12]. Significant reduction in the extent and severity score was found after nicorandil, which indicates that coronary flow became homogeneous over the myocardium. Low-dose nicorandil causes only a minimal change in HR, BP, RPP, cardiac output, and pulmonary capillary pressure during exercise as well as the resting state [38]. The hemodynamic measurements in our study were consistent with this report. Thus, we suspect that decreased cardiac work brought about by hemodynamic alteration, or increased coronary flow associated with increased cardiac output, might not be the cause of the improved ^{201}Tl perfusion. One might speculate that the improvement resulted from opening of potassium channels in the myocardium to augment the conductance of thallium into myocardial cells. However, this speculation seems unlikely for several reasons. First, vasodilation with nicorandil was reported to occur prior to the myocardial action resulting from potassium channel opening [39]. Second, relief of angina and ST-segment depression was associated with improved ^{201}Tl perfusion in our patients. Third, the mean washout rate was significantly hastened after nicorandil, which suggests that coronary flow was increased. Thus, we think that nicorandil primarily augments coronary flow in response to exercise.

These results agree with the preliminary report by Yamazaki et al. [40], who showed a beneficial effect of nicorandil on exercise ^{201}Tl perfusion in patients, including two cases of syndrome X. It has been reported that verapamil [6,7], nifedipine [7,8], and aminophylline [36] relieve anginal symptoms and ST-segment changes, but, beta-blockers [6,9], nitrates [10], clonidine, and prazosin [11] do not, or are controversial. These results suggest that calcium equilibrium and adenosine concentration are important, but cyclic GMP formation and sympathetic alpha or beta receptor–mediated regulation are not, or are less important. Nicorandil activates both GMP cyclase [41,42] and the potassium channel. The latter leads to vasodilation, especially in the small arteries [12–14], rather like a calcium antagonist [14,43–45]. We postulate that nicorandil can produce an additional benefit if the potassium channel of small coronary arteries is involved in patients with angina pectoris and normal coronary arteriograms.

Limitations of this study

Although we did not measure the plasma concentration of nicorandil in this study, previous measurements [46] determined it to be 238 ± 58 ng/ml, which exceeded the level reported to be effective for angina pectoris [41]. Since four subjects revealed nonsignificant atherosclerotic lesions, it may be considered that the improvement resulted from vasodilation of large coronary arteries. However, the conductance arteries have a small resistance component, and the presence or absence of nonsignificant lesions did not affect the efficacy of nicorandil. Patient profiles that include hypertension and diabetes, however, would limit the

value of our study because such conditions lead to an impaired coronary microcirculation [47–49]. The abnormal coronary flow in our patients could be the result of an interaction among different pathophysiological states. The effect of nicorandil on each state remains unclear. Our inferences have to be limited to the patient category defined by the diagnostic criteria chosen. Future studies that address the broader questions raised in this study are warranted.

Conclusions

Nicorandil improves coronary flow reserve as assessed by exercise ^{201}Tl scintigraphy in patients with angina pectoris and nearly normal coronary arteriograms, possibly due to opening of the potassium channels of the small arteries.

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