Hemodynamic Mechanisms of Antianginal Action of Calcium Channel Blocker Nisoldipine in Dynamic Exercise-Induced Angina

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To investigate the mechanism of antianginal action of the calcium channel blocker nisoldipine and to determine the reproducibility of the clinical and hemodynamic events induced by supine leg exercise, 30 patients with stable effort angina pectoris were studied. They were divided into two groups; one group of 19 patients received a single 10-mg dose of nisoldipine orally, and the other group of 11 patients received a single dose of placebo orally. Chest pain was induced in all of 30 patients during the control exercise test. After nisoldipine administration, chest pain was not induced in 13 of 19 patients and was of lessened severity in five patients with the same work load as those performing control exercise. ST segment at peak exercise showed less severe depression after nisoldipine. Systemic vascular resistance was reduced by 38% (p<0.001) at rest and 22% (p<0.001) at peak exercise, and coronary vascular resistance was reduced by 31% (p<0.001) at rest and 18% (p<0.01) at peak exercise. Pulmonary artery wedge pressure fell from 6±1 to 3±1 mm Hg (p<0.001) at rest and from 28±3 to 11±2 mm Hg (p<0.001) at peak exercise. Coronary sinus flow at rest and myocardial oxygen uptake both at rest and during exercise was not modified by nisoldipine. However, coronary sinus flow at peak exercise increased significantly from 219±24 to 249±31 ml/min (p<0.01) after nisoldipine, and myocardial oxygen uptake was not significantly changed despite decreased coronary vascular resistance. The clinical and hemodynamic events induced by the exercise during invasive studies (except pulmonary artery wedge pressure at rest) were reproducible after placebo administration. Our data demonstrate that increased coronary blood flow could be the major mechanism of the antianginal action of nisoldipine in supine leg exercise-induced angina. (Circulation 1990;81:1887–1898)

Calcium channel blockers have obtained wide acceptance in the treatment of exercise-induced angina pectoris. Recently, much interest has been focused on the mechanisms of their antianginal actions and their effects on exercise performance in patients with angina. The exact mechanisms are multifactorial and complex and are related to a combination of effects on heart rate, myocardial contractility,1–3 possibly myocardial oxygen supply through coronary vasodilation,4 and peripheral vascular resistance. The various calcium channel blockers are not equal in their systemic vascular, coronary vascular, electrophysiological, and myocardial effects.5–8 Negative inotropic effect of the drug in intact human is variable and controversial. Accordingly, it is reasonable to consider that these drugs might have different effects on rest and exercise left ventricular performance in patients with exercise-induced angina pectoris.

Nisoldipine is a calcium channel blocker of the dihydropyridine class, similar in chemical structure to nifedipine,9,10 and exhibits greater smooth muscle selectivity than the parent compound, resulting in more potency as a vasodilator with fewer myocardial depressant effects.10 Oral administration of nisoldipine has been shown to have antianginal effects in recent clinical trials.11,12 However, it is still unclear

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whether the beneficial effects of the drug are achieved by a decrease in myocardial oxygen demand at any level of exertional stress or if they are a result of an increase in myocardial oxygen supply in humans.

Dynamic exercise is the most common physiological stress in a human and can bring out cardiac abnormalities not present at rest. For this reason, dynamic exercise can be considered the most practical test to provoke chest pain in patients with effort angina pectoris, to evaluate the efficacy of antianginal agents, and to elucidate the antianginal mechanism.

The main purposes of the present study was to evaluate the effect of nisoldipine on systemic and coronary hemodynamics in dynamic exercise-induced angina pectoris and to elucidate its antianginal mechanisms in patients with stable effort angina pectoris subjected to supine leg exercise before and after oral administration of a single dose of 10 mg nisoldipine. The study was also designed to determine whether the clinical and hemodynamic events induced by supine leg exercise during invasive studies are reproducible after placebo administration in patients with stable effort angina pectoris.

### Methods

#### Patients

The study group consisted of 30 patients (29 men and one woman) with stable effort angina pectoris (age, 38–71 years; mean age, 54 years). They were admitted to the Nagoya University Hospital for investigation of suspected coronary artery disease. They were randomly (in a nonblinded manner) divided into two groups—one group of 19 patients who received a single 10 mg dose of nisoldipine orally (Table 1), and another group of 11 patients who received a single dose of identical placebo orally (Table 2). The groups were unequal in size because of the inability to obtain satisfactory coronary sinus blood flow measurements in some patients. Each patient had previous positive exercise tests with chest pain and significant ischemic ST-segment depression on angiogram-limited supine multistage bicycle ergometer exercise tests on at least 2 different days before the definitive study. These tests were done to familiarize patients with supine leg exercise and to avoid poor reproducibility of the exercise test results. This study was approved by an appropriate institutional review committee, and each patient gave informed consent.

#### Hemodynamic Studies

A triple-lumen thermistor Swan-Ganz catheter was positioned in the pulmonary artery percutaneously through the brachial vein to measure cardiac output and pulmonary artery wedge pressure. Thermodilution technique was used to determine cardiac output. The thermodilution curve, recorded with the thermodilution cardiac output computer (model R1-5DCP, General Scanning Inc., Los Angeles, California), was checked for consistency before the results were accepted as reflecting cardiac output. Irregular (not smooth and not characterized by a rapid peak) curves, especially during exercise, were excluded from the study. A double-thermistor catheter (model

### Table 1. Summary of Pertinent Clinical and Angiographic Findings in 19 Patients Receiving Nisoldipine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr) and sex</th>
<th>Coronary angiogram (% diameter reduction)</th>
<th>Collateral filling</th>
<th>Left ventricular angiogram</th>
<th>Exercise duration (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55 M</td>
<td>LAD 75, LCx 0, RC 0</td>
<td>None</td>
<td>EF 83, Normal</td>
<td>600</td>
</tr>
<tr>
<td>2</td>
<td>45 M</td>
<td>LAD 0, LCx 100, RC 90</td>
<td>Fair</td>
<td>EF 75, Anterior hypokinesia</td>
<td>540</td>
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<tr>
<td>3</td>
<td>66 M</td>
<td>LAD 95, LCx 0, RC 0</td>
<td>None</td>
<td>EF 74, Normal</td>
<td>615</td>
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<tr>
<td>4</td>
<td>71 M</td>
<td>LAD 75, LCx 50, RC 99</td>
<td>Good</td>
<td>EF 79, Normal</td>
<td>540</td>
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<tr>
<td>5</td>
<td>60 F</td>
<td>LAD 99, LCx 50, RC 0</td>
<td>Fair</td>
<td>EF 80, Anterior hypokinesia</td>
<td>255</td>
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<tr>
<td>6</td>
<td>38 M</td>
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<td>Fair</td>
<td>EF 62, Anterior hypokinesia</td>
<td>270</td>
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<tr>
<td>7</td>
<td>55 M</td>
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<td>EF 74, Normal</td>
<td>405</td>
</tr>
<tr>
<td>8</td>
<td>55 M</td>
<td>LAD 99, LCx 0, RC 0</td>
<td>Fair</td>
<td>EF 66, Anterior hypokinesia</td>
<td>270</td>
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<tr>
<td>9</td>
<td>71 M</td>
<td>LAD 50, LCx 100, RC 0</td>
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<td>EF 72, Normal</td>
<td>540</td>
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<tr>
<td>10</td>
<td>63 M</td>
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<td>EF 35, Anterior and inferior hypokinesia</td>
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<tr>
<td>11</td>
<td>63 M</td>
<td>LAD 75, LCx 99, RC 90</td>
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<td>EF 60, Inferior akinesia</td>
<td>285</td>
</tr>
<tr>
<td>12</td>
<td>60 M</td>
<td>LAD 0, LCx 99, RC 50</td>
<td>None</td>
<td>EF 72, Posterior hypokinesia</td>
<td>220</td>
</tr>
<tr>
<td>13</td>
<td>52 M</td>
<td>LAD 99, LCx 90, RC 90</td>
<td>Poor</td>
<td>EF 74, Anterior hypokinesia</td>
<td>345</td>
</tr>
<tr>
<td>14</td>
<td>49 M</td>
<td>LAD 95, LCx 95, RC 90</td>
<td>None</td>
<td>EF 50, Posterior hypokinesia</td>
<td>360</td>
</tr>
<tr>
<td>15</td>
<td>68 M</td>
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<td>Good</td>
<td>EF 56, Inferior and anterior hypokinesia</td>
<td>420</td>
</tr>
<tr>
<td>16</td>
<td>52 M</td>
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<td>None</td>
<td>EF 84, Normal</td>
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</tr>
<tr>
<td>17</td>
<td>56 M</td>
<td>LAD 75, LCx 0, RC 0</td>
<td>None</td>
<td>EF 84, Normal</td>
<td>660</td>
</tr>
<tr>
<td>18</td>
<td>54 M</td>
<td>LAD 100, LCx 0, RC 0</td>
<td>Good</td>
<td>EF 73, Anterior hypokinesia</td>
<td>490</td>
</tr>
<tr>
<td>19</td>
<td>41 M</td>
<td>LAD 75, LCx 100, RC 99</td>
<td>Good</td>
<td>EF 64, Inferior hypokinesia</td>
<td>540</td>
</tr>
</tbody>
</table>

LAD, left anterior descending artery; LCx, left circumflex artery; RC, right coronary artery; EF, ejection fraction; M, male; F, female.
CCS/TU-GOK, Wilton-Webster Laboratories, Los Angeles, California) was placed percutaneously in the coronary sinus through the brachial vein. The distal external thermistor was advanced to the great cardiac vein, and the proximal external thermistor was positioned in the coronary sinus between the ostium and the termination of the middle cardiac vein under fluoroscopic guidance. Coronary sinus and great cardiac vein flows were calculated according to the method of Ganz et al.\textsuperscript{13} using a computer system (Thermo Flow, Goodman Co., Ltd., Nagoya, Japan). The injectate was normal saline solution at room temperature delivered by a Harvard pump at a flow rate of 40 ml/min. Coronary sinus flow and great cardiac vein flow were recorded on a six-channel recorder (Unicorder, Nippon Denshi Kagaku Co., Ltd., Kyoto, Japan) at a paper speed of 100cm/min. A Teflon catheter was also cannulated in the brachial artery for direct measurement of arterial pressure. Pulmonary artery wedge pressure and arterial pressure were measured by a Siemens pressure transducer (model 746, Solna, Sweden) from a zero reference midchest level.

### Bicycle Ergometer Exercise Testing

All drugs (except sublingual nitroglycerin) administered for relief of chest pain were withdrawn by 3 days before the study. The method of invasive hemodynamic exercise testing has been reported elsewhere.\textsuperscript{14–16} Angina-limited bicycle ergometer (electronically braked ergometer) exercise testing was performed in patients in the supine position before administration of nisoldipine or placebo to obtain control values. The exercise end point in the control study was chest pain. The work load was begun at 150 kpm/min (25 W) and increased by 150 kpm/min at 3-minute intervals. A single oral dose of 10 mg nisoldipine or placebo was administered at the end of the control exercise test, and exercise testing using the same method, duration, and work load was performed 1.5 hours after the administration of nisoldipine or placebo. During exercise testing, a multilead electrocardiogram (modified 12 leads\textsuperscript{17} and Frank X, Y, and Z leads) was recorded continuously. Pulmonary artery wedge pressure, arterial pressure, cardiac output, and coronary sinus flow were measured at rest and every 3 minutes during exercise, at peak exercise, and 3 and 6 minutes after exercise. We could not obtain a measurement of coronary sinus flow in four patients either at rest or during exercise in the nisoldipine group.

### Blood Sampling

Samples of blood for oxygen saturation were simultaneously obtained in the brachial artery, the pulmonary artery, and the coronary sinus at rest, at peak exercise, and 6 minutes after exercise in 11 of 19 patients in the nisoldipine group. Blood oxygen saturation was determined with a hemoximeter (model ABL3, Radiometer, Copenhagen, Denmark). Some parts of the sample were packed in dry ice for later determination of norepinephrine levels by a modification of a method described by de Champlain et al.\textsuperscript{18} Samples of blood for nisoldipine plasma levels were obtained at 0.5, 1, 1.5, 2, 3, and 5 hours after nisoldipine administration. The total plasma concentration of nisoldipine and its active metabolites (as nisoldipine equivalent) were measured by radioreceptor assay.\textsuperscript{19}

### Angiographic Assessment of Coronary Stenosis

Selective coronary arteriography and left ventriculography were performed in all patients studied using the Sones technique in the same day after the nisoldipine or the placebo study. Left ventricular volume in each patient was calculated by the use of biplane cineangiography. Each coronary artery was viewed in multiple projections. Coronary cineangiograms, recorded on 35-mm films, were reviewed on a Tagarno projector. Collateral filling of the coronary arterial branch was judged angiographically. Good filling was defined as opacification of the collaterally filled branch equal to that of vessels directly filled; poor filling was
defined as just detectable opacification; and fair filling
was defined as between good and poor.

Calculations

The baseline from which observed electrocardio-
graphic changes were measured was taken from a
line joining two consecutive P-Q junctions. The mag-
nitude of ST-segment depression was measured using
a \( \times 7 \) magnifying glass calibrated in 10ths of a milli-
meter. Test results were reviewed by a second
observer, and differences were resolved by joint study
of the record. The use of a calibrated magnifying
glass substantially increased agreement between
readers. Each exercise test was interpreted without
knowledge of the results during control study or
during nisoldipine study. The electrocardiographic
criteria for a positive test in any lead were horizontal
or downsloping ST-segment depression \( \geq 1 \) mm for
0.08 seconds or a slow upsloping ST-segment depres-
sion \( \geq 2 \) mm 0.08 seconds after the J point in at least
three consecutive complexes. The degree of ST
changes was expressed by the maximal value of
ischemic ST-segment depression in any of the 15
leads recorded.

Hemodynamic variables were calculated as fol-
lows: (rate-pressure product)\( \times ( \text{heart rate} ) = \) (cardiac
index \( [ \text{l/min/m}^2] = \) cardiac output/body surface area); (stroke
volume index \( [ \text{ml/m}^2] = \) cardiac index/heart rate); (mean
erterial pressure)\( = \) (systolic arterial pressure +
2\( \times \) diastolic arterial pressure)\( /3 \); (systemic vascular
resistance \( [ \text{dynes-sec-cm}^{-2}] = \) (mean arterial pressure/
cardiac output\( \times 80 \); (stroke work index \( [ \text{g/beats/}
m^2] = \) (stroke volume index\( \times \) (mean arterial pressure−
mean pulmonary arterial wedge pressure))\( \times 0.0136 \) (a
conversion factor from \( \text{mm Hg} \cdot \text{cm}^{-2} \) to \( \text{g} \cdot \text{m} \), having
units of \( \text{g} \cdot \text{m/mm Hg} \cdot \text{cm}^{-3} \); (coronary vascular
resistance \( [ \text{mm Hg/ml/min}] = \) (mean arterial pressure/
coronary sinus flow)); \( \mid \text{Oxygen content [vol\%]} = \) \( \frac{\text{Oxy-
gen saturation[\%]}}{\text{Hemoglobin concentration values}} \times 1.34 \) (a conversion factor to get from percent
saturation to oxygen content)\( /100 \); (myocardial oxygen
uptake \( [ \text{ml/min}] = \) (arterial oxygen content−coronary
sinus oxygen content)\( \times ( \text{coronary sinus flow}/100 \).

Statistics

Hemodynamic variables at rest and at peak exercise
were compared between the control period and
the nisoldipine period or the placebo period, respec-
tively, using a paired \( t \) test. Pulmonary artery wedge
pressure, systemic vascular resistance, coronary sinus
flow, and coronary vascular resistance measured dur-
ing the exercise test in the control period were
compared with those in the nisoldipine period using
a paired \( t \) test; a \( p \) value of less than 0.05 was
considered statistically significant. Linear regression
analysis was made using myocardial oxygen uptake
during the exercise test before nisoldipine as an
independent variable and after nisoldipine as a
dependent one. The test of regression coefficient
and the test of regression constant were made in the
obtained regression equation. All values in the text,
figures, and tables are mean\( \pm \)SEM.

Results

Clinical and Angiographic Findings

Among 30 patients studied, 13 had three-vessel
disease, nine had two-vessel disease, and eight had
one-vessel involvement. Left ventricular ejection frac-
tion ranged from 28% to 84% (mean, 63\( \pm \)3%) in all
patients studied, from 35% to 84% (mean, 69\( \pm \)3%) in
the nisoldipine group, and from 28% to 79% (mean,
53\( \pm \)6%) in the placebo group. The ejection fraction
showed a significant difference between the two
groups (\( p < 0.01 \). Exercise duration ranged from 220
to 660 seconds (mean, 453\( \pm \)24 seconds) in all patients
studied, from 220 to 660 seconds (mean, 441\( \pm \)34
seconds) in the nisoldipine group, and from 240 to 620
seconds (mean, 418\( \pm \)35 seconds) in the placebo

group. The exercise duration did not show a significant
difference between the two groups.

Effects of Nisoldipine on Exercise-Induced Chest Pain
and Ischemic ST-Segment Depression

The symptom-limited bicycle ergometer exercise
duration of the subjects in the nisoldipine group of 19
patients ranged from 220 to 660 seconds (mean,
440\( \pm \)34 seconds) (Table 1). Chest pain was induced
in all 19 patients studied during the control exercise
test, but after nisoldipine administration, chest pain
was not induced in 13 patients. In five patients, it was
of lessened severity, and only one patient (8) showed
the same severity of chest pain before and after
nisoldipine administration.

Comparative analysis of exercise-induced ischemic
ST-segment depression before and after nisoldipine
administration was possible in all of 19 patients
(Figure 1). Exercise-induced ST-segment depression
was lessened in severity in all 19 patients after
nisoldipine administration. Mean ST-segment
depression was 0.18\( \pm \)0.03 mV in the control period
and was significantly reduced to 0.10\( \pm \)0.02 mV after
nisoldipine administration (\( p < 0.001 \).

Effects of Placebo on Exercise-Induced Chest Pain
and Ischemic ST-Segment Depression

The symptom-limited bicycle ergometer exercise
duration of the placebo group of 11 patients ranged
from 240 to 620 seconds (mean, 418\( \pm \)35 seconds)
(Table 2). Chest pain was induced in all of 11 patients
during the control exercise test and in 10 patients
after placebo administration chest pain. In only one
patient was pain of lessened severity. Comparative
analysis of exercise-induced ischemic ST-segment
depression before and after placebo administration
was possible in all 11 patients. Exercise-induced ST-
segment depression was 0.17\( \pm \)0.02 mV in the control
period and 0.16\( \pm \)0.03 mV in the placebo period;
these changes were not significant.
**TABLE 3.** Changes in Left Ventricular and Systemic Hemodynamic and Metabolic Responses to Supine Bicycle Ergometer Exercise Before and After Nisoldipine Administration in 19 Patients With Stable Effort Angina Pectoris

<table>
<thead>
<tr>
<th></th>
<th>Control period</th>
<th>Nisoldipine period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Peak exercise</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64±2</td>
<td>118±4</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>159±6</td>
<td>196±8</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>85±3</td>
<td>93±3</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>110±4</td>
<td>127±4</td>
</tr>
<tr>
<td>Rate-pressure product (×102)</td>
<td>96±8</td>
<td>220±20</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure (mm Hg)</td>
<td>6±1</td>
<td>28±3</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.5±0.1</td>
<td>5.3±0.4</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>39±1</td>
<td>45±2</td>
</tr>
<tr>
<td>Stroke work index (g·m/beat/m²)</td>
<td>55±3</td>
<td>62±5</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes/sec/cm⁻²)</td>
<td>2,204±143</td>
<td>1,218±81</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>26.9±7.5</td>
<td>89.2±20.6</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>133.1±15.9</td>
<td>502.3±97.0</td>
</tr>
</tbody>
</table>

n=13 patients.

* p<0.001, †p<0.01, Δp<0.05 vs. control.

**Effects of Nisoldipine on Systemic and Cardiac Hemodynamics**

Heart rate increased from 64±2 to 79±3 beats/min (p<0.001) at rest and from 118±4 to 128±5 beats/min (p<0.001) at peak exercise, whereas systolic arterial pressure decreased from 159±6 to 130±4 mm Hg (p<0.001) at rest and from 196±8 to 174±5 mm Hg (p<0.001) at peak exercise. As a result, rate-pressure product during exercise testing was not significantly modified by nisoldipine administration. Cardiac index increased from 2.5±0.1 to 3.2±0.1 l/min/m² (p<0.001) at rest and from 5.3±0.4 to 5.9±0.3 l/min/m² (p<0.05) at peak exercise after nisoldipine administration. In the control exercise test, a marked elevation of pulmonary artery wedge pressure with an increase in work load was observed, whereas after nisoldipine administration the pressure decreased significantly throughout the exercise test (Figure 2). Pulmonary artery wedge pressure fell from 6±1 to 3±1 mm Hg (p<0.001) at rest and from 28±3 to 11±2 mm Hg (p<0.001) at peak exercise after nisoldipine administration. Systemic vascular resistance decreased significantly throughout the exercise test after nisoldipine administration (Figure 3).

**Effects of Nisoldipine on Coronary Hemodynamics**

Comparative analysis of coronary blood flow was permitted in 15 of 19 patients studied during bicycle ergometer exercise testings (Tables 4 and 5). In the control study, exercise induced an increase in coronary sinus flow and a decrease in coronary vascular resistance. After administration of nisoldipine, coronary sinus flow significantly increased from 219 to 249 ml/min (p<0.01) at peak exercise (Figure 4). Coronary vascular resistance decreased from 1.30±0.10 to 0.90±0.09 mm Hg/ml/min (p<0.01) at rest and from 0.71±0.08 to 0.58±0.07 mm Hg/ml/min (p<0.01) at peak exercise after nisoldipine administration (Figure 5). Arteriocoronary sinus oxygen difference showed no significant difference at rest or at peak exercise. Myocardial oxygen uptake showed no significant difference throughout the exercise test after nisoldipine administration (Figure 6).

**Effects of Placebo on Systemic, Cardiac, and Coronary Hemodynamics**

Systemic, cardiac, and coronary hemodynamic measurements including heart rate, rate-pressure product, cardiac index, and coronary sinus flow showed no significant changes at rest and at peak exercise after placebo administration (Table 6). Only

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Plots of effects of nisoldipine on exercise-induced maximal ST-segment depression. Ischemic ST-segment depression induced by supine bicycle ergometer exercise was improved from 0.18±0.03 to 0.10±0.02 mV (p<0.001) by oral administration of nisoldipine in all of the 19 patients evaluated.
pulmonary artery wedge pressure at rest fell significantly from 7±1 to 5±1 mm Hg (p<0.05).

**Arterial Cathecholamine Levels**

Arterial norepinephrine levels tended to increase at rest and at peak exercise in nisoldipine period (Table 3). However, this increase was not significant.

**Plasma Concentration of Nisoldipine**

The total plasma concentration-time data of nisoldipine and its active metabolites after a single oral dose of 10 mg were fit to a one-compartment model for seven patients. Nisoldipine was rapidly absorbed with T_max (time to reach peak plasma concentration) of 1.6±0.2 hours, and elimination half-life (T_1/2) was 1.3±0.4 hours. C_max (peak plasma concentration) was 17.6±5.1 ng/ml, and mean AUC (areas under plasma concentration–time curves) was 50.8±11.7 ng·hr/ml.

**Discussion**

The present study has demonstrated a clear-cut effect of nisoldipine on dynamic exercise-induced angina pectoris in terms of disappearance or lessening of chest pain and marked alleviation of ischemic ST-segment depression after nisoldipine administration; these effects are consistent with other recent

**FIGURE 2.** Plots of effects of nisoldipine on pulmonary artery wedge pressure (PAWP) during supine bicycle ergometer exercise testing. Marked elevation of PAWP with increase in work load was observed in the control exercise testing, but after nisoldipine administration a significant decrease in the pressure was noted throughout the exercise testing.

**TABLE 4.** Coronary Hemodynamic and Metabolic Effects of Nisoldipine at Rest

<table>
<thead>
<tr>
<th>Patient</th>
<th>CSF (ml/min)</th>
<th>CVR (mm Hg/ml/min)</th>
<th>AV difference (ml/dl)</th>
<th>MVO_2 (ml/min)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>N</td>
<td>C</td>
<td>N</td>
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<tr>
<td>1</td>
<td>148</td>
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<td>2</td>
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</tr>
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<td>3</td>
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<tr>
<td>6</td>
<td>121</td>
<td>103</td>
<td>0.83</td>
<td>0.87</td>
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<td>8</td>
<td>77</td>
<td>63</td>
<td>1.34</td>
<td>1.46</td>
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<tr>
<td>9</td>
<td>75</td>
<td>68</td>
<td>1.83</td>
<td>1.56</td>
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<tr>
<td>10</td>
<td>110</td>
<td>149</td>
<td>1.44</td>
<td>0.70</td>
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<tr>
<td>12</td>
<td>47</td>
<td>63</td>
<td>2.72</td>
<td>1.84</td>
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<td>14</td>
<td>63</td>
<td>114</td>
<td>1.67</td>
<td>0.72</td>
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<tr>
<td>16</td>
<td>94</td>
<td>85</td>
<td>1.26</td>
<td>1.10</td>
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<tr>
<td>17</td>
<td>64</td>
<td>102</td>
<td>1.77</td>
<td>0.80</td>
</tr>
<tr>
<td>18</td>
<td>54</td>
<td>75</td>
<td>2.02</td>
<td>1.31</td>
</tr>
<tr>
<td>19</td>
<td>57</td>
<td>134</td>
<td>1.81</td>
<td>0.75</td>
</tr>
<tr>
<td>Mean</td>
<td>97</td>
<td>109</td>
<td>1.30</td>
<td>0.90</td>
</tr>
<tr>
<td>±SEM</td>
<td>9</td>
<td>9</td>
<td>0.10</td>
<td>0.09</td>
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</tbody>
</table>

CSF, coronary sinus blood flow; CVR, coronary vascular resistance; AV difference, myocardial arteriovenous oxygen difference; MVO_2, myocardial oxygen uptake; C, control; N, nisoldipine.
climatic studies with nisoldipine.\textsuperscript{11,12,20,21} To explain these improvements, both direct cardiac effects and the influence of nisoldipine on the systemic and coronary circulations must be considered. Possible mechanisms of action of nisoldipine for angina relief are discussed on the basis of myocardial oxygen demand and supply relation in dynamic exercise-induced angina.

The routine daily dose of nisoldipine for patients with effort angina pectoris was 10–20 mg in the clinical studies reported.\textsuperscript{11,12,20} We examined the exercise tolerance of 10 patients with stable effort angina pectoris using treadmill exercise at 2, 4, 7, and 24 hours after a single oral dose of 10 mg nisoldipine in a placebo-controlled study.\textsuperscript{21} Significant prolongation of treadmill exercise duration was observed in this group for 24 hours after nisoldipine administration. Crean et al\textsuperscript{20} also reported that treadmill exercise duration increased significantly after 5- and 20-mg nisoldipine administration. Accordingly, the 10-mg oral dose of nisoldipine used in the present study seems to be appropriate for a single-dose study.

**Systemic Hemodynamic Effects of Nisoldipine**

Major changes in the systemic hemodynamic response after a single oral dose of nisoldipine

| Table 5. Coronary Hemodynamic and Metabolic Effects of Nisoldipine at Peak Exercise |
|---|---|---|---|---|
| Patient | CSF (ml/min) | CVR (mm Hg/ml/min) | AV difference (ml/dl) | MVO\textsubscript{2} (ml/min) |
|   | C | N | C | N | C | N | C | N |
| 1  | 327 | 372 | 0.48 | 0.33 | ... | ... | ... | ... |
| 2  | 251 | 294 | 0.48 | 0.40 | ... | ... | ... | ... |
| 3  | 332 | 361 | 0.44 | 0.36 | 14.7 | 13.9 | 48.6 | 53.4 |
| 4  | 371 | 451 | 0.42 | 0.29 | 12.2 | 13.4 | 32.7 | 41.1 |
| 5  | 168 | 147 | 0.68 | 0.75 | 8.1 | 9.1 | 13.7 | 13.4 |
| 6  | 169 | 144 | 0.60 | 0.80 | 15.6 | 15.4 | 26.3 | 22.2 |
| 7  | ... | ... | ... | ... | ... | ... | ... | ... |
| 8  | 109 | 104 | 1.12 | 1.11 | ... | ... | ... | ... |
| 9  | 193 | 186 | 0.82 | 0.78 | 14.4 | 12.1 | 27.8 | 22.4 |
| 10 | 161 | 202 | 1.02 | 0.68 | 14.5 | 14.5 | 23.3 | 29.2 |
| 11 | ... | ... | ... | ... | ... | ... | ... | ... |
| 12 | 89  | 131 | 1.52 | 1.13 | 12.7 | 13.3 | 11.3 | 17.5 |
| 13 | ... | ... | ... | ... | ... | ... | ... | ... |
| 14 | 150 | 137 | 0.97 | 0.82 | ... | ... | ... | ... |
| 15 | ... | ... | ... | ... | ... | ... | ... | ... |
| 16 | 209 | 234 | 0.69 | 0.50 | 14.7 | 13.2 | 30.6 | 30.8 |
| 17 | 379 | 506 | 0.35 | 0.24 | 8.0 | 8.1 | 30.3 | 40.9 |
| 18 | 108 | 179 | 1.23 | 0.72 | 9.7 | 8.4 | 10.7 | 15.1 |
| 19 | 265 | 294 | 0.56 | 0.47 | 14.6 | 13.9 | 38.7 | 40.7 |
| Mean | 219 | 249 | 0.71 | 0.58 | 12.7 | 12.3 | 26.7 | 29.7 |
| ±SEM | 24 | 31 | 0.08 | 0.07 | 0.9 | 0.8 | 3.9 | 4.3 |

\( p < 0.01 \)

CSF, coronary sinus blood flow; CVR, coronary vascular resistance; AV difference, myocardial arteriovenous oxygen difference; MVO\textsubscript{2}, myocardial oxygen uptake; C, control; N, nisoldipine.
observed at rest and during exercise in the present study were a marked decrease in systemic vascular resistance and a decrease in arterial blood pressure associated with an increase in cardiac index. The inhibition of the transmembrane flux of calcium ions in smooth muscle causes vasodilation, resulting in a decrease in total peripheral resistance and ventricular afterload.\textsuperscript{10,22} Nisoldipine has been reported to have a significant effect on vascular smooth muscle relative to cardiac muscle.\textsuperscript{10}

Myocardial ischemia induced by dynamic exercise is associated with abnormal ventricular function characterized by a marked increase in left ventricular filling pressure.\textsuperscript{23,24} The mechanism of this increase is still controversial. Abnormal left ventricular compliance\textsuperscript{25-27} or impairment of left ventricular contractility due to acute myocardial ischemia\textsuperscript{28,29} are possible mechanisms. In the present study, a marked decrease in pulmonary artery wedge pressure was observed during supine leg exercise testing after nisoldipine administration; this is probably caused by an alleviation of myocardial ischemia or a decrease in its severity. Pulmonary artery wedge pressure reflects left ventricular end-diastolic pressure in most clinical settings\textsuperscript{30} and even during dynamic exercise.\textsuperscript{31} Nisoldipine-induced decrease in pulmonary artery wedge pressure could be assumed to reflect a similar fall in left ventricular end-diastolic pressure, which would induce a decrease in left ventricular wall tension.

Heart rate increased both at rest and at peak exercise after nisoldipine administration, but the rate-pressure product, which is believed to reflect

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**FIGURE 4.** Plots of effects of nisoldipine on coronary sinus flow (CSF) during supine bicycle ergometer exercise testing. A significant increase in CSF was noted at peak exercise after nisoldipine administration.

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**FIGURE 5.** Plots of effects of nisoldipine on coronary vascular resistance (CVR) during supine bicycle ergometer exercise testing. After nisoldipine administration, a significant decrease in CVR was noted throughout the exercise testing.
myocardial oxygen uptake\textsuperscript{32} was not modified at all by nisoldipine administration. An increase in heart rate would be caused by a reflex sympathetic stimulating action originating from marked dilation of systemic vascular vessels as in the case of other calcium channel blockers based on dihydropyridine derivatives.\textsuperscript{33}

Arterial norepinephrine levels in the present study tended to increase at rest and at peak exercise after nisoldipine administration; this is considered to be a result of a reflex increase in sympathetic activity.\textsuperscript{33} The precise mechanism, however, remains unclear. Increased sympathetic activity may produce an oxygen-wasting effect by increasing inotropic state.

Coronary Hemodynamic Effects of Nisoldipine

Myocardial oxygen uptake during supine leg exercise testings was not significantly modified by nisoldipine administration. Coronary vascular resistance was markedly reduced after nisoldipine administration, which did not result in an increased coronary sinus flow at rest because of nisoldipine-induced hypotension and the associated decrease in coronary perfusion pressure. However, coronary sinus flow at peak exercise showed a significant increase after nisoldipine administration. This increase in coronary blood flow may play an important role in the mechanism of antianginal action of nisoldipine. Tumas et al\textsuperscript{34} have reported no effects of nisoldipine on myocardial blood flow. There are several reports in which nisoldipine increased coronary blood flow despite a decrease in systemic blood pressure at rest.\textsuperscript{35,36} There are very few reports, however, about the effects of nisoldipine on coronary blood flow during dynamic exercise in patients with effort angina pectoris.

Previous investigators have suggested that exercise may induce positional catheter changes, thereby increasing variability among repeated thermodilution measurements of coronary sinus flow.\textsuperscript{37,38} However, Magorien et al\textsuperscript{39} found a highly significant correlation between the measurement obtained during exercise. In the present study, we displayed the thermodilution curves on a multichannel recorder. Irregular curves were discarded to keep reliability of the data and to avoid contamination by right atrial blood.

Antianginal Mechanism of Nisoldipine

The mechanisms of antianginal action of calcium channel blockers have been considered to involve a decrease in myocardial oxygen uptake, an increase in coronary blood flow, improvement in the distribution of coronary blood flow, an increase in collateral blood flow, and protective action on the myocardium.

In the present study, nisoldipine administration induced no evident changes in myocardial oxygen

### TABLE 6. Changes in Left Ventricular, Systemic, and Coronary Hemodynamic Responses to Supine Bicycle Ergometer Exercise Before and After Placebo Administration in 11 Patients With Stable Effort Angina Pectoris

<table>
<thead>
<tr>
<th></th>
<th>Control period</th>
<th>Placebo period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Peak exercise</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72±3</td>
<td>112±3</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>143±7</td>
<td>186±9</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>81±3</td>
<td>92±3</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>102±4</td>
<td>123±5</td>
</tr>
<tr>
<td>Rate-pressure product (×102)</td>
<td>102±8</td>
<td>208±11</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure (mm Hg)</td>
<td>7±1</td>
<td>17±2</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.7±0.2</td>
<td>5.0±0.2</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>38±3</td>
<td>45±3</td>
</tr>
<tr>
<td>Stroke work index (g · m/beat/m²)</td>
<td>50±6</td>
<td>66±5</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes/sec/cm²)</td>
<td>1,835±68</td>
<td>1,197±81</td>
</tr>
<tr>
<td>Coronary sinus flow (ml/min)</td>
<td>109±10</td>
<td>190±17</td>
</tr>
<tr>
<td>Coronary vascular resistance (mm Hg/ml/min)</td>
<td>1.00±0.10</td>
<td>0.71±0.08</td>
</tr>
</tbody>
</table>

\*p<0.05 vs. control.
uptake. Rate-pressure product also showed no significant changes after nisoldipine administration. As the result, a reduction in myocardial oxygen uptake could not be a major factor of the antianginal action of nisoldipine. Coronary blood flow is one of the principal factors regulating myocardial oxygen supply. Because approximately 85% of coronary sinus blood flow arises from the left ventricle, measurements of coronary sinus flow reflect left ventricular coronary blood flow. The present study suggests that the mechanism of protection by nisoldipine is mainly the result of an increase in coronary blood flow.

The calcium channel blockers nifedipine and diltiazem have been found to inhibit ischemia-induced vasodilation of the resistance vessels after the acute dilation has resolved.\(^40\) In the presence of a proximal coronary stenosis, ischemic vasodilation of the coronary resistance vessels causes a decrease in perfusion pressure distal to the stenosis and loss of the ability for local autoregulation. These effects may result in redistribution of coronary blood flow away from the subendocardium.\(^42\) Nifedipine has been found to attenuate this redistribution of coronary blood flow and to increase subendocardial flow,\(^41\) possibly by blunting the intense vasodilator response to ischemia.\(^44\) Heusch et al.\(^145\) have demonstrated the presence of significant coronary vasodilator reserve during exercise-induced myocardial ischemia in conscious dogs and that nifedipine can recruit this reserve and induce an improvement of ischemic regional myocardial blood flow and function without major effects on systemic hemodynamics. One of the possible antianginal mechanisms of nisoldipine would be an improvement in the distribution of coronary blood flow to the subendocardium. The improved myocardial relaxation and diastolic compliance produced by nisoldipine like nifedipine\(^46\) could have been a possible contributing factor to the increase in myocardial blood flow by increasing the perfusion pressure gradient to the subendocardium.\(^47\)

Waltier et al.\(^48\) have reported that nisoldipine increase coronary collateral blood flow to the ischemic zone with equal distribution to the subendocardium and epicardium in dogs with acutely occluded left anterior descending arteries. In the present study, seven of 19 patients did not show collateral filling, whereas their exercise-induced ischemic ST-segment depression improved and their exercise-induced chest pain was not induced or was of lesserened severity after nisoldipine administration. These results may suggest that an increase in collateral blood flow could not be a principal mechanism of antianginal action of nisoldipine in humans.

In addition to modulating coronary blood flow, nisoldipine could be involved in a variety of calcium-dependent processes to protect myocardium from ischemia including reduction of nucleotide breakdown,\(^49\) stabilization of membrane permeability,\(^50\) protection of the integrity of sarcolemmal membranes,\(^51\) and inhibition of leukotriene actions.\(^52\) Any combination of these or other factors may play an important role in the mechanism of protection by nisoldipine from acute myocardial ischemia, but we could not distinguish among any of these mechanisms in the present study.

Reproducibility of Exercise Test Results

When the symptom-limited bicycle ergometer exercise test was performed in patients with stable effort angina pectoris, the exercise time, heart rate, and left ventricular end-diastolic pressure for evaluation of left ventricular function have been generally said to be reproducible.\(^53,54\) In the present study, the clinical and hemodynamic events induced by supine leg exercise during invasive studies were reproducible after placebo administration in patients with stable effort angina pectoris. Excellent reproducibility was demonstrated in heart rate, rate-pressure product, and cardiac output as well as coronary sinus flow and coronary vascular resistance both at rest and at peak exercise. Only pulmonary artery wedge pressure at rest dropped significantly, compared with control study, after placebo administration. However, this pressure at peak exercise was not affected at all by placebo administration. Accordingly, the hemodynamic effects of nisoldipine, except pulmonary artery wedge pressure at rest, observed in this study should be reliable.

Pharmacokinetics of Nisoldipine

In the present study the total plasma concentration of nisoldipine and its active metabolites reached a peak 1.6 hours after administration, and the elimination half-life was 1.3 hours. The bicycle ergometer exercise test was performed 1.5 hours after nisoldipine administration, and it should be possible to obtain sufficient effects of nisoldipine at this time. Despite this short half-life the pharmacodynamic effect of nisoldipine was shown to persist for a much longer period.\(^12,21\) This discrepancy may be due to tissue binding or to formation of an active metabolite. Recently it has been elucidated that nisoldipine has three active metabolites and exhibits dose-proportional pharmacokinetics at oral dose from 2.5 to 20 mg.\(^54\)

Limitation of Study

Dynamic exercise tests with invasive hemodynamic studies may be the most important practical test to elucidate the mechanism of antianginal drugs in patients with effort angina pectoris. However, this invasive study may have some limitations. In this study nisoldipine or placebo was always given after the control exercise. A possible order effect of this study design cannot be denied. However, as nisoldipine has a long pharmacodynamic effect, it was not possible to reverse the order of exercise tests with invasive hemodynamic monitoring. For the same reason, this was a study of only a single dose of nisoldipine since repeated invasive studies could not be justified. An oral dose of 10 mg nisoldipine used in this study has been reported to be significantly effective\(^11,12,20\) and is a frequently used dose in clinical practice. Although a double-blinded design may
be recommended for the evaluation of drug effects, the present study was a single-blinded design, and this may be an important limitation of this study. Invasive hemodynamic measurements, including coronary sinus flow, which is a very important parameter in this study, are not always easy to be obtained during exercise in humans. The number of the patients whose coronary sinus flows could not be measured led to unequal group sizes, which is another potential limitation, but the placebo group was used only to demonstrate the reproducibility of the exercise protocol.

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