Effects of nifedipine on systemic and regional oxygen transport and metabolism at rest and during exercise


ABSTRACT In a placebo-controlled, randomized, cross-over, double-blind study of 12 patients with stable exertional angina, we measured at rest and during bicycle exercise the effects of 20 mg of nifedipine administered sublingually on hemodynamics and systemic and regional oxygen extraction and metabolism. Nifedipine decreased systemic vascular resistance by 38% at rest (p < .001) and by 28% during exercise (p < .001). Cardiac output increased from 4.6 ± 0.6 to 6.0 ± 0.9 liters/min (p < .001) at rest after nifedipine and from 10.6 ± 3.7 to 11.8 ± 3.4 liters/min (p < .005) during exercise. After nifedipine, the arterial-mixed venous O₂ content difference decreased from 4.7 ± 0.6 to 3.5 ± 0.5 ml/100 ml (p < .001) at rest and from 10.5 ± 1.7 to 8.8 ± 1.6 ml/100 ml (p < .001) during exercise. After nifedipine the arterial-iliac venous O₂ content difference also decreased at rest, from 5.9 ± 1.5 to 4.8 ± 1.7 ml/100 ml (p = .06) but increased during exercise from 13.1 ± 1.5 to 14.0 ± 1.8 ml/100 ml (p < .05). Oxygen consumption was not significantly altered at rest or during exercise. Nifedipine decreased mixed venous carbon dioxide tension (PCO₂) during exercise from 53 ± 3.5 to 50 ± 4.0 mm Hg (p < .05) but increased iliac venous PCO₂ slightly from 61 ± 4.6 to 63 ± 5.2 mm Hg (p < .01). Exercise pH was not significantly altered, but arterial lactate increased more after nifedipine (2.65 ± 1.95 mmol/liter placebo, 3.54 ± 2.74 mmol/liter nifedipine; p < .05). Thus nifedipine produces similar changes in O₂ extraction in mixed venous and iliac venous blood at rest but directionally opposite changes during exercise. The data support the hypothesis that nifedipine does not alter the distribution of cardiac output to the legs at rest, but during dynamic leg exercise reduces the redistribution of cardiac output to the legs. This probably results from the shunting of blood flow away from exercising muscles by the generalized vasodilatation of nifedipine.


NIFEDIPINE, a calcium blocker, is a potent arteriolar vasodilator that is effective in the treatment of exertional¹-⁴ and vasospastic⁵ angina. Investigations of its potential use as an afterload-reducing agent in patients with cardiac failure have recently been reported.⁶-⁸ At rest it decreases systemic vascular resistance and arterial pressure and reflexly increases heart rate and cardiac output.⁹-¹² Regional blood flow to the legs and splanchnic organs increases.¹³-¹⁵ However, the important effect of nifedipine on regional blood flow to working muscles during dynamic exercise has not been described.

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During dynamic exercise the increase in cardiac output is accompanied by local vasodilatation in the exercising muscles and reflex vasoconstriction in nonexercising muscles and other vascular beds. This important adaptation diverts a much larger proportion of the cardiac output to the active muscles.¹⁶ Nifedipine produces systemic vasodilatation during exercise beyond that occurring physiologically, so that systemic vascular resistance falls further and arterial pressure increases less.¹¹ Heart rate and cardiac output increase more.¹⁰-¹² It is possible that nifedipine, by dilating the vascular beds that normally vasoconstrict during exercise, may reduce the normal redistribution of cardiac output to exercising muscles. Although the concept of such a steal phenomenon is not new,¹⁷ objective data during exercise in man are few, and these effects of nifedipine have not been previously reported.

In a previous study of 15 patients with stable exer-
tional angina, we found that 20 mg of nifedipine administered sublingually improved exertional angina and increased cardiac output during exercise,\textsuperscript{11} but leg fatigue increased in some patients. We postulated that this might have resulted from a reduced distribution of cardiac output to exercising muscles after nifedipine. Although the measurement of leg blood flow during bicycle exercise in man has been reported,\textsuperscript{18-22} it is technically difficult. However, a change in blood flow to exercising muscle may alter oxygen extraction and metabolism and the content of $O_2$ and other metabolites in venous blood leaving the muscle.\textsuperscript{23-26}

The aims of this study were to measure the effects of 20 mg of nifedipine administered sublingually on central hemodynamics and to compare its effects on systemic and regional leg $O_2$ extraction and metabolism at rest and during bicycle exercise.

\textbf{Methods}

\textbf{Patients.} Twelve male patients, mean age 55 years (range 41 to 67), with stable NYHA class II or III exertional angina of at least 3 months’ duration, were studied. Six patients had previous myocardial infarction, but none had cardiac failure. All patients had positive exercise tests (at least 1 mm flat or downsloping ST segment depression at 80 msec from the J point) with angina. No patient had intermittent claudication of the calf muscles.

\textbf{Study design.} The project was approved by the hospital ethics committee, and informed consent was obtained from all patients. The study was placebo controlled and was conducted in a double-blind fashion on 2 days 1 week apart. All antianginal medications, apart from nitrates, were stopped 72 hr before each study day. The order of drug administration was randomized so that half the patients received placebo and the other half nifedipine on the first day, with cross-over of the drugs on the second day.

On each day, studies were performed in the morning with the patients fasting and without premedication. Patients rested for 30 min after the insertion of catheters. Control rest measurements were then performed, after which two placebo capsules or two 10 mg nifedipine capsules were given. The patients were asked to bite the capsules and the contents were retained sublingually. Twenty minutes after drug administration, rest measurements were repeated, and symptom-limited bicycle exercise was performed.

\textbf{Hemodynamics.} For pressure measurements and blood sampling, a 17-gauge cannula (Teflon Dwellocath) was inserted percutaneously under local anesthesia in the radial artery and a No. 7F Swan-Ganz thermodilution catheter was inserted via the right cubital vein to the pulmonary artery. The zero reference point for pressure was set at the fourth intercostal space in the midaxillary line. Phasic and mean systemic arterial, pulmonary arterial, pulmonary arterial wedge, and right atrial pressures were measured (Bell and Howell 4-327-I transducers) and recorded on an Electronics for Medicine VR12 recorder. A No. 6F Goodale-Lubin catheter (USCI) was inserted in the right femoral vein and advanced proximally under fluoroscopic control to lie just proximal to the anterior pelvic brim in the anteroposterior projection. In this position, the catheter tip was well away from the insertion of the internal iliac vein. Care was taken to obtain the same catheter tip position on the 2 days by using skeletal landmarks and by measuring the length of catheter inserted.

\textbf{Rest studies.} Rest measurements were made over 6 min with the patient seated in a semiprurch background on a bicycle ergometer (Atomic Products Corp.), set at 45 degrees to the vertical. Intravascular pressures were continuously recorded and a 12-lead electrocardiogram was recorded every minute. Five or six cardiac output measurements were obtained by thermodilution with 10 ml boluses of ice-cooled 5% dextrose injectate and calculated by an Instrumentation Laboratory computer (Model 701). The average value was obtained. At the end of the study, blood was sampled simultaneously from the radial artery, pulmonary artery (mixed venous), and external iliac vein for hemoglobin concentration and blood gas analyses (pH, $O_2$ saturation, carbon dioxide tension [PCO$\text{$_2$}[/ ]] (Corning 175 Blood Gas Analyser). At the end of the second rest studies (i.e., after drug), blood was also sampled from the radial artery for plasma lactate measurements. An enzymatic method (Du Pont Automatic Clinical Analyser) was used.

\textbf{Exercise studies.} All exercise tests were symptom limited and commenced at individually predetermined workloads, which were then increased by 15 W every 3 min. A CM5 lead electrocardiogram was continuously recorded and a standard 12-lead electrocardiogram was recorded at 1 min intervals. Intravascular pressures were continuously recorded, and three or four thermodilution cardiac output measurements were made in the last 2 min of each exercise level and the values were averaged. At the end of the workload level, radial arterial, pulmonary arterial, and iliac venous blood were simultaneously sampled for hemoglobin concentration and blood gas analyses, and radial arterial blood was also sampled for plasma lactate concentration. At the end of each workload level, patients were asked to describe the severity of angina, dyspnea, and leg fatigue on a score of 0 to 5 (0 = none, 1 = symptom just noticeable, 2 = mild, 3 = medium, 4 = moderately severe, 5 = very severe).

\textbf{Calculations.} Systemic vascular resistance (dyne-sec-cm$^{-5}$) was calculated by the standard formula: (mean arterial pressure – mean right arterial pressure) $\times$ 80/cardiopulmonary output (liters/min).

Arterial-mixed venous $O_2$ content difference (AVOD) was calculated as AVOD (ml/100 ml) = 1.39 $\times$ (radial arterial $O_2$ saturation – pulmonary arterial $O_2$ saturation) $\times$ hemoglobin concentration (g/dl)/100. Arterial-iliac venous $O_2$ content difference (AVOD) was calculated as AVOD (ml/100 ml) = 1.39 $\times$ (radial arterial $O_2$ saturation – iliac venous $O_2$ saturation) $\times$ hemoglobin concentration (g/dl)/100.$^{27}$ Total $O_2$ consumption ($VO_2$) was calculated as $VO_2$ (ml/min/kg) = AVOD (ml/100 ml) $\times$ cardiac output (liters/min) $\times$ 10/body weight (kg). In our laboratory this method of measuring $VO_2$ correlated well with measurements by respiratory gas exchange (Hewlett Packard Pneumotach. Applied Electrochemistry, Inc., S-3A Oxygen Analyser) at rest and exercise in 12 patients ($VO_2$ [calculated] = 1.10 $VO_2$ [gas exchange] – 0.61; $r = .98$, SEE = 1.25 ml/min/kg). The reproducibility 1 week apart of two $VO_2$ measurements calculated from the product of cardiac output and simultaneous AVOD was evaluated in six patients with stable angina in another study.\textsuperscript{28} The group means $\pm$ SDs at rest on the 2 days were 3.1 $\pm$ 0.5 and 3.4 $\pm$ 0.7 ml/min/kg ($p = NS$). The group means $\pm$ SDs during exercise on the 2 days were 12.5 $\pm$ 2.2 and 12.4 $\pm$ 2.6 ml/min/kg ($p = NS$). The means $\pm$ SDs of the unsigned difference on the 2 days were 0.33 $\pm$ 0.39 ml/min/kg at rest and 0.38 $\pm$ 0.42 ml/min/kg during exercise.

\textbf{Statistical analysis.} Two-way analysis of variance was used to compare the results of the four rest studies (one control on each day, one after placebo, and one after nifedipine). When a significant difference between treatment groups was found, orthogonal partitioning was performed to locate the source and
TABLE 1
Hemodynamic data at rest

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nifedipine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>67 ± 11</td>
<td>67 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>123 ± 17</td>
<td>123 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>PAW (mm Hg)</td>
<td>9 ± 3</td>
<td>10 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>5 ± 2</td>
<td>5 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.6 ± 0.8</td>
<td>4.7 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>SVR (dyne-sec-cm⁻⁵)</td>
<td>2087 ± 409</td>
<td>2065 ± 420</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD.

MAP = mean arterial pressure; PAW = pulmonary arterial wedge pressure; RA = mean right atrial pressure; CO = cardiac output; SVR = systemic vascular resistance.

magnitude of the difference. The paired t test was used to compare exercise data at identical workloads after placebo and nifedipine, chosen at the highest common workloads after placebo and nifedipine. Differences at the p < .05 level were considered statistically significant, and all results in the text and tables are shown as mean ± 1 SD.

Results

Exercise capacity. On exercise after placebo, all patients developed angina and positive exercise electrocardiograms. Exercise was stopped by angina in six patients and by leg fatigue in the other six. After nifedipine, mean exercise capacity did not change (72.5 ± 30.6 W placebo, 68.8 ± 28.9 W nifedipine; p = NS). The onset of angina was abolished or delayed by at least 1 min in eight patients, unchanged in three patients, and occurred earlier in one patient. ST segment depression at identical workloads decreased from 2.5 ± 1.1 mm after placebo to 2.0 ± 1.0 mm after nifedipine (p < .05). Leg fatigue increased in five patients. Four of these five patients stopped exercise at one workload level less because of the increased leg fatigue. In the remaining seven patients leg fatigue was unaltered.

Hemodynamics (tables 1 and 2). At rest there was no difference in the hemodynamic parameters between the two control rest studies and between control studies and the study after placebo. Nifedipine reduced resting systemic vascular resistance from 2100 ± 391 to 1305 ± 238 dyne-sec-cm⁻⁵ and mean arterial pressure from 122 ± 15 to 100 ± 8 mm Hg, and increased heart rate from 68 ± 10 to 79 ± 11 beats/min and cardiac output from 4.6 ± 0.6 to 6.0 ± 0.9 liters/min (figure 1). Pulmonary arterial wedge pressure and right atrial pressure did not change.

During exercise at identical workloads (68 ± 30.3 W) compared with placebo, nifedipine decreased systemic vascular resistance from 1143 ± 409 to 828 ± 243 dyne-sec-cm⁻⁵ and mean arterial pressure from 148 ± 12 to 123 ± 11 mm Hg, and increased heart rate from 118 ± 20 to 128 ± 18 beats/min and cardiac output from 10.6 ± 3.7 to 11.8 ± 3.4 liters/min. Nifedipine decreased pulmonary arterial wedge pressure from 29 ± 6 to 21 ± 5 mm Hg and right atrial pressure from 12 ± 4 to 8 ± 2 mm Hg.

Metabolic changes

Rest (table 3). There was no difference in all parameters between the control studies on the 2 days and between the control studies and the rest study after placebo.

After nifedipine, systemic arterial O₂ saturation did not change significantly. Mixed venous O₂ saturation increased from 73 ± 3% to 79 ± 3% and iliac venous O₂ saturation increased by a similar degree from 67 ± 7% to 72 ± 8% (figure 2).

Thus AVOD decreased from 4.7 ± 0.6 to 3.5 ± 0.5 ml/100 ml and A10D decreased from 5.9 ± 1.5 to 4.8 ± 1.7 ml/100 ml, although the latter difference was just statistically insignificant (p = .06) (figure 3).

Arterial Pco₂ did not change. Mixed venous Pco₂ decreased from 45 ± 2 to 43 ± 3 mm Hg. Iliac venous Pco₂ was also lower, but this was not statistically significant (figure 4). Arterial pH did not change. Mixed venous pH increased slightly from 7.39 ± 0.02 to 7.40 ± 0.02. Iliac venous pH showed a similar

TABLE 2
Hemodynamic data at identical maximum workloads

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nifedipine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>118 ± 20</td>
<td>128 ± 18</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>148 ± 12</td>
<td>123 ± 11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PAW (mm Hg)</td>
<td>29 ± 6</td>
<td>21 ± 5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>12 ± 4</td>
<td>8 ± 2</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>10.6 ± 3.7</td>
<td>11.8 ± 3.4</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>SVR (dyne-sec-cm⁻⁵)</td>
<td>1143 ± 409</td>
<td>828 ± 243</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD.

Abbreviations as in table 1.
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**FIGURE 1.** Systemic vascular resistance (SVR), mean arterial pressure (MAP), cardiac output (CO), and heart rate (HR) at rest before and after drug therapy, at identical intermediate workloads (SUBMAX), and at the common maximum workloads (MAX) on the placebo and nifedipine days. Means ± 1 SEM are shown. In this and all other figures, data at the intermediate workloads are not included in the text. The p values at rest compare data before and after drug therapy, and p values during exercise compare nifedipine data with placebo data.

**TABLE 3**

Metabolic data at rest

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Radial artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.02</td>
<td>7.41 ± 0.02</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>42 ± 2.3</td>
<td>41 ± 2.0</td>
</tr>
<tr>
<td>O₂SAT (%)</td>
<td>97 ± 0.5</td>
<td>97 ± 0.6</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>0.23 ± 0.21</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.02</td>
<td>7.40 ± 0.02</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>46 ± 3.0</td>
<td>45 ± 2.5</td>
</tr>
<tr>
<td>O₂SAT (%)</td>
<td>72 ± 4.1</td>
<td>73 ± 4.1</td>
</tr>
<tr>
<td>Iliac vein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.02</td>
<td>7.39 ± 0.02</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>48 ± 2.5</td>
<td>48 ± 2.6</td>
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<tr>
<td>O₂SAT (%)</td>
<td>63 ± 9.7</td>
<td>62 ± 7.0</td>
</tr>
<tr>
<td>AVOD (ml/100 ml)</td>
<td>4.8 ± 0.8</td>
<td>4.7 ± 0.8</td>
</tr>
<tr>
<td>AIOD (ml/100 ml)</td>
<td>6.6 ± 1.8</td>
<td>6.7 ± 1.3</td>
</tr>
<tr>
<td>VO₂ (ml/min/kg)</td>
<td>2.9 ± 0.4</td>
<td>2.9 ± 0.4</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD.

O₂SAT = O₂ saturation; VO₂ = O₂ consumption.

^Statistical tendency (p < .1, two-way analysis of variance, or <.05, paired t test).
change, which did not achieve statistical significance (p = .09) (figure 5).

Exercise (table 4). Exercise metabolic data were taken from the same workloads as the hemodynamic data. Total VO₂ was 15.2 ± 5.9 ml/min/kg after placebo and was slightly lower after nifedipine, but this difference was not statistically significant (14.2 ± 4.9 ml/min/kg; p = .09) (figure 6).

After nifedipine, compared with placebo, arterial O₂ saturation did not change. Associated with the higher cardiac output, mixed venous O₂ saturation increased. In contrast, iliac venous O₂ saturation decreased mar-

FIGURE 2. Oxygen saturation in arterial, mixed venous, and iliac venous blood at rest before and after drug therapy, at identical intermediate workloads (SUBMAX), and at the common maximum workloads (MAX) on the placebo and nifedipine days. Means ± 1 SEM are shown.

FIGURE 3. AVOD and AIOD at rest before and after drug therapy, at identical intermediate workloads (SUBMAX), and at the common maximum workloads (MAX) on the placebo and nifedipine days. Means ± 1 SEM are shown.
Arterial Pco2 did not change after nifedipine. Mixed venous Pco2 fell from 53 ± 4 to 50 ± 4 mm Hg but iliac venous Pco2 increased from 61 ± 5 to 63 ± 5 mm Hg (figure 4).

Arterial pH did not change. Mixed venous pH was slightly higher, and iliac venous pH was slightly lower, but the changes were not significant (figure 5).
TABLE 4
Metabolic data at identical maximum workloads

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nifedipine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial artery</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.03</td>
<td>7.39 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>39 ± 2.3</td>
<td>39 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>O₂SAT (%)</td>
<td>97 ± 0.7</td>
<td>97 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>2.65 ± 1.95</td>
<td>3.54 ± 2.74</td>
<td>&lt;.05</td>
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<tr>
<td>Pulmonary artery</td>
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<tr>
<td>pH</td>
<td>7.31 ± 0.05</td>
<td>7.32 ± 0.94</td>
<td>NS</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>53 ± 3.5</td>
<td>50 ± 4.0</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>O₂SAT (%)</td>
<td>44 ± 8.7</td>
<td>54 ± 7.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Iliac vein</td>
<td></td>
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</tr>
<tr>
<td>pH</td>
<td>7.27 ± 0.05</td>
<td>7.26 ± 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>61 ± 4.6</td>
<td>63 ± 5.2</td>
<td>&lt;.01</td>
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<tr>
<td>O₂SAT (%)</td>
<td>30 ± 7.8</td>
<td>27 ± 9.3</td>
<td>NS^</td>
</tr>
<tr>
<td>AVOD (ml/100 ml)</td>
<td>10.5 ± 1.7</td>
<td>8.8 ± 1.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AIOD (ml/100 ml)</td>
<td>13.1 ± 1.5</td>
<td>14.0 ± 1.8</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>VO₂ (ml/min/kg)</td>
<td>15.2 ± 5.9</td>
<td>14.2 ± 4.9</td>
<td>NS^</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD.
Abbreviations as in table 3.
^Statistical tendency (p < .1 paired t test).

Arterial lactate concentration increased from 2.7 ± 1.9 mmol/liter after placebo to 3.5 ± 2.7 mmol/liter after nifedipine (figure 7).

Discussion

An important physiologic adaptation to exercise is the redistribution of cardiac output to the active muscles. This may normally increase from 18% to both legs at rest to 84% during maximal bicycle exercise.29 These changes result from local vasodilatation in active muscles accompanied by reflex vasoconstriction in other vascular beds.16 Nifedipine is a potent systemic vasodilator that may inhibit this adaptation. The hemodynamic changes produced by nifedipine in this study were similar to those reported previously by us11 and by others.10, 12 Both with patients at rest and during exercise, nifedipine decreased systemic vascular resistance and arterial pressure and increased heart rate and cardiac output.

The higher resting cardiac output after nifedipine reduced the AVOD and AIOD by similar amounts. Resting total VO₂ did not change, and assuming that leg VO₂ also did not change, the data are consistent with an increase in regional leg blood flow in proportion to the increase in cardiac output (+ 30%). An increase in leg blood flow at rest after nifedipine was reported recently by others using strain-gauge plethysmography and radioactive xenon washout techniques.13, 14

Mixed venous PCO₂ decreased slightly after nifedipine and could have resulted from the increased transport of CO₂ according to the Fick principle. Iliac venous PCO₂ was also lower, but this was not statistically significant.

During exercise after placebo, O₂ saturation and pH decreased and PCO₂ increased in iliac venous blood, as described by others.24, 25, 30 Mixed venous blood showed smaller changes because of the contribution from nonexercising tissues. At identical workloads after nifedipine, mixed venous O₂ saturation increased and AVOD decreased compared with values after placebo. However, iliac venous O₂ saturation changed in the opposite direction, so that AIOD actually increased. Although this change was small, it contrasted sharply with the larger and opposite change in AVOD. These changes also contrasted with the parallel de-
crease in AVOD and AIOD at rest. The higher O₂ saturation in mixed venous blood during exercise after nifedipine could be explained by a higher O₂ saturation in venous blood from nonexercising tissues or by an increased contribution to venous flow from nonexercising tissues, or probably by both factors.

The increased AIOD after nifedipine cannot be interpreted with certainty, since leg blood flow was not measured. During bicycle exercise, VO₂ by the legs accounts for most (72%) of the increase in total VO₂. Assuming that the total VO₂ reflected regional leg VO₂, then on the Fick principle leg blood flow probably decreased. The alternative explanation, that regional VO₂ increased in the legs but decreased elsewhere after nifedipine, is less plausible.

To estimate the magnitude of these changes, we adopted the equation of Jorfeldt and Wahren, which was derived from their data on upright bicycle exercise in normal men. The equation assumed that 24% of the total VO₂ at rest and 72% of the increase in total VO₂ during exercise were used by both legs. Because our patients served as their own controls, the exact percentages used were not critical. However, an implicit assumption was that nifedipine did not alter these percentages. Leg blood flow was calculated by dividing leg VO₂ by the AIOD. Allowing for the limitations of this equation, we found that the calculated blood flow to both legs decreased by 13% from 5.45 ± 2.45 to 4.74 ± 1.98 liters/min at identical workloads after nifedipine (p < .006). Because the cardiac output was higher, the distribution of cardiac output fell by 22% from 50 ± 7% to 39 ± 7% (p < .001) (figure 8).

Blood sampled from the distal external iliac vein drains both muscular and nonmuscular tissues in the leg, and an increase in O₂ saturation of mixed venous blood was more plausible. The Pco₂ also showed opposite changes in mixed venous and iliac venous blood during exercise after nifedipine. The decrease in mixed venous blood and increase in iliac venous blood, on the Fick principle, could be caused by the increased cardiac output and reduced leg flow. Increased CO₂ or hydrogen ion (H⁺) production caused by increased anaerobic metabolism in the leg muscles could also increase iliac venous Pco₂. Changes in pH were small and not significant, and could have been the result of buffering of H⁺ in blood.

Arterial lactate concentration increased during exercise after placebo and increased more after nifedipine, indicating increased anaerobic metabolism. This sup-

![Figure 8](http://circ.ahajournals.org/)

**FIGURE 8.** Left: Blood flow to both legs at rest before and after drug therapy, at identical intermediate workloads (SUBMAX) and at the common maximum workloads (MAX) on the placebo and nifedipine days. Blood flow is calculated from the formulas of Jorfeldt and Wahren (see text). Right: The same data expressed as a percent distribution of the cardiac output. Means ± 1 SEM are shown.
ports the concept of reduced nutrient flow and O₂ availability to the exercising muscles. The effects of nifedipine directly on respiratory enzymes and lactate production in skeletal muscle cannot be discounted, but little information on this phenomenon is available.

Five patients reported more leg fatigue during exercise after nifedipine and no patient reported less leg fatigue. This corroborates our previous single-blind observations and supports the concept of reduced nutrient flow to the exercising muscles. Increased leg fatigue after nifedipine has not been previously reported. We used symptom-limiting bicycle exercise, which tends to produce more fatigue in leg muscles than treadmill exercise. Patient selection may also be a factor, particularly with patients who are limited by both angina and leg fatigue. The biochemistry of leg fatigue is poorly understood, and both O₂ supply and removal of metabolites may be important. The intracellular concentrations of H⁺ and lactate in skeletal muscle are probably more relevant than the peripheral blood concentrations measured here.

The effects of nifedipine on regional O₂ metabolism and blood flow during exercise have not been previously described. Kugler et al. recently showed that captopril administered acutely in patients with congestive cardiac failure did not significantly increase maximum VO₂ or exercise duration. Although cardiac output and pulmonary arterial O₂ content at maximal exercise were higher after captopril, femoral venous O₂ content was unchanged. Wilson et al. found that during exercise in patients with cardiac failure, intravenous administration of hydralazine increased cardiac output and thermoliation-determined leg blood flow. Both systemic and leg O₂ extraction decreased. The conflict between the results of these two studies and ours may be the result of differences in patient population, vasodilators tested, and study design. An important consideration is the fact that we reduced blood pressure to a greater extent and made exercise measurements at higher workloads, which were associated with a greater distribution of cardiac output to the legs.

This study has demonstrated that generalized vasodilatation by nifedipine can produce opposite changes in regional and systemic O₂ extraction and metabolism during exercise. Thus, in studies of the peripheral effects of vasodilators, measurements should be made in the periphery and should not be estimated from central changes. The data presented here are consistent with the hypothesis that nifedipine shunts blood flow away from exercising leg muscles as a result of generalized vasodilatation. However, the accurate and reliable measurement of exercise leg blood flow is required for firmer conclusions to be drawn.

We are aware of limitations in the interpretation of results from short-term drug studies, and the effects of long-term nifedipine therapy remain to be investigated for their clinical relevance. Although central hemodynamic responses to long-term nifedipine therapy may differ, it is possible that generalized vasodilatation and therefore the steal phenomenon during exercise will remain. The relevance to clinical practice is potentially important. Although patients with exercise angina are usually limited by inadequate myocardial perfusion, the worsening of leg fatigue or peripheral vascular disease may be clinically relevant in some patients. These results may also have implications in the treatment of patients with cardiac failure with nifedipine.

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