Changes in myocardial metabolism during therapy in patients with chronic stable angina: a comparison of long-term dosing with propranolol and nicardipine

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ABSTRACT The long-term effects of antianginal therapy on coronary blood flow and myocardial metabolism were studied in 35 patients with chronic stable angina. Arterial and coronary sinus blood samples and coronary blood flow measurements were obtained before and after 1 month of oral administration of propranolol or of the calcium antagonist nicardipine. When the data obtained at a fixed heart rate (10% to 15% above the pretreatment sinus rhythm) were compared, no significant differences were evidenced between the propranolol and the nicardipine groups. Coronary blood flow and myocardial oxygen uptake were unchanged with both drugs. Myocardial lactate uptake increased in 11 patients of the propranolol group (from −2 ± 42 to 66 ± 47 μmol/min, p < .001) and in 11 patients of the nicardipine group (from 0 ± 36 to 31 ± 29 μmol/min, p < .001). In these 22 patients, the increase in lactate uptake was accompanied by reductions in uptake of free fatty acids and by a decrease in the coronary sinus concentration of thromboxane B<sub>2</sub> from 131 ± 87 to 61 ± 32 pg/ml (p < .01), whereas the transcardiac release of prostacyclin increased. None of these changes in free fatty acids or in prostanoid handling were observed in the nine patients (five in the propranolol and four in the nicardipine group) in whom lactate uptake was not augmented. During pacing-induced tachycardia, the metabolic effects of the two drugs appeared different. Myocardial lactate uptake decreased more in the patients receiving propranolol than in those receiving nicardipine and the combined productions of alanine and glutamine rose by 3.2 ± 5.8 μmol/min in the propranolol group while it decreased by 3.1 ± 8.2 μmol/min in the nicardipine group (p < .025 propranolol vs nicardipine). In conclusion, long-term antianginal therapy with propranolol or nicardipine improved several markers of myocardial ischemia in approximately two-thirds of the patients. Although the changes observed at low heart rates were similar with the two drugs, the data also suggest that better metabolic protection is provided by the calcium antagonist during pacing-induced tachycardia.

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β-ADRENOCEPTOR-BLOCKING AGENTS and calcium antagonists are widely used to prevent anginal attacks and have been found to produce symptomatic improvement in more than 50% of the patients with chronic stable angina.1-5 Anginal pain, however, is only one aspect of myocardial ischemia. Alterations in myocardial metabolism, impairment of systolic or diastolic function, and electrocardiographic signs of ischemia are, indeed, frequently observed in the absence of anginal pain.6-10 It is not yet clearly established to what extent these signs of silent myocardial ischemia are also improved during long-term therapy with β-blockers or calcium antagonists.

Moreover, although the short-term effects of these agents on myocardial metabolism and oxygen demand have been widely studied,11-15 to our knowledge, nothing is known about the effects of their long-term administration on coronary blood flow, myocardial metabolism, and oxygen uptake. Finally, there is no evidence that, in this respect, one class of drug might be superior to another.

The aim of this study was therefore to assess the changes in myocardial metabolism produced by ad-
ministration, for 4 weeks, of a β-blocking agent (propranolol) or a calcium antagonist (nicardipine). Nicardipine is a new calcium-channel blocker currently undergoing clinical trials in the United States and Europe. We chose to use it in this study first because its short-term administration improves myocardial metabolism in patients with angina pectoris, and second because at therapeutic doses it has no negative inotropic effects and does not produce bradycardia. The two selected agents therefore had opposite pharmacologic profiles.

Patients and methods

Thirty-five patients (33 men and two women; mean age 55 ± 8 years; range 38 to 71) entered the study. Table 1 summarizes their individual clinical and angiographic characteristics. All suffered from typical exercise-induced angina pectoris and eight also complained of anginal pain at rest. Coronary stenosis of 75% or more of at least one major coronary vessel was demonstrated in all patients. Previous medical therapy included short- or long-acting nitrates in all cases, β-blockers (propranolol or atenolol) in 12 patients, calcium antagonists (nifedipine or diltiazem) in five patients, and combined administration of β-antagonists and calcium blockers in seven patients. The study had been approved by the ethical committee of our institution. All patients gave their informed consent and no complications were observed.

Control study. All cardioactive and antiplatelet drugs, except sublingual nitroglycerin, were withdrawn at least 2 days before the exercise test and the diagnostic cardiac catheterization. The exercise tests were performed the day before catheterization on a bicycle ergometer, as described previously. The initial workload was 20 W and the exercise intensity was increased by 20 W every minute until the patient experienced typical anginal pain or until exhaustion. Three Frank orthogonal leads were constantly monitored and analyzed by computer. The amount of ST segment depression during maximal exercise was measured 60 msec after the end of QRS, with the PR interval as reference level. A positive exercise electrocardiogram was defined by horizontal ST depression of 0.1 mV or more.

The next day, left and right heart catheterization was performed with the patient in the fasting state and without premedication. A No. 7F thermomodulation catheter with pacing electrodes (Webster Laboratories) was introduced into the coronary sinus through an antecubital vein and its position was checked by fluoroscopy and oxygen saturation. Coronary sinus pacing was started at a rate 10% to 15% above the patient’s sinus rhythm and measurements of coronary sinus flow and arterial and coronary sinus blood samples were obtained before any contrast medium injection. Amino acids, free fatty acids, prostacyclin, and thromboxane B2 were measured for determinations of oxygen content and plasma concentrations of lactate, amino acids, free fatty acids, prostacyclin, and thromboxane B2.

After these measurements, heparin was administered and the pacing rate was increased to 135 beats/min. This heart rate was maintained for 3 min before repeating measurements (coronary flow and blood samples for determinations of oxygen content, amino acids, and lactate). When chest pain occurred at a frequency lower than 135 beats/min, measurements were immediately obtained without a further increase in heart rate. After completion of the metabolic study, diagnostic left ventriculography and coronary arteriography were performed.

Therapy and Prevention—Angina Pectoris

Study in patients on long-term therapy. The third day, each consecutive patient was randomly assigned to nicardipine (n = 17) or propranolol (n = 18) therapy and received a 5 week supply of anonymous capsules containing either 40 mg of propranolol or 30 mg of nicardipine. The randomization was made on a double-blind basis following a random list established before the start of the study and independently of the investigators. The initial dose was fixed at 2 capsules/day. On the seventh day, all patients were called and the dose was adjusted according to the number of anginal attacks or the occurrence of side effects. At this stage, the physician could normally guess which drug the patient had received, although the study was initially designed as a double-blind one. In the nicardipine group, 13 patients received a final dose of 90 mg/day; the dose was increased to 120 mg/day in one patient and to 75 mg/day in another one. Two patients were withdrawn from the nicardipine group because of aggravation of their angina. In the propranolol group, the dose was augmented to 120 mg daily in 15 patients and increased up to 200 and 240 mg daily in two patients. One patient with chronic bronchitis dropped out of this group because of dyspnea. The patients were instructed to record their anginal attacks and to use short-acting nitrates if necessary but no aspirin or other antiplatelet agents were allowed during this period. Twenty-eight to thirty-five days after the control study, the exercise test was repeated by patients on drug therapy. The brachial artery was catheterized to record arterial blood pressure and to obtain arterial blood samples. Measurements of coronary blood flow and coronary venous blood samples were obtained by the same protocol and pacing frequencies as in the control study. This metabolic study, done without new hospitalization, was performed 3 to 5 h after the intake of oral drug.

Data analysis. Intra-arterial pressure, measured through a fluid-filled catheter connected to a Statham P23ID strain gauge, and the electrocardiogram were continuously recorded on analog magnetic tape and processed off-line to derive heart rate and the systolic, diastolic, and mean arterial pressure. Coronary flow was measured according to the method of Ganz et al. and coronary vascular resistance was calculated as the ratio of mean arterial pressure to coronary sinus flow. Myocardial metabolite uptake or production was calculated as the ratio (arterial content–coronary sinus content) × coronary blood flow. All blood sample analyses were performed in duplicate. Oxygen contents were determined with a Lex-O2-con analyzer and lactate uptake was assessed by the method of Hohorst. Acid amino acid determinations were performed on a Kontron Liquimat III amino acid analyzer with the use of an MCI cation exchange resin. Free fatty acid levels were determined by an enzymatic colorimetric method (WAKO NEFAC kit; WAKO Chemicals, Neuss, West Germany). The plasma concentrations of 6-keto-prostaglandin (PGF1α), the inactive metabolite of prostacyclin, and of thromboxane B2, the metabolite of thromboxane A2, were determined by radioimmunoassay (Amersham Kit). The variability of 40 analyses of arterial blood in duplicate was 2.7 ± 2.0% for lactate, 2.7 ± 2.2% for the free fatty acids, 4.7 ± 3.5% for alanine, 3.4 ± 2.7% for glutamine, and 8.6 ± 6.0% for glutamic acid. The detection limit for thromboxane B2 and 6-keto-PGF1α was 3.4 pg/sample. The specificity data for the thromboxane B2 antisera used showed 100% cross-reactivity for thromboxane B2, 0.25% for 6-keto-PGF1α, 0.8% for PGF2α, 0.3% for PGE2, and 0.05% for PGE1. The antisera used for 6-keto-PGF1α determinations showed 100% cross-reactivity for 6-keto-PGF1α, 2% for PGE1, 1.4% and 1.2% for PGF2α and PGE1, respectively, and less than 1% for PGI2 and thromboxane B2.

Statistical analysis. The data are presented as mean ± SD. The comparisons between the data obtained before and after therapy were performed with a paired t test, with use of the
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Clinical and angiographic data

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Propranolol group

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AMI, IMI = anterior or inferior myocardial infarction; LMCA = left main coronary artery; LAD = left anterior descending coronary artery; DIAG = diagonal branch; CXA = circumflex coronary artery; MARG = marginal branch; RCA = right coronary artery; COLL = collateral development; EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure;ApiController = apical hypokinesia, Ant. = anterior; Akis = akinesia; Inf. = inferior; P = proximal; M = mid; D = distal; D1, D2, D3 = segments of the right coronary artery; Dip = diprydamole; N = nitrates; Nif = nifedipine; BB = β-blockers (atenolol or propranolol); Dilt = diltiazem.

Angina classification: 1 = exercise-induced angina; 2 = angina at rest.

Bonferroni correction when repeated comparisons were made. The comparisons of the changes observed in the nicardipine and in the propranolol groups were made with a Mann-Whitney U test; rank correlations were calculated with the Spearman rank test.

Results

Data before and after therapy were obtained in 15 patients treated with nicardipine and 17 treated with propranolol. As shown in table 1, these two groups were comparable in terms of age, severity of angina pectoris, incidence of previous myocardial infarction, coronary lesions, global left ventricular pump function, and regional wall motion abnormalities.

Changes in exercise tolerance. During nicardipine therapy, the control heart rate (sitting on the bicycle) increased slightly in 10 patients and decreased in five, the average changes (from 84 ± 21 to 89 ± 19 beats/min) being insignificant. The changes in systolic blood
pressure before exercise (152 ± 24 to 143 ± 21 mm Hg, NS) and in diastolic blood pressure (87 ± 16 to 87 ± 11 mm Hg, NS) were also small. Exercise duration was unchanged in four patients and increased in all the others so that, for the whole group, there was a statistically significant increase in exercise duration from 420 ± 97 to 475 ± 108 sec (p < .002). This increase in exercise duration was accompanied by improvements in ST segment depression at peak exercise (from −0.17 ± 0.09 to −0.14 ± 0.08 mV, p < .05) and by an increase in maximal heart rate from 134 ± 21 to 149 ± 20 beats/min (p < .001). Nicardipine had no effect on the product of systolic pressure and heart rate in either the control state (12,793 ± 4594 vs 12,985 ± 3362 mm Hg/min, NS) or at peak exercise (25,415 ± 6224 vs 26,732 ± 5011 during treatment, NS). Nicardipine plasma levels ranged from 3.5 to 46.9 ng/ml (mean 18.3 ± 13.2). There was a significant correlation between nicardipine plasma levels and the extent of improvement in ST depression during exercise (r = .81; p < .001, Spearman rank test).

During propranolol therapy, the control heart rate was reduced in all but two patients, who experienced an increase in sinus rhythm from 74 to 76 and from 57 to 66 beats/min, respectively. For the whole group, the control heart rate decreased from 84 ± 17 to 68 ± 9 beats/min (p < .001). As in the nicardipine group, there was little change in systolic (152 ± 18 to 146 ± 24 mm Hg; NS) or diastolic (90 ± 14 to 91 ± 10 mm Hg; NS) blood pressure. However, because of the bradycardia, the control pressure-rate product decreased from 12,768 ± 3440 to 9900 ± 1906 mm Hg/min (p < .005). During exercise, maximal heart rate and pressure-rate product were reduced in all patients from 144 ± 23 to 117 ± 17 beats/min (p < .001) and from 25,010 ± 6170 to 18,608 ± 3829 mm Hg/min (p < .001), respectively. ST segment depression improved from −0.17 ± 0.09 to −0.13 ± 0.06 mV (p < .015). Exercise duration was augmented in eight patients only and for the whole group the average increase from 431 ± 119 to 460 ± 105 sec was not statistically significant.

When the changes induced by nicardipine and propranolol were compared, there were no significant differences in improvement in exercise duration or in ST segment depression. As expected, however, the changes in maximal heart rate (+15 ± 12 beats/min after nicardipine vs −27 ± 12 after propranolol) and in pressure-rate product (+5% with nicardipine vs −26% with propranolol) were highly significant (p < .001).

Hemodynamic and metabolic changes. Tables 2 and 3 summarize the average hemodynamic and metabolic changes before and after treatment in the 15 patients of the nicardipine group and in 16 patients of the propranolol group (the coronary sinus could not be catheterized during the second study in the patient 29; table 1).

Data obtained during basal pacing. When the data obtained at a fixed heart rate (10% to 15% above control sinus rhythm) were compared, few hemodynamic or metabolic changes were observed at the group level. Nicardipine and propranolol decreased mean arterial pressure by 12 and 8 mm Hg, respectively (NS, nicardipine vs propranolol), but the coronary sinus flow, the arterio-coronary sinus difference in oxygen content,
TABLE 2

Hemodynamic and metabolic effects of long-term dosing with nicardipine

<table>
<thead>
<tr>
<th></th>
<th>Pacing — Basal</th>
<th>Pacing — Tachycardia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control I</td>
<td>Nicardipine I</td>
</tr>
<tr>
<td>Heart rate</td>
<td>91 ± 12</td>
<td>91 ± 12</td>
</tr>
<tr>
<td>(beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean AP (mm Hg)</td>
<td>104 ± 12</td>
<td>92 ± 17</td>
</tr>
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</tr>
<tr>
<td>CBF (ml/min)</td>
<td>145 ± 42</td>
<td>145 ± 52</td>
</tr>
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</tr>
<tr>
<td>CVR (mm Hg min/ml)</td>
<td>0.77 ± 0.23</td>
<td>0.68 ± 0.17</td>
</tr>
<tr>
<td>Dav oxygen (ml%)</td>
<td>12.5 ± 1.7</td>
<td>12.5 ± 1.4</td>
</tr>
<tr>
<td>Dav lactate (nmol/ml)</td>
<td>91 ± 284</td>
<td>218 ± 268</td>
</tr>
</tbody>
</table>

Lactate EF (%)  
0 ± 46 19 ± 25  -1 ± 21  15 ± 27  p < .05

MV oxygen (ml/min)  
17 ± 5  18 ± 6  21 ± 5\*  22 ± 1\*  p < .05

MV lactate (μmol/min)  
13 ± 41  24 ± 28  4 ± 33  22 ± 40

MV alanine (μmol/min)  
-4.4 ± 4.2  -3.1 ± 2.9  -3.6 ± 4.2  -0.8 ± 7.1

MV glutamine (μmol/min)  
-4.5 ± 4.6  -2.7 ± 1.7  -4.4 ± 5.0  -1.9 ± 2.4

MV glutamic acid (μmol/min)  
5.3 ± 1.7  5.8 ± 2.0  5.5 ± 2.2  5.3 ± 1.9

MV FFA (μeq/min; n = 12)  
35 ± 34  20 ± 13  —  —

Data are mean ± SD; n = 15 unless otherwise specified.
AP = arterial pressure; CBF = coronary blood flow; CVR = coronary vascular resistance; Dav = arteriocoronary sinus difference; EF = extraction fraction; FFA = free fatty acids; MV = myocardial uptake or release.
\*p < .05, control I vs control II; \#p < .05, nicardipine I vs nicardipine II.

and the myocardial oxygen uptake were unchanged in both groups (tables 2 and 3). There was a tendency in both groups for lactate extraction fraction and glutamic acid uptake to increase and for the alanine productions to be reduced. None of these changes were significant-

ly different when the two groups were compared. The examination of the individual results further confirmed the similarity of the hemodynamic and metabolic effects of the drugs under these basal experimental conditions.

TABLE 3

Hemodynamic and metabolic effects of long-term dosing with propranolol

<table>
<thead>
<tr>
<th></th>
<th>Pacing — Basal</th>
<th>Pacing — Tachycardia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control I</td>
<td>Propranolol I</td>
</tr>
<tr>
<td>Heart rate</td>
<td>93 ± 9</td>
<td>93 ± 9</td>
</tr>
<tr>
<td>(beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean AP (mm Hg)</td>
<td>110 ± 21</td>
<td>102 ± 18</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>CBF (ml/min)</td>
<td>147 ± 67</td>
<td>144 ± 56</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVR (mm Hg min/ml)</td>
<td>0.85 ± 0.38</td>
<td>0.79 ± 0.29</td>
</tr>
<tr>
<td>Dav oxygen (ml%)</td>
<td>12.6 ± 1.5</td>
<td>12.2 ± 0.9</td>
</tr>
<tr>
<td>Dav lactate (nmol/ml)</td>
<td>78 ± 231</td>
<td>333 ± 368</td>
</tr>
</tbody>
</table>

Lactate EF (%)  
10 ± 34  25 ± 23  10 ± 13  10 ± 25\*  p < .05

MV oxygen (ml/min)  
18 ± 6  18 ± 7  23 ± 10\*  22 ± 9\*  p < .05

MV lactate (μmol/min)  
10 ± 39  47 ± 47  9 ± 16  30 ± 49\*  p < .05

MV alanine (μmol/min)  
-2.5 ± 3.2  -1.8 ± 2.3  -2.9 ± 2.2  -3.2 ± 2.8

MV glutamine (μmol/min)  
-1.7 ± 1.4  -2.7 ± 2.5  -2.6 ± 2.8  -3.7 ± 3.3

MV glutamic acid (μmol/min)  
4.1 ± 1.8  5.1 ± 1.3  4.0 ± 1.6  5.0 ± 1.8

MV FFA (μeq/min; n = 14)  
27 ± 15  24 ± 29  —  —

Data are mean ± SD; n = 16 unless otherwise specified.
Abbreviations are as in table 2:
\*p < .05, control I vs control II; \#p < .05, propranolol I vs propranolol II.
PATIENTS WITH AN INCREASE IN MYOCARDIAL LACTATE EXTRACTION. Myocardial lactate extraction fraction increased in 11 of 15 patients treated with nicardipine (patients 1 to 11; table 1) and in 11 of 16 patients treated with propranolol (patients 18 to 28; table 1). All these patients reported a subjective decrease in the number of anginal attacks. The reduction was greater than that obtained with previous medical therapy in 13 and similar in nine. In the 11 patients in the nicardipine group, myocardial lactate uptake increased from $-0.3 \pm 36.0$ to $31.0 \pm 29.0 \mu$mol/min ($p < .001$), whereas oxygen uptake was unchanged. Thus, the ratio of lactate uptake/oxygen uptake rose in these patients from $0.0 \pm 1.9$ to $2.1 \pm 2.3$ ($p < .001$). The combined productions of glutamine and alanine also tended to decrease in these patients, from $-9.0$ to $-4.9 \mu$mol/min ($p < .1$). Free fatty acid uptake ranged from 2 to $102 \mu$mol/min (mean $33 \pm 35 \mu$mol/min) before treatment and decreased in the whole subgroup, from $33 \pm 35$ to $10 \pm 17 \mu$mol/min ($p < .05$) after treatment. It is also noteworthy that all but one patient in this group had a nicardipine plasma level greater than 8 ng/ml. One patient had a very low plasma level (3.5 ng/ml), but his improvement in lactate extraction, from 8% to 11%, was also the smallest.

In the 11 patients in the propranolol group in whom there was an increase in myocardial lactate uptake (from $-1.8 \pm 42.0$ to $66.0 \pm 47.1 \mu$mol/min, $p < .001$), the ratio of lactate uptake/oxygen uptake also increased from $0.0 \pm 1.8$ to $4.0 \pm 2.8$ ($p < .001$), but amino acid release remained unchanged. The free fatty acid uptake in these patients ranged from 8 to $44 \mu$mol/min (mean $26 \pm 12 \mu$mol/min). It decreased by an average of $15 \pm 13 \mu$mol/min during therapy in 10 patients, but in one patient it increased from 44 to 113 $\mu$mol/min.

In these 22 patients, the improvements in lactate metabolism were also accompanied by changes in transcardiac handling of thromboxane $B_2$ and prostacyclin. The coronary sinus levels of thromboxane $B_2$ diminished from $131 \pm 87$ to $61 \pm 32$ pg/ml ($p < .01$), thereby reducing the coronary sinus/arterial ratio for thromboxane $B_2$ from $1.12 \pm 0.52$ to $0.62 \pm 0.46$ ($p < .05$). In addition, the coronary sinus/arterial ratio for 6-keto-PGF$_{1\alpha}$ rose from $1.18 \pm 0.48$ before treatment to $1.69 \pm 1.28$ ($p < .05$) during treatment.

PATIENTS WITH A DECREASE IN MYOCARDIAL LACTATE EXTRACTION. In the nine remaining patients, five in the propranolol group and four in the nicardipine group, lactate extraction fraction decreased during treatment. Compared with their previous medical therapy, five patients had an unchanged rate of anginal attacks, three reported an increase, and one a reduction. Only one patient showed a deterioration in exercise duration and ST segment depression during exercise. The eight remaining patients had improved ST depression and unchanged or improved exercise duration. In these patients, however, the coronary sinus/arterial ratio for thromboxane $B_2$ rose during treatment ($0.43 \pm 0.42$ to $0.76 \pm 0.39$, $p < .05$) and the ratio for 6-keto-PGF$_{1\alpha}$ diminished from $1.24 \pm 0.27$ to $1.11 \pm 0.20$ (NS). Myocardial free fatty acid uptake was unchanged in these patients. No statistically significant differences were noted between patients in this subgroup who received propranolol and those who received nicardipine.

Moreover, no differences in coronary anatomy or in the changes in resting heart rate or blood pressure were observed between the nine patients who did not have improved lactate metabolism after drug therapy and the 22 who did. All five nonresponders in the propranolol group had reductions in resting heart rate ($-21 \pm 10$ beats/min) and in maximal heart rate during exercise ($-25 \pm 5$ beats/min) of the same magnitude as those in the responders. In the nicardipine group, however, three of the four nonresponders had a low nicardipine plasma level (patients 14 to 16; table 1).

Data obtained during pacing-induced tachycardia. Tables 2 and 3 show that the administration of nicardipine and propranolol had no significant effects on the coronary blood flow or myocardial oxygen consumption achieved during the pacing-stress test. The reductions in mean arterial pressure ($7 \pm 7$ mm Hg with nicardipine and $8 \pm 8$ mm Hg with propranolol) were also comparable with both drugs and did not reach statistical significance. Nevertheless, when the pacing-stress test was performed in the propranolol group, lactate extraction fraction and lactate uptake fell in all but one patient from 25% to 10% ($p < .02$) and from 47 to 30 $\mu$mol/min ($p < .02$), respectively (table 3). Such a consistent decrease in lactate uptake during pacing-stress test was not observed in this group before therapy. It was also absent in the nicardipine group before or after therapy. Moreover, the reduction in lactate uptake during tachycardia was accompanied by a tendency to produce more alanine and glutamine (from $-1.8$ to $-3.2$ and $-2.7$ to $-3.7 \mu$mol/min, respectively), whereas production of these amino acids was reduced after nicardipine therapy, from $-3.1$ to $-0.8$ and $-2.7$ to $-1.9 \mu$mol/min (tables 2 and 3).

These observations suggested that the protective effects of a $\beta$-blocker might have been different from those of a calcium antagonist during a rise in oxygen demand. The individual results were therefore exam-
ined to verify this hypothesis in various subgroups of patients.

Figure 1 summarizes the changes in myocardial lactate uptake during the pacing-stress test in all the patients in whom therapy had increased myocardial lactate extraction fraction in the basal state (patients 1 to 11 and 18 to 28; Table 1). When the pacing-stress test was performed in these patients before therapy, lactate uptake increased slightly in the two groups. In contrast, when the same test was repeated during therapy, there was a drop in lactate uptake in the propranolol group and the difference between nicardipine and propranolol therapy was statistically significant.

The subgroup of patients in whom lactate production was present during the first pacing-stress test was also examined. Before therapy, nine patients in the nicardipine group (patients 3 to 9, and 11 and 12) and six in the propranolol group (patients 18, 23, 25, 27, 30, and 31) had produced lactate during the pacing-stress test. As shown in Figure 2, in the nine patients treated with nicardipine there was significant improvement with a shift from lactate production to extraction. In contrast, no changes were observed in the six patients treated with propranolol.

The changes in production of alanine and glutamine during the pacing-stress test also significantly differed in the nicardipine and propranolol groups. The combined alanine and glutamine production increased by 3.2 ± 5.8 μmol/min during the pacing-stress test in the patients on propranolol therapy, but was reduced by 3.1 ± 8.2 μmol/min in the nicardipine group (p < .025, nicardipine vs propranolol).

As shown in Tables 2 and 3, the differences between nicardipine and propranolol during the pacing-stress test could not be explained by differences in changes in coronary sinus flow, arterial pressure, or oxygen uptake. It was observed, however, that the oxygen content in the coronary sinus increased during the pacing-stress test before treatment and during propranolol therapy, but that this effect was abolished in nicardipine-treated patients (Figure 3). Moreover, the protective effects of nicardipine during pacing-induced tachycardia appeared related to the nicardipine plasma levels. In the 11 patients with a plasma level greater than 8 ng/ml, the lactate extraction fraction improved from −7 ± 22% during pacing before therapy to 17 ± 31% (p < .01) during treatment. In the four patients with a plasma level of 8 ng/ml or less, the lactate extraction was unchanged (12 ± 10% to 9 ± 18%, NS). Similar results were observed with regard to the production of alanine and glutamine.

**Discussion**

The aim of the study was to assess the long-term effects on the myocardial metabolism of two antian- ginal drugs with different pharmacologic actions. The first drug was propranolol, a β-adrenoceptor antago-
The second drug tested was nicardipine, a calcium antagonist with systemic and coronary dilator properties but devoid, at therapeutic doses, of effects on left ventricular contractility.

The first step before interpreting the results of such a study is to ensure that effective doses of the drugs were really administered to the patients. For that purpose, the protocol allowed the titration of the dose of drug according to the symptomatic relief. The patients were also asked to record the number of their anginal attacks and to perform exercise tests. The significant changes in heart rate observed at rest and during exercise in the propranolol group and during exercise in nicardipine group represent a first indication that the doses used in this study had significant cardiovascular effects.

Nineteen patients (11 receiving nicardipine and eight receiving propranolol) had increased exercise duration after drug therapy, and 16 of these were free of angina and stopped exercising because of leg fatigue or exhaustion. Ten other patients achieved the same workload with less ST segment depression and only three patients showed a deterioration of exercise tolerance during treatment. The average increase in exercise duration appeared slightly greater in the nicardipine than in the propranolol group, but it must be kept in mind that two patients had to be withdrawn from the former group because of an aggravation of their angina. Fifteen patients (seven on nicardipine and eight on propranolol) had fewer anginal attacks during the study than when they were on their previous medications, 12 (six in each group) reported no change, and four in each group reported an increase. The magnitude of the clinical improvement observed in our study group therefore appears comparable to that obtained with similar therapeutic agents in daily clinical practice.

These data also show that a sufficient number of patients in each group had received an optimal dose of the study drug to allow a meaningful analysis of the metabolic data.

Three aspects of our results are worth discussing in detail. The first is the lack of changes in myocardial oxygen uptake and coronary flow during treatment. The second is the marked increase in myocardial lactate uptake accompanied by a reduction in transcardiac release of thromboxane B2 observed in approximately two-thirds of the patients. The third is the fact that the effects of nicardipine and propranolol were significantly different during the pacing-stress test.

Effects of therapy on myocardial oxygen uptake and coronary blood flow. Previous studies have shown that the short-term administration of nicardipine or of other dihydropyridine derivatives has no effect on myocardial oxygen consumption in patients with angina pectoris. Accordingly, the lack of change in this parameter was not unexpected in the nicardipine group. These previous studies also reported an increase in coronary blood flow and coronary sinus oxygen content after short-term dosing with these agents, a finding that was not confirmed in our long-term study. The mean plasma level reached 3 to 5 hr after oral intake of the drug (18 ± 13 ng/ml) is, however, much lower than the mean plasma levels obtained after short-term intravenous administration (96 ± 35 ng/ml after 2.5 mg iv). Our data therefore indicate that improvements in exercise tolerance and myocardial metabolism may be obtained at relatively low plasma levels of nicardipine at which changes in global coronary blood flow are negligible. From our measurements, we cannot exclude the possibility that myocardial blood flow may have been increased at the time of the peak plasma level and we cannot rule out a blood flow redistribution. Nevertheless, these observations cast some doubt on the hypotheses that coronary vasodilation or a reduction in myocardial oxygen demand is the main mechanism of action of the calcium antagonists in patients with chronic stable angina.

In the propranolol group, the major reason that myocardial oxygen consumption was not decreased in the basal state probably was the fact that the measurements were made at a constant heart rate, thereby suppressing the reduction in oxygen demand related to the bradycardia induced by propranolol. Nevertheless, the intravenous administration of propranolol has been shown to decrease myocardial oxygen uptake even when the heart rate is held constant. During oral administra-
tion, this direct oxygen-sparing effect of propranolol, likely to be related to its negative inotropic action, was not observed. With respect to nicardipine, this discrepancy could perhaps be related to lower plasma levels after oral dosing than after intravenous injections. It might also be related to an increase in heart size, offsetting the beneficial effect of the negative inotropic action on the myocardial oxygen requirements.

**Effects of therapy on myocardial metabolism.** In two-thirds of the patients, an increase in myocardial lactate extraction fraction was noted. In these patients, this increase occurred independently of the drug used and independently of changes in oxygen uptake. It resulted in a significant augmentation of the ratio lactate uptake/oxygen uptake. Such changes have been reported after intravenous administration of calcium antagonists or propranolol and have been interpreted as reflecting an improvement in aerobic metabolism in ischemic areas. Other investigators have established that, even in the absence of anginal pain and of net myocardial lactate production, anaerobic glycolysis occurs and lactate is released by the myocardium in most patients with coronary artery disease. When ischemia is reduced, this concealed lactate production decreases, resulting in an increase in net lactate extraction similar to that observed in our patients. These signs of silent myocardial ischemia may reflect the presence of myocardial areas underperfused at rest or of areas "stunned" by previous ischemic episodes that have not yet recovered a normal oxidative metabolism. The reduction in free fatty acid utilization that was also noted in practically all these patients is also thought to improve the viability of the ischemic myocardium. Our data therefore suggest that in a large subset of patients, the prevention of anginal attacks was accompanied by a reduction of the metabolic signs of chronic ischemia. Two other observations support this hypothesis.

The first is the reduction in transcardiac release of thromboxane B2 paralleled by an increase in transcardiac release of 6-keto-PGF1α. High coronary sinus/arterial ratios for thromboxane B2 have been found in patients with severe angina pectoris and are thought to reflect increased thromboxane A2 generation in the coronary vasculature. A reduction in this ratio, accompanied by a rise in the ratio for the stable metabolite of prostacyclin, should indicate a much more normal balance in transcardiac prostaglandin metabolism. Such favorable changes were not observed in the absence of an improvement in lactate uptake. It is not possible from our data to determine if these modifications in transcardiac handling of prostanoids are a cause or a consequence of the reduction in ischemia. Nevertheless, this finding supports the hypothesis that the increase in lactate uptake truly indicates a reduction in myocardial suffering.

A second point is raised by the changes in amino acid production. Alanine and glutamine are released and glutamic acid is taken up by the myocardium as a way to detoxify ammonium ions. The utilization of these metabolic pathways is increased in patients with coronary artery disease, probably because of intracellular pyruvate accumulation and an increased rate of deamination of compounds such as the high-energy phosphate stores. The short-term administration of dihydropyridine derivatives, but not of propranolol, has been shown to reduce alanine and glutamine production in patients with angina pectoris. In the present study, we also observed a trend (p < .1 in basal state, p < .05 during pacing-stress test) for combined alanine and glutamine production to be reduced in patients treated with nicardipine. This suggests that, during long-term treatment, the use of these catabolic pathways is reduced.

**Comparison of nicardipine and propranolol therapy.** The changes in sinus rhythm at rest and at peak exercise were very different in the propranolol and in the nicardipine groups, but no significant hemodynamic or metabolic changes could be demonstrated when values obtained in patients with fixed low heart rates were compared.

During the pacing-stress test, however, lactate uptake and amino acid metabolism were better preserved during nicardipine therapy than after administration of propranolol. Two hypotheses could account for this effect of propranolol during the pacing-stress test. First, it is possible that, when heparin is infused in the presence of propranolol, there is more of an increase in the availability of free fatty acids than under control conditions or in the presence of nicardipine. In this view, the decrease in lactate uptake during the second pacing-stress test would merely reflect a switch in substrate utilization by the myocardium. A second, and more likely, hypothesis is that propranolol provides no special myocardial protection when myocardial oxygen consumption is artificially forced to increase. As expected from its pharmacologic profile, propranolol exerts its anti-ischemic effects mainly by preventing a rise in heart rate and oxygen demand. Thus, its usefulness is limited when myocardial oxygen demand is increased by nonphysiologic means.

In contrast, when oxygen demand rises, nicardipine seems to help the myocardium to maintain an oxidative metabolism and to preserve its high-energy phosphate.
stores from deamination. It is generally postulated that calcium antagonists exert such a protective action largely through an increase in regional perfusion.\(^{13-15}\)

Although no changes in global coronary sinus flow were measured during our pacing-stress test, our data indicate that a favorable redistribution of blood flow might have occurred during the pacing-stress test in the nicardipine group. Indeed, during the control pacing-stress test, we observed a decrease in oxygen content in the coronary venous blood. Such a paradoxical increase in oxygen content of the venous blood at a time of increased oxygen uptake is commonly observed in patients with angina pectoris. It is likely to reflect a detrimental redistribution of the coronary flow: reduction of endocardium/epicardium ratio\(^{29}\) or steal between two different coronary vessels.\(^{30}\)

During propranolol therapy in our study, this detrimental effect was slightly enhanced but the administration of nicardipine abolished it (figure 3), thereby probably allowing more oxygen to be extracted by previously under-perfused areas. A protection of intracellular metabolic pathways by nicardipine through the prevention of an intracellular calcium overload\(^{31}\) cannot be ruled out but remains purely speculative.

In conclusion, the prevention of anginal attacks by the administration of nicardipine or propranolol is accompanied by an improvement in several markers of silent myocardial ischemia in approximately two-thirds of the patients. Our data also indicate that the response of the ischemic myocardium to tachycardia is different in the presence of nicardipine or propranolol. Other studies are needed to determine if an increase in dose or a combination of these therapeutic agents\(^{32}\) might have further beneficial effects. Additional studies are also necessary to determine if other therapeutic approaches should be considered when the metabolic response to medical therapy appears unfavorable.

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ROUSSEAU et al.


Changes in myocardial metabolism during therapy in patients with chronic stable angina: a comparison of long-term dosing with propranolol and nicardipine.

M F Rousseau, C Hanet, E Pardonge-Lavenne, G Van den Berghe, F Van Hoof and H Pouleur

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