Effects of a Calcium-channel Antagonist on Large and Small Coronary Arteries in Conscious Dogs

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SUMMARY The effects of i.v. nifedipine, 20 μg/kg, on left ventricular (LV) pressure, dp/dt, aortic pressure, heart rate, LV diameters, cardiac output, coronary blood flow and left circumflex coronary arterial diameter, and calculations of late diastolic coronary and total peripheral resistances and left circumflex coronary cross-sectional area were examined in 11 conscious dogs. In dogs with spontaneous rhythm, nifedipine induced an early, transient response characterized by hypotension and peak increases in coronary blood flow and decreases in total peripheral and late diastolic coronary vascular resistances. The peak effects on large coronary arteries were observed 2–5 minutes later, when mean arterial pressure was only 8.2 ± 1.6 mm Hg below control and LV end-diastolic pressure and diameter were not significantly different from control. LV dp/dt was elevated by 7.1 ± 1.1%, heart rate was elevated by 25 ± 3.3 beats/min, and cardiac output remained elevated by 54 ± 7.4%. At this time, coronary cross-sectional area was elevated by 26 ± 3.0%, late diastolic coronary vascular resistance was reduced by 50 ± 2.7%, and total peripheral resistance was 40 ± 3.8% below control. The coronary sinus oxygen content was elevated by 3.4 ± 0.8 vol% and the arteriovenous oxygen difference fell by 3.5 ± 0.8 vol%. After β-adrenergic blockade with propranolol and with heart rate constant or varying, the increases in coronary cross-sectional area and decreases in late diastolic coronary vascular resistance induced by nifedipine were still observed, but were significantly smaller (p < 0.01). Thus, nifedipine dilates both large coronary arteries and coronary resistance vessels, effects that could be attributed in part to β-adrenergic mechanisms. Nifedipine also exerts potent effects on coronary and peripheral arterial vessels, but has little effect on preload.

ANTAGONISTS of slow-channel calcium exchange are now widely used to treat coronary vasospasm and typical angina pectoris. These drugs dilate peripheral vessels and coronary resistance vessels under normal conditions and enhance blood flow to ischemic myocardium during coronary artery occlusion. In patients with coronary artery disease, calcium antagonists increase coronary blood flow. Despite the mass of recent data on the action of these drugs, several questions about the effects of calcium antagonists on the coronary circulation have not been resolved. These questions relate to: (1) the specificity of these drugs for small or large coronary arteries, (2) whether the dilation of coronary vessels involves β-adrenergic mechanisms, (3) whether the dilation of coronary vessels is independent of changes in heart rate and myocardial contractility, (4) the relationship of the potency for dilation of coronary vessels to that of the systemic circulation, and (5) the extent to which the drugs re-
duce preload as well as afterload. The ability of calcium antagonists, especially nifedipine, to dilate large coronary arteries is controversial. Reports of the effects of intracoronary nifedipine in patients indicate that it dilates epicardial coronary arteries, but recent studies in open-chest, anesthetized dogs demonstrate no effect on the large coronary arteries after administration of the drug.

To answer these questions, we studied the effects of nifedipine in the presence and absence of β-adrenergic blockade on measurements of large coronary arterial and left ventricular (LV) dimensions, coronary blood flow and coronary sinus oxygen content, LV and arterial pressures and cardiac output, and on calculations of left circumflex coronary internal cross-sectional area and late diastolic coronary and total peripheral vascular resistances. Nifedipine was selected because it exhibits relatively potent vascular effects in contrast to those on the heart and its conduction system. These experiments were conducted in healthy, conscious dogs to avoid the mitigating influences of recent surgery and general anesthesia.

Methods

Thirteen mongrel dogs were anesthetized with sodium pentobarbital, 30 mg/kg. Transducers were implanted through a thoracotomy in the fifth left intercostal space. Two miniature 7-MHz ultrasonic transducers (2 x 1 mm, 12 mg) were implanted on opposing surfaces of the left circumflex coronary artery, 3–6 cm from its origin. The ultrasonic transducers were covered with Insl-X (Ins1-X Products Corp.) and attached to a Dacron backing. The Dacron was sutured to the outer adventitia of the coronary artery using 5–0 suture (Ethicon, Inc.). An electromagnetic or Doppler flow transducer was implanted on the same vessel in 10 dogs and on the left anterior descending coronary artery in three dogs. In dogs in which an electromagnetic flowmeter was used, a hydraulic occluder was implanted distally to confirm zero blood flow. Pacing electrodes were implanted on the right atrium and right ventricle. In all dogs, miniature pressure gauges (Konigsberg Instruments, Inc.) were implanted in the left ventricle and descending thoracic aorta, and heparin-filled Tygon catheters were implanted in the left atrium and descending thoracic aorta. Electromagnetic flow transducers were implanted around the ascending aorta in five dogs to measure cardiac output minus coronary blood flow, and ultrasonic transducers were implanted on opposing endocardial surfaces of the left ventricle to measure LV diameters. During a subsequent operation in five dogs anesthetized with sodium pentobarbital, 30 mg/kg, a Tygon catheter was implanted in the coronary sinus through a right thoracotomy.

LV pressure was measured with the implanted miniature gauges, which were calibrated in vitro with a mercury manometer and cross calibrated in vivo with pressure measurements from the aortic and left atrial catheters attached to Statham P23Db strain-gauge manometers. Coronary blood flow was measured using either a square-wave electromagnetic flowmeter (Benton Instruments) (four dogs), or a Doppler ultrasonic flowmeter (nine dogs). Cardiac output minus coronary blood flow was measured with the Benton electromagnetic flowmeter in five dogs. Arterial and coronary sinus oxygen contents were measured with a Lex O, Con Oximeter (Lexington Instruments) in five dogs. Phasic coronary arterial (13 dogs) and LV diameters (five dogs) were measured instantaneously and continuously with an improved ultrasonic dimension gauge. To measure the relatively small dimensions of coronary arterial diameter accurately, the instrument used in this study was further modified to minimize the acoustic disturbance generated by the electrical excitation of the transmitting crystal. This was accomplished by placing 1000-Ω rheostats in parallel with the crystals at the exciter output and receiver input. These rheostats were adjusted to minimize the ringing observed in the receiving crystal, without substantially affecting the amplitude of the received echo. In addition, the basic 1-MHz repetition rate of the dimension gauge was changed to 2 MHz, which doubled the amplitude of the output voltage and permitted precise calibrations in 0.5-μsec steps. The frequency response of the dimension gauge is flat to 100 Hz. The drift of the instrument is minimal (< 0.01 mm in 6 hours). To further ensure the reliability of the data, repeated calibration references were obtained regularly throughout the experiments, and the received ultrasonic signal was monitored continuously on an oscilloscope. Any major change in crystal alignment was detected in the received signal and invalidated the experiment. Terminal calibrations indicated that over the range of arterial pressures raised or lowered mechanically, coronary arterial diameter and cross-sectional area (CSA) followed passively as long as no active vasodilation or vasoconstriction intervened. Previously, we showed that marked changes in cardiac size or stroke volume have no significant mechanical effect on the spatial relationship of these transducers.

The experiments were conducted 1–3 weeks after operation in healthy conscious dogs lying quietly. Measurements of left circumflex coronary arterial diameter, arterial pressure, LV pressure, LV dP/dt, left atrial pressure, left circumflex or left anterior descending coronary artery blood flow, LV diameters, cardiac output, and heart rate were continuously recorded during control and for 1 hour after nifedipine. The various interventions were carried out on different days. Nifedipine (20 mg) was dissolved in 15 ml of polyethylene glycol, 20 ml of ethyl alcohol, and 65 ml of distilled water and was protected from light. Injection of the vehicle induced no detectable hemodynamic effects.

The effects of bolus i.v. injections of nifedipine, 0.1, 0.2, 1.0, 2.0, 10, 20 and 40 μg/kg, were examined in four dogs. The 20-μg/kg dose was studied extensively because it appeared to be the lowest dose at the top of the dose-response curve (fig. 1). Moreover, this dose approximates the i.v. dose used in patients and is roughly 10 times the intracoronary dose used in patients. On one day, i.v. nifedipine, 20 μg/kg, was administered over 30 seconds. One hour later, when all hemodynamic variables had returned to baseline, propranolol, 1.0 mg/kg, was administered.
Nifedipine, 20 μg/kg, was again injected i.v. In four dogs, α₁-adrenergic blockade was induced with prazosin, 1 mg/kg, in the presence of β-adrenergic blockade, and i.v. nifedipine, 20 μg/kg, was again injected. On a separate day, the effects of nifedipine infused at 4 μg/kg/min for 5 minutes were examined first in the absence and then in the presence of β-adrenergic blockade. The absence of an increase in LV dP/dt response to either norepinephrine, 0.5 μg/kg, or isoproterenol, 0.5 μg/kg, after propranolol confirmed the completeness of β-adrenergic blockade. The effectiveness of α₁-adrenergic blockade was tested with phenylephrine, 5.0 μg/kg. This dose of phenylephrine increased the mean arterial pressure by 33 ± 4 mm Hg before prazosin and by 3 ± 1 mm Hg after prazosin.

The effects of nifedipine, 20 μg/kg, were examined in eight dogs in which the heart rate was held constant by atrial pacing. One week after the dogs had recovered from implantation of the coronary sinus catheter, the experiments were repeated, and simultaneous arterial and coronary sinus blood samples were drawn before and during the peak coronary flow and diameter responses, first in the absence and then in the presence of β-adrenergic blockade.

The data were recorded on a 14-channel magnetic tape recorder (Bell & Howell Co.) and played back on two multichannel oscillographs (Gould-Brush). Mean pressures and coronary diameters and blood flows were assessed using RC filters with 2-second time constants; the mean aortic blood flow was assessed using an RC filter with over 8-second time constant. LV dP/dt was derived by differentiating the LV pressure signal using a Philbrick operational amplifier (Teledyne Philbrick) connected as a differentiator and having a frequency response of 700 Hz. A triangular signal with known slope (rate of change) was substituted for the pressure signal to calibrate the differentiator directly.

Heart rate was measured continuously with a cardiometer triggered by the LV pressure pulse. While external coronary diameter was measured continuously, the internal radius was calculated at autopsy. While measuring external coronary diameter, a known length of coronary artery was excised to evaluate wall mass and wall thickness. Thus, wall volume could be calculated as the quotient of mass and density (d = 1.06 g/cm³). After the wall volume, one wall thickness value, and external diameter were known, the internal coronary diameter and CSA were calculated. Late diastolic coronary resistance (LDCR), which primarily reflects small coronary vessel resistance, was calculated as the quotient of late diastolic arterial pressure and late diastolic coronary blood flow. Total peripheral resistance was calculated on the quotient of mean arterial pressure and cardiac output.

The mean and SEM were calculated for all variables. Data for multiple responses were analyzed before and after β-adrenergic blockade using analysis of variance, whereas single responses in the same dogs were analyzed by t test for paired comparisons.

**Results**

The results are expressed as mean ± SEM. Control values and confidence levels for statistics are given in the tables and figures. Although the data were collected continuously, the data presented are for the initial, peak changes in mean arterial pressure and coronary blood flow, which occurred 20–30 seconds after injection (early response) and again for the peak increase in coronary diameter, which occurred 2–5 minutes later (fig. 2). The effects of nifedipine, 0.1–40.0 μg/kg, on calculations of coronary CSA are shown in figure 1. Since 20 μg/kg was the lowest dose on the flat portion of the dose-response curve, the results for this dose will be described in detail.

**Effects of Intravenous Nifedipine (20 μg/kg) in Intact, Conscious Dogs with Spontaneous Rhythm (table 1)**

A bolus of i.v. nifedipine, 20 μg/kg, caused profound hemodynamic effects initially and transiently in the 13 dogs studied. At the time of peak large coronary vessel dilation (2–5 minutes later), LV systolic and mean arterial pressures were reduced by only 5.8 ± 1.3 and 8.2 ± 1.6 mm Hg, respectively; LV dP/dt was elevated by 7.1 ± 1.1%, and heart rate was increased by 25 ± 3.3 beats/min, while LV end-diastolic pressure and diameter were not different from control. The peak effects on coronary blood flow, cardiac output, LDCR, and total peripheral resistance occurred earlier, but mean coronary blood flow and cardiac output remained elevated by 79 ± 8.5% and 54 ± 7.4%, respectively, and LDCR and total peripheral resistance remained depressed by 50 ± 2.7% and 40 ± 3.8%, respectively, during the later response. At this time mean coronary arterial diameter and CSA increased to peak levels of 6.2 ± 0.7% and 26 ± 3.0% above control, respectively. The effects of the drug were more persistent on coronary diameter and CSA, which required 46 ± 5 minutes to subside, than on coronary blood flow, which returned to control within 15 ± 3
minutes. Coronary sinus oxygen content rose and the arteriovenous oxygen (A-V $O_2$) difference fell by maximal amounts initially. During the later response, coronary sinus oxygen content was elevated by $3.4 \pm 0.8$ vol% and the A-V $O_2$ difference was depressed $3.5 \pm 0.8$ vol%.

Infusions of nifedipine induced effects similar to those during the later peak coronary diameter response (table 2). The mean arterial pressure decreased by $14.4 \pm 1.3$ mm Hg, and LV dP/dt increased by $17 \pm 6.7\%$. LV end-diastolic diameter and pressure were not significantly different from control, and heart rate increased by $47 \pm 4.1$ beats/min. Coronary blood flow and cardiac output increased by $131 \pm 19\%$ and $60 \pm 12\%$, respectively, and LDCR and total peripheral resistance decreased by $64 \pm 3.8\%$ and $51 \pm 3.3\%$, respectively. The mean coronary diameter and CSA were elevated by $5.0 \pm 1.5\%$ and $21 \pm 6.4\%$, respectively, coronary sinus $O_2$ content increased by $4.4 \pm 0.3$ vol%, and the A-V $O_2$ difference decreased by $2.7 \pm 0.5$ vol%. All these changes were significant ($p < 0.01$).

**Effects of Intravenous Nifedipine (20-μg/kg Bolus)**
**After β-adrenergic Blockade and with Heart Rate Constant (table 1)**

The initial hemodynamic responses to an i.v. bolus of nifedipine (20 μg/kg) after propranolol and with heart rate constant were similar to those without blockade, except that LV end-diastolic pressure increased ($p < 0.05$) and the initial peak effects on mean coronary blood flow and LDCR were less pronounced ($p < 0.01$).

During the time of peak large coronary arterial effects, changes from control for LV systolic and mean arterial pressures were not significantly different from those in the absence of β-adrenergic blockade. However, LV end-diastolic pressure increased by $1.8 \pm 0.3$ mm Hg ($p < 0.01$) and LV dP/dt decreased by $6.0 \pm 1.6\%$ ($p < 0.01$ vs without blockade). The increases in mean coronary blood flow ($20 \pm 4.1\%$), mean coronary diameter ($2.0 \pm 0.3\%$), and CSA ($7.7 \pm 1.1\%$) and reductions in LDCR ($20 \pm 3.0\%$) were significantly less ($p < 0.01$) than those in the absence of β-adrenergic blockade and with heart rate constant.

**Effects of Intravenous Nifedipine (20 μg/kg) Before and After β-adrenergic Blockade in Conscious Dogs with Spontaneous Rhythm**

Because pacing at a rapid rate elevated coronary CSA and reduced LDCR, it could be argued that the depressed coronary vascular effects of the drug after β-adrenergic blockade were merely due to the altered baseline. To obviate this criticism, the effects of nifedipine were compared in some of the dogs before and after β-adrenergic blockade, but in spontaneous...
TABLE 1. Effects of Nifedipine, 20 μg/kg, in Spontaneous Rhythm Without Blockade, and After β Blockade with Heart Rate Constant

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Peak coronary blood flow</th>
<th>Peak coronary diameter</th>
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<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
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<tr>
<td>Spontaneous rhythm</td>
<td>98 ± 2.2</td>
<td>-26 ± 1.3*</td>
<td>-9.4 ± 1.3*</td>
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<tr>
<td>β block, HR constant</td>
<td>102 ± 3.5</td>
<td>-30 ± 3.2*</td>
<td>-7.0 ± 1.8*</td>
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<tr>
<td>Heart rate (beats/min)</td>
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<tr>
<td>Spontaneous rhythm</td>
<td>86 ± 2.8</td>
<td>83 ± 8.3*</td>
<td>30 ± 4.5*</td>
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<tr>
<td>β block, HR constant</td>
<td>155 ± 3.9‡</td>
<td>0 ± 0§</td>
<td>0 ± 0§</td>
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<td>LV systolic pressure (mm Hg)</td>
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<tr>
<td>Spontaneous rhythm</td>
<td>126 ± 3.7</td>
<td>-16 ± 1.3*</td>
<td>-4.5 ± 1.0*</td>
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<td>β block, HR constant</td>
<td>122 ± 4.5</td>
<td>-24 ± 1.8*</td>
<td>-6.0 ± 2.3*</td>
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<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
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<tr>
<td>Spontaneous rhythm</td>
<td>8.8 ± 0.6</td>
<td>3.3 ± 7.4</td>
<td>6.1 ± 4.0</td>
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<td>β block, HR constant</td>
<td>5.9 ± 0.8</td>
<td>85 ± 46</td>
<td>33 ± 7.6*</td>
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<td>LV dP/dt (mm Hg/sec)</td>
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<tr>
<td>Spontaneous rhythm</td>
<td>3247 ± 193</td>
<td>-21 ± 3.8*</td>
<td>+7.1 ± 1.1*</td>
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<td>β block, HR constant</td>
<td>2367 ± 94‡</td>
<td>-31 ± 2.5*</td>
<td>-6.0 ± 1.6‡</td>
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<td>Coronary diameter (mm)</td>
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<tr>
<td>Spontaneous rhythm</td>
<td>3.99 ± 0.15</td>
<td>0.0 ± 0.4</td>
<td>6.2 ± 0.7*</td>
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<td>β block, HR constant</td>
<td>4.34 ± 0.24‡</td>
<td>-1.0 ± 0.5</td>
<td>2.0 ± 0.3*‡</td>
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<tr>
<td>CSA (mm²)</td>
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<tr>
<td>Spontaneous rhythm</td>
<td>6.22 ± 0.46</td>
<td>0.2 ± 1.6</td>
<td>26 ± 3.0*</td>
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<td>β block, HR constant</td>
<td>7.43 ± 0.80‡</td>
<td>-4.1 ± 2.2</td>
<td>7.7 ± 1.1*‡</td>
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<tr>
<td>Mean coronary flow (ml/min)</td>
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<tr>
<td>Spontaneous rhythm</td>
<td>34.8 ± 3.3</td>
<td>169 ± 13*</td>
<td>79 ± 8.5*</td>
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<tr>
<td>β block, HR constant</td>
<td>39.2 ± 4.3</td>
<td>52 ± 7.7*‡</td>
<td>20 ± 4.1*‡</td>
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<tr>
<td>LDCR (mm Hg/ml · min⁻¹)</td>
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<tr>
<td>Spontaneous rhythm</td>
<td>2.60 ± 0.18</td>
<td>-68 ± 1.9*</td>
<td>-50 ± 2.7*</td>
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<tr>
<td>β block, HR constant</td>
<td>1.84 ± 0.13‡</td>
<td>-43 ± 4.4*‡</td>
<td>-20 ± 3.0*‡</td>
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</table>

*p < 0.01 vs control.
*‡p < 0.05 vs control.
*§p < 0.01 vs spontaneous rhythm.
Abbreviations: HR = heart rate; LV = left ventricular; CSA = left circumflex coronary artery cross-sectional area; LDCR = late diastolic coronary resistance.

Nifedipine induced effects that were qualitatively similar to those before and after β-adrenergic blockade with heart rate constant. During the later peak coronary diameter response to nifedipine, similar reductions in mean arterial pressure were observed in the presence and absence of β-adrenergic blockade are included in the figures.

Nifedipine induced smaller increases in mean coronary blood flow (58 ± 12%), mean external coronary diameter (4.3 ± 0.9%), and coronary CSA (18 ± 3.8%), and reduced LDCR less (47 ± 4.0%) in the presence of β-adrenergic blockade. However, coronary sinus oxygen content increased (4.5 ± 0.7 vol%) and the A-V O₂ difference decreased (3.7 ± 0.7 vol%) to similar degrees with nifedipine after β-adrenergic blockade (fig. 6).
after β-adrenergic blockade in the three dogs studied caused differences before and after β-adrenergic blockade (Fig. 7) that were qualitatively similar to those during the later response to bolus injections described above. The augmentation of coronary diameter with nifedipine was less after than before β-adrenergic blockade.

Effects of Intravenous Nifedipine (20-μg/kg Bolus)

After Combined Beta- and Alpha1-adrenergic Blockade

Intravenous nifedipine, 20 μg/kg, was administered to four conscious dogs in the presence of β-adrenergic blockade and α1-adrenergic blockade with i.v. prazosin, 1 mg/kg. The late response was characterized by reductions in mean arterial pressure (12 ± 1.9 mm Hg from 75 ± 2.5 mm Hg), LV dP/dt (11 ± 1.8% from 2370 ± 212 mm Hg/sec), and LDCR (36 ± 7.8% from 2.58 ± 0.28 mm Hg/ml/min), and increases in coronary diameter (3.5 ± 1.1% from 3.51 ± 0.11 mm) and CSA (15 ± 4.6% from 4.76 ± 0.30 mm²) and coronary blood flow (47 ± 20% from 24 ± 2.3 ml/min). The absolute changes from control in response to nifedipine in these experiments were not statistically different from those in experiments with nifedipine after β-adrenergic blockade.

Discussion

One of the major findings of the present investigation is that nifedipine is a potent dilator of large coronary vessels in terms of both the magnitude and duration of its effect. We studied conscious dogs and measured coronary arterial dimensions instantaneously and continuously. Nifedipine induced a substantial increase in large coronary vessel CSA while other major hemodynamic variables were altered only slightly. Similar results were observed with infusions of nifedipine. Nifedipine has been shown to dilate large coronary arteries in conscious man.9,10 Thus, the data from the current investigation are more compatible with data from unanesthetized man than data from anesthetized, open-chest dogs.

The time course of the effects of nifedipine on systemic hemodynamics, coronary resistance vessels and large coronary vessels differed. The peak systemic hemodynamic effects were observed soon after the i.v. bolus administration of the drug. The mean arterial pressure decreased by 25 mm Hg, and peak increases in coronary blood flow and cardiac output and decreases in LDCR and total peripheral resistance were observed. In contrast, large coronary arterial diameter and CSA increased and reached peak dilation 2–5 minutes later, when the major systemic hemodynamic effects were subsiding. The effects on coronary diameter and CSA were sustained; these variables required 46 ± 5 minutes to return to control levels. In contrast, coronary blood flow returned to control levels within 15 ± 3 minutes. The long-lasting effects on large coronary arteries are particularly important therapeutically, as these vessels may be crucial in directing flow to ischemic myocardium. Thus, in terms of clinical efficacy, the less persistent effects on the coronary resistance vessels are probably less important than the

<table>
<thead>
<tr>
<th>Table 2. Effects of Nifedipine Infusion (4 μg/kg/min)</th>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<tr>
<td>Heart rate (beats/min)</td>
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<td>LV systolic pressure (mm Hg)</td>
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<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
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<tr>
<td>LV dP/dt (mm Hg/sec)</td>
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<tr>
<td>Coronary diameter (mm)</td>
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<td>CSA (mm²)</td>
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<td>Mean coronary flow (ml/min)</td>
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<td>LDCR (mm Hg/ml · min⁻¹)</td>
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<td>Coronary sinus O₂ (vol%)</td>
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<td>LV end-diastolic diameter (mm)</td>
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<td>Cardiac output (ml/min)</td>
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<td>Total peripheral resistance (mm Hg/ml · min⁻¹)</td>
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Abbreviations: See table 1.
relatively minor negative inotropic effects of the drug. Even when reflex effects were minimized by maintaining the heart rate constant and inducing β-adrenergic blockade, the negative inotropic effects of nifedipine, while present, were trivial during the later response, as reflected by a 6.0 ± 1.6% reduction in LV dP/dt and 1.8 ± 0.3 mm Hg elevation in LV end-diastolic pressure and a nonsignificant elevation in LV end-diastolic diameter. Although these effects were trivial in these healthy, conscious dogs, when these agents are administered in the clinical setting to patients with coronary artery disease, the cumulative negative inotropic effects of the calcium antagonist, β-adrenergic blockade and myocardial ischemia could be deleterious.

A recent study from our laboratory indicated that increases in myocardial metabolic demand affect not only coronary resistance vessels, but also the large coronary arteries, which dilate in response to these stimuli. For this reason, and because calcium-channel blockers might frequently be administered to patients receiving β blockers, we examined the effects of nifedipine after propranolol. Under these conditions, nifedipine induced significant dilation of large coronary arteries as well as coronary resistance vessels, albeit to a significantly diminished extent whether the experiments were carried out in spontaneous rhythm (fig. 5) or with heart rate held constant (table 1). Thus, a portion of the coronary vascular effects of the drug can be attributed to reflex changes in myocardial metabolic demand. However, the effects of nifedipine on coronary vessels may be underestimated in the presence of β-adrenergic blockade. Under these conditions, when the drug reduces myocardial metabolic demand by decreasing afterload and myocardial contractility, the direct effects of the drug on the coronary circulation would tend to be masked by the competing effects on the coronary circulation induced by reductions in myocardial metabolic demand.

Alternatively, the mechanism of action of nifedipine...
may in part depend on β-adrenergic activation. This concept has been proposed for another calcium-channel blocker, iopveratril. Greenberg and Wilson observed that vasodilator responses to isoproterenol, but not to nitroglycerin, were attenuated by iopveratril. However, subsequent studies have not supported a role for β-adrenergic mechanisms in mediating the vasodilation of calcium antagonists, and it is currently believed that their vasodilating effects on the coronary circulation are not affected by β-adrenergic blockade. The data from the present investigation provide clear evidence for a link in the mechanisms of action of coronary and systemic dilation. However, this effect indicating a β-adrenergically mediated role for calcium antagonists could merely reflect differences in inotropic and chronotropic responses, which in turn would modify responses of cardiac output as well as coronary blood flow. In support of this argument are the experiments in which coronary sinus oxygen content and the A-V O₂ difference were measured.

If the difference in coronary dilation before and after β blockade were merely due to differences in inotropic and chronotropic responses, then increases in coronary sinus oxygen content and decreases in the A-V O₂ difference should have been similar under these two conditions. Indeed, these responses were observed, further supporting the concept that a fraction of nifedipine’s action on the coronary circulation is controlled by β-adrenergically mediated changes in cardiac rate and contractility. Studies using intracoronary injections in isolated heart preparations or studies in open-chest, anesthetized dogs, in which reflex control of the circulation is depressed, might not find differences in responses to calcium antagonists in the presence and absence of propranolol. In contrast, in the beating heart, particularly in the conscious animal, a β-adrenergically mediated effect on the coronary and systemic circulations appears to play a more prominent role.

The differences between the conclusions of the present study and those of Rowe et al. are more difficult to reconcile. However, in that study, iopveratril was examined in anesthetized, intact dogs, rather than nifedipine in conscious dogs. Although Rowe et al. concluded that the coronary vascular effects of iopveratril were not modified after β-adrenergic blockade, in their study coronary blood flow increased significant-

Figure 6. Late responses (average ± sem) to nifedipine. 20 μg/kg, are shown as absolute change (Δ) for coronary sinus (CS) oxygen content and arteriovenous oxygen (A-V O₂) difference in the absence and presence of β-adrenergic blockade. Pretreatment with β blockade did not affect the ability of nifedipine to augment coronary sinus oxygen content. Asterisk indicates significant change from control.

Figure 7. The effects of nifedipine infusion, 4.0 μg/kg/min, on phasic and mean measurements of coronary diameter (CD), mean arterial pressure (AP), left ventricular (LV) pressure, LV dP/dt, and heart rate (HR) in the same conscious dog studied on separate days in the absence (left) and presence (right) of β-adrenergic blockade. The increase in coronary diameter with nifedipine was significantly attenuated by β-adrenergic blockade.
ly ($p < 0.01$) before, but not after, $\beta$-adrenergic blockade.

The responses to nifedipine could have been smaller because of enhanced $\alpha$-adrenergic vasoconstriction, which was unopposed in the presence of $\beta$-adrenergic blockade. To rule out this possibility, experiments were conducted after $\beta$-adrenergic blockade alone and then after combined $\beta$- and $\alpha$-adrenergic blockade with prazosin. If unopposed $\alpha$-adrenergic vasoconstrictor tone was a major factor, then the response to nifedipine would have been greater after $\alpha$-adrenergic blockade. However, under these conditions, the coronary vascular effects of nifedipine were similar to those in the presence of $\beta$-adrenergic blockade alone. Thus, the differences in coronary vascular responses to nifedipine in the presence and absence of $\beta$-adrenergic blockade are probably related to $\beta$-adrenergic mechanisms or to changes in myocardial metabolic demands, and not to alterations in $\alpha$-adrenergic tone. In a recent study, we studied the possibility that unopposed $\alpha$-adrenergic vasoconstriction mediated the increase in coronary vascular resistance induced by $\beta$-adrenergic blockade, but found no evidence to support that potential mechanism.20

Nifedipine is clearly not a selective coronary vasodilator. The reductions in total peripheral resistance ($40 \pm 3.8\%$) were similar to those in late diastolic coronary vascular resistance ($50 \pm 2.7\%$). However, because nifedipine dilates peripheral vessels, it reduces afterload, which is of major therapeutic importance. In this manner, nifedipine is similar to nitroglycerin. However, nitroglycerin’s mechanism of action appears to be related to its ability to reduce preload as well as afterload23,28 and to dilate large coronary arteries.14,29 In contrast, nifedipine failed to reduce preload as measured by LV end-diastolic diameter or pressure. However, it still reduced afterload and increased large coronary arterial CSA.

In conclusion, nifedipine exerts a potent and long-acting vasodilator effect on coronary vessels in conscious dogs. The vasodilation is not selective for large conductive or smaller resistance arteries. The coronary dilation could be attributed partially to $\beta$-adrenergic mechanisms and to reflex increases in heart rate and myocardial contractility, but also was due to nifedipine’s action on coronary vessels, which increased the coronary sinus oxygen content and reduced the A–V O₂ difference. These potent effects should be of importance not only in alleviating vasospasm, but also in enhancing collateral perfusion to ischemic myocardium. The effects of nifedipine on coronary resistance vessels might be construed as disadvantageous in the presence of regional myocardial ischemia, but several studies argue against this possibility. When nifedipine was administered to patients with myocardial ischemia, blood flow increased to the ischemic as well as to the normally perfused area.10 Moreover, studies in dogs with regional myocardial ischemia indicate that calcium antagonists augment blood flow to severely ischemic myocardium,6,8 further arguing against the possibility that the “coronary steal” phenomenon plays an important role. The sustained effects on large coronary arteries may play a more important role than the relatively transient effects on coronary resistance vessels.

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Clinical Characteristics Associated with Sudden Death in Patients with Variant Angina

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SUMMARY After hospital discharge, 114 patients with variant angina were followed for a mean period of 26 months. Six died suddenly and 13 others were resuscitated from sudden cardiac death. The extent of coronary disease and the prevalence of left ventricular dysfunction in these 19 “sudden death” patients were similar to those in the patients who did not experience sudden death (“survivors”). During spontaneous episodes of ST elevation recorded in hospital, 56 of the 114 patients had serious arrhythmias: ventricular fibrillation in two, ventricular tachycardia in 28, ventricular couplets or bigeminy in 17, second- or third-degree atrioventricular block in six and asystole in three. Patients with and those without these arrhythmias during attacks were similar with respect to extent of coronary disease, left ventricular function and most other clinical variables. The maximal ST elevation, however, was higher in the arrhythmia group (7.4 ± 5.7 vs 3.3 ± 2.3 mm, p < 0.01). Serious arrhythmias were detected in 16 of the 19 sudden death patients, compared with 36 of the 86 survivors (p < 0.01). Sudden death occurred during follow-up in 15 of the 36 patients (42%) with ventricular fibrillation, ventricular tachycardia, high-degree atrioventricular block or asystole during attacks, compared with only four of 69 (6%) without these arrhythmias (p < 0.001).

We conclude that variant angina patients with serious arrhythmias during spontaneous attacks differ from other variant angina patients only in the degree of ischemia during attacks, as reflected by maximal ST elevation, but are at a much higher risk for sudden death.

SUDDEN DEATH is a frequent complication in most subsets of coronary artery disease. Severe multivessel involvement and left ventricular dysfunction are usually present both in patients who die suddenly1,2 and in those resuscitated from sudden death,3,4 and various clinical factors that correlate with sudden death have been identified.5-8

Variant angina is a rare diagnosis in sudden death patients, but sudden death is a common complication of variant angina. Variant angina patients who die suddenly or are resuscitated probably differ from other sudden death patients and other variant angina patients, but the differences between these groups have never been described. The identification of factors associated with sudden death in variant angina could have important therapeutic implications and would also permit stratification of these patients into high- and low-risk subsets. In this study, we compared the clinical characteristics of variant angina patients who died suddenly or were resuscitated with the clinical characteristics of variant angina patients who did not experience sudden death (“survivors”).

Methods

Patients

Variant angina was defined as spontaneous angina at rest with transient ST-segment elevation, rapidly relieved by nitroglycerin, without evidence of myocardial necrosis. The study population consists of 114 consecutive patients who met these criteria and were hospitalized between 1975 and 1981 in the coronary care unit of the Montreal Heart Institute. Forty-seven patients who had ergonovine-induced variant angina attacks but no spontaneous episodes documented during hospitalization were excluded.

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