Nifedipine-Induced Coronary Vasodilation in Ischemic Hearts Is Attributable to Bradykinin- and NO-Dependent Mechanisms in Dogs

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Background—Dihydropyridine calcium channel blockers protect endothelial cells against ischemia and reperfusion injury, suggesting that nifedipine may increase the in vivo cardiac NO level and thus coronary blood flow (CBF) in ischemic hearts. We tested this hypothesis.

Methods and Results—In open-chest dogs, coronary perfusion pressure (CPP) was reduced in the left anterior descending coronary artery so that CBF decreased to one third of the control level, and thereafter CPP was maintained constant (103±8 to 43±3 mm Hg, n=9). We obtained fractional shortening (FS) and lactate extraction ratio (LER) as indices of regional myocardial contraction and metabolism. Both FS (26.4±2.1% to 6.7±2.0%, n=9, P<0.001) and LER (32±6% to −37±5%, n=9, P<0.001) showed a decrease when CPP was reduced. After intracoronary infusion of nifedipine (4 μg·kg⁻¹·min⁻¹), CBF increased from 30±1 to 48±4 mL·100 g⁻¹·min⁻¹ (P<0.01) without a change of CPP (n=9). Both FS (14.0±1.9%, n=9) and LER (−9±7%, n=9) also increased (P<0.01). Nifedipine increased the difference in the level of metabolites of NO (nitrate+nitrite; 9±3 to 25±5 nmol/mL, n=9, P<0.01) and bradykinin (22±5 to 58±4 pmol/mL, n=9, P<0.01) between coronary venous and arterial blood. L-NAME (an NO synthase inhibitor) or HOE-140 (a bradykinin receptor antagonist) attenuated (P<0.05) the increase in CBF (29±3 and 35±2 mL·100 g⁻¹·min⁻¹, n=5 each), FS (4.8±0.6% and 6.9±1.7%, n=5 each), LER (−47±8% and −35±9%, n=5 each), and nitrate+nitrite (3±2 and 8±4 nmol/mL, n=5 each) due to nifedipine infusion.

Conclusions—These results indicate that the calcium channel blocker nifedipine mediates coronary vasodilation and improves myocardial ischemia through both bradykinin/NO-dependent and -independent mechanisms. (Circulation. 2000;101:311-317.)

Key Words: nitric oxide ■ bradykinin ■ ischemia ■ blood flow

Calcium channel blockers are widely used for the treatment of ischemic heart disease because these drugs achieve effective coronary vasodilation.¹ Calcium channel blockers are believed to increase coronary blood flow (CBF) by inhibition of Ca²⁺ entry into smooth muscle cells.² Vascular endothelial function is important for the preservation of organs against ischemic or hypertensive stress,³ and indeed, nifedipine is reported to be cardioprotective against myocardial ischemia and reperfusion injury.⁴ Interestingly, amlodipine increases NO production by unstressed coronary artery endothelial cells via a bradykinin-dependent mechanism,⁵ and nifedipine does not have this action.⁶ However, because the difference between unstressed and ischemic conditions may influence nifedipine-induced coronary vasodilation and because another dihydropyridine calcium channel blocker (benidipine) increases NO production in ischemic hearts,⁷ nifedipine may have the potential to increase cardiac NO levels in ischemic hearts even if it does not increase NO levels in unstressed coronary vessels.

Therefore, we examined whether the calcium channel blocker nifedipine increases CBF via either NO-dependent or -independent mechanisms in ischemic canine hearts. We measured the concentrations of stable degradation products of NO (nitrate+nitrite) in coronary arterial and venous blood. We found that nifedipine increases CBF via both NO-dependent and -independent mechanisms in ischemic canine hearts. L-NAME (an NO synthase inhibitor) or HOE-140 (a bradykinin receptor antagonist) attenuated the increase in CBF due to nifedipine infusion.

Methods

Instrumentation

Mongrel dogs weighing 12 to 23 kg were anesthetized with sodium pentobarbital (30 mg/kg IV). The trachea was intubated, and each

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dog was ventilated with room air mixed with oxygen. The chest was opened through the left fifth intercostal space, and the heart was suspended in a pericardial cradle. The proximal portion of the left anterior descending coronary artery (LAD) was cannulated and perfused with blood via the left carotid artery through an extracorporeal bypass tube. Coronary perfusion pressure (CPP) was monitored at the tip of the coronary arterial cannula, and CBF in the perfused region was measured with an electromagnetic flow probe attached to the bypass tube. A femoral artery was also cannulated for the sampling of reference (control) blood.

In 39 dogs subjected to protocols I through III, a small, short collecting tube (diameter 1 mm, length 7 cm) was inserted into a small coronary vein near the center of the perfused region to sample coronary venous blood. The drained venous blood was collected in a reservoir placed at the level of the left atrium and was returned via the jugular vein. Left ventricular pressure was measured with a micromanometer (Konigsberg P-5) placed through the apex into the left ventricular cavity. Two pairs of ultrasonic crystals were placed on the inner one-third of the myocardiun \( \sim 1 \) centimeter apart to measure the myocardial segmental length with an ultrasonic dimension gauge (Schuessler, 5 MHz). End-diastolic length was determined at the R wave of the ECG, and end-systolic length was determined at the minimum dP/dt. We calculated fractional shortening (FS) as an index of myocardial contractility in the perfused region.\(^6\)

Nifedipine was obtained from Bayer, and we purchased N\(^6\)-nitro-L-arginine methyl ester (L-NAME), HOE-140, and bradykinin from Sigma. L-NAME, HOE-140, and bradykinin were dissolved in saline. Nifedipine was dissolved in a mixture of 15% ethanol, 15% polyethylene glycol 400, and 70% distilled water (by volume) and was administered into the coronary artery. The amount of solvent infused was the same in protocols I through IV (0.33 mL/min). In the preliminary study, intracoronary infusion of the solvent for 30 minutes did not change CBF (91 \( \pm \) 0.33 mL/min). In the preliminary study, intracoronary infusion of the solvent (n \( = \) 5) or HOE-140 (0.5 ng \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \), n \( = \) 5) was infused into the LAD, and measurement of all hemodynamic and metabolic parameters was repeated after 10 minutes. The dose of 4 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) of nifedipine was the maximum dose that caused maximal coronary vasodilation. Thereafter, the infusion of nifedipine was discontinued, and hemodynamic and metabolic parameters were observed at 20 minutes. In other dogs, we infused nifedipine after treatment with either L-NAME (10 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \), n \( = \) 5) or HOE-140 (0.5 ng \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \), n \( = \) 5). The time and order of administration of the drugs before the onset of coronary hypoperfusion were the same as in protocol 1. We observed the hemodynamic parameters and sampled coronary arterial and venous blood as in the control group at 4 minutes after the onset of infusion of either L-NAME or HOE-140.

**Experimental Protocols**

**Protocol 1: Effect of Intracoronary Administration of Nifedipine on Coronary Hemodynamic and Metabolic Parameters in the Nonischemic Myocardium**

Five dogs were used in this protocol. Coronary arterial and venous blood were sampled for blood gas analysis and for determination of the levels of NO metabolites (nitrate+nitrite) and bradykinin. Hemodynamic parameters, ie, left ventricular pressure, dP/dt, and segmental length in the perfused region, were also measured. Four doses (1, 2, 4, and 8 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) of nifedipine were administered into the LAD for 5 minutes each (n \( = \) 5). It took 3 minutes to obtain stable coronary hemodynamic conditions. Between 4 and 5 minutes into each infusion of nifedipine, coronary arterial and venous blood were sampled and systemic and coronary hemodynamic parameters were measured. In the preliminary study (n \( = \) 3), we infused the same 4 doses of nifedipine (1, 2, 4, and 8 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) of nifedipine) without adding any solvent, and we observed that the dose that increased CBF by 100% was the maximum dose that did not cause systemic hemodynamic effects when infused into the coronary artery for 10 minutes. The order of nifedipine doses for intracoronary infusion was randomized. In the same dogs, we also infused the same 4 doses of nifedipine for 5 minutes each after the onset of infusion of L-NAME (10 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \)) or HOE-140 (0.5 ng \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \)). In a preliminary study, we confirmed that the dose of either L-NAME or HOE-140 attenuated the coronary vasodilatory action of bradykinin (20 ng \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) IC) by 85.6% and 89±7%, respectively (n \( = \) 5). Either L-NAME (n \( = \) 5) or HOE-140 (n \( = \) 5) was administered into the LAD 5 minutes before the administration of nifedipine. We measured the hemodynamic parameters and sampled coronary arterial and venous blood 4 minutes after the onset of infusion of either L-NAME or HOE-140. In 5 dogs, we also examined whether this dose of L-NAME attenuated papaverine (15, 30, and 60 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \))-induced coronary vasodilation.

**Protocol 2: Effect of Nifedipine on Coronary Hemodynamic and Metabolic Parameters in the Ischemic Myocardium (Constant Low CPP)**

Nineteen dogs were used in this protocol. After hemodynamic stabilization, CPP was reduced so that CBF was decreased to 33% of the control CBF with an occluder attached to the extracorporeal bypass tube. After a low level of CPP was obtained, the occluder was adjusted to keep CPP constant. All of the hemodynamic parameters were measured 10 minutes after the onset of hypoperfusion, and both coronary arterial and venous blood were sampled. After these measurements, nifedipine (4 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) of nifedipine was the maximum dose that caused maximal coronary vasodilation. Thereafter, the infusion of nifedipine was discontinued, and hemodynamic and metabolic parameters were observed at 20 minutes. In other dogs, we infused nifedipine after treatment with either L-NAME (10 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \)), n \( = \) 5) or HOE-140 (0.5 ng \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \), n \( = \) 5). The time and order of administration of the drugs before the onset of coronary hypoperfusion were the same as in protocol 1. We observed the hemodynamic parameters and sampled coronary arterial and venous blood as in the control group at 4 minutes after the onset of infusion of either L-NAME or HOE-140.

**Protocol 3: Effect of Nifedipine on Coronary Hemodynamic and Metabolic Parameters in the Ischemic Myocardium (Constant Low CBF)**

Because an increase in CBF may increase shear stress in the coronary arteries, which may secondarily increase the cardiac NO level in ischemic hearts, we tested the effect of nifedipine on cardiac NO levels under constant low CPP. In 15 dogs, after hemodynamic stabilization, CPP was reduced so that CBF was decreased to 33% of the control CBF with an occluder attached to the extracorporeal bypass tube. After a low level of CBF was obtained, the occluder was adjusted to keep CBF constant. All of the hemodynamic parameters were measured 10 minutes after the onset of hypoperfusion, and both coronary arterial and venous blood were sampled. After these measurements, nifedipine (4 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \)) was infused into the LAD, and measurements of all hemodynamic and metabolic parameters were repeated after 10 minutes. Thereafter, the infusion of nifedipine was discontinued, and hemodynamic and metabolic parameters were observed at 20 minutes. In other dogs, we infused nifedipine after treatment with either L-NAME (10 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \)), n \( = \) 5) or HOE-140 (0.5 ng \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \), n \( = \) 5). The time and order of administration of the drugs before the onset of coronary hypoperfusion were the same as in protocol 2.

**Protocol 4: Effect of Nifedipine on the cGMP Content of Epicardial Coronary Arteries in Ischemic Hearts**

In 20 dogs, we investigated whether nifedipine increased the cGMP content of the epicardial arteries in the ischemic myocardium. With an occluder attached to the extracorporeal bypass tube, CPP was reduced so that CBF decreased to one third of the control CBF. After a low CPP was established, the occluder was adjusted to keep CPP at a constant low level. After this low CPP was maintained for 10 minutes, we infused either nifedipine (4 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \), n \( = \) 10) or the solvent (n \( = \) 10) into the LAD for 10 minutes with and without L-NAME. Next, we rapidly removed the epicardial LAD (ischemic region) and left circumflex coronary artery (nonischemic control region) using precooled scissors and a pair of large tweezers and stored the sampled vessels in liquid nitrogen.

**Biochemical Analysis**

Lactate concentration was assessed by an enzymatic assay. LER was calculated by multiplying the coronary arteriogenous difference
in the lactate concentration by 100 and dividing it by the arterial lactate concentration.

The methods for NO\textsuperscript{8} and bradykinin\textsuperscript{9} measurement have been described previously. For these measurements, 2 mL of blood was sampled.

The method of tissue cGMP measurement has been described previously.\textsuperscript{10}

**Statistical Analysis**

Statistical analysis was performed among the groups by ANOVA.\textsuperscript{11,12} When ANOVA revealed a significant difference, Bonferroni’s correction was applied. All values were expressed as mean±SEM. A value of $P<0.05$ was considered significant.

**Results**

**Effect of Intracoronary Administration of Nifedipine on Coronary Hemodynamic and Metabolic Parameters in the Nonischemic Myocardium (Protocol 1)**

The baseline systolic and diastolic blood pressure, heart rate, and CPP were 138±5 (n=5) and 84±6 (n=5) mm Hg, 136±6 bpm (n=5), and 105±6 mm Hg (n=5), respectively, and the intracoronary administration of either L-NAME, HOE-140, or nifedipine did not significantly change any of these parameters. In the untreated condition, nifedipine increased the nitrate+nitrite level in the coronary venous blood relative to that in arterial blood [ΔVA(NO)], as shown in Figure 1. Nifedipine also increased the bradykinin level in the coronary venous blood relative to that in arterial blood [ΔVA(bradykinin): 1.2±1.8 pmol/mL at baseline to 3.4±1.5, 12±2 ($P<0.01$), 23±4 ($P<0.05$), and 27±2 ($P<0.01$) pmol/mL with 1, 2, 4, and 8 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} of nifedipine, respectively (n=5 each)]. Nifedipine increased CBF dose-dependently (Figure 2). This increase in CBF was partially attenuated by either L-NAME or HOE-140. Papaverine increased CBF, and this increase was not attenuated by L-NAME [92±2 and 89±2 mL·100 g\textsuperscript{-1}·min\textsuperscript{-1} at baseline with and without L-NAME (n=5 each); 130±6 and 126±6 mL·100 g\textsuperscript{-1}·min\textsuperscript{-1}, 163±7 and 159±8 mL·100 g\textsuperscript{-1}·min\textsuperscript{-1}, and 198±6 and 205±9 mL·100 g\textsuperscript{-1}·min\textsuperscript{-1} at 15, 30, and 60 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} of papaverine with and without L-NAME (n=5 each)].

**Effect of Nifedipine on Coronary Hemodynamic and Metabolic Parameters in the Ischemic Myocardium (Constant Low CPP) (Protocol 2)**

The baseline systolic and diastolic blood pressure and heart rate were 142±4 (n=19) and 82±4 (n=19) mm Hg and 136±4 bpm, respectively (n=19) in the control state. Neither the intracoronary administration of L-NAME, HOE-140, or nifedipine nor the reduction of CPP significantly changed these parameters. In the low-constant-CPP protocol, 10 minutes after the reduction in CPP, ΔVA(NO) (Figure 3) and ΔVA(bradykinin) (2.0±3.3 at baseline to 22±5 pmol/mL, $P<0.05$, n=9 each) were increased, and nifedipine further increased ΔVA(NO) (Figure 3) and ΔVA(bradykinin) (58±4 pmol/mL, $P<0.01$, n=9 each). In accordance with the in-

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**Figure 1.** Changes in NOx (nitrate+nitrite) levels in coronary venous blood vs arterial blood (left) and NO release (right) during intracoronary administration of nifedipine. Statistical analysis was performed by ANOVA followed by Bonferroni’s correction.

**Figure 2.** Changes in CBF during intracoronary administration of nifedipine with and without L-NAME (10 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}) or HOE-140 (0.5 ng·kg\textsuperscript{-1}·min\textsuperscript{-1}). Statistical analysis was performed by ANOVA followed by Bonferroni's correction.
crease in DVA(NO), nifedipine increased CBF despite the constant CPP (Figure 4). FS and LER, which were reduced after the onset of coronary hypoperfusion, were increased by nifedipine administration (Figure 5). These beneficial effects of nifedipine on the ischemic heart were attenuated by either L-NAME or HOE-140.

Effect of Nifedipine on Coronary Hemodynamic and Metabolic Parameters in the Ischemic Myocardium (Constant Low CBF) (Protocol 3)

The baseline systolic and diastolic blood pressure and heart rate were 140±3 (n=15) and 86±2 (n=15) mm Hg and 141±2 bpm (n=15), respectively, in the control state. Neither the intracoronary administration of L-NAME, HOE-140, or nifedipine nor the reduction of CPP significantly changed these parameters. In the ischemic hearts with a low constant CBF, ΔVA(bradykinin) (2.0±3.0 pmol/mL at baseline to 28±5 pmol/mL, P<0.05, n=5 each) was increased, and nifedipine further increased ΔVA(bradykinin) (56±7 pmol/mL, P<0.05, n=5 each). Nifedipine also increased ΔVA(NO), which was attenuated by L-NAME (Figure 6). Nifedipine decreased CPP because of coronary vasodilation, and this change was attenuated by either L-NAME or HOE-140 (Figure 7). Because CBF remained constant, neither FS nor LER was altered (Figure 8).

Effect of Nifedipine on the cGMP Content of Epicardial Coronary Arteries in Ischemic Hearts (Protocol 4)

Because NO increases cellular cGMP levels, we measured cGMP levels in the epicardial coronary artery with and without nifedipine. Without L-NAME (CPP 105±3 to 47±3 mm Hg, CBF 89±2 to 30±2 mL·100 g−1·min−1, n=5 each), nifedipine increased the cGMP content of the epicardial coronary arteries (247±13 versus 156±15 fmol/mg wet wt (P<0.05) with and without nifedipine in the ischemic region, n=5 each), and this effect was blunted by treatment with L-NAME (49±8 versus 56±9 fmol/mg wet wt, P=NS, with and without nifedipine in the ischemic region, n=5 each).

Discussion

We showed here that nifedipine increases CBF via a bradykinin/NO-dependent mechanism in addition to the bradykinin/NO-independent relaxation of coronary resistance vessels via the blockade of calcium channels, both of which contribute to coronary vasodilation and attenuate the severity of myocardial ischemia.

Nifedipine-Induced NO Production and Coronary Vasodilation in Nonischemic or Ischemic Hearts

It is reported that amlodipine increases NO production by canine coronary endothelial cells but that nifedipine does

Figure 3. Changes in NOx (nitrate+nitrite) levels in coronary venous blood vs arterial blood by intracoronary administration of nifedipine (constant CPP model) during coronary hypoperfusion. Nifedipine increased cardiac NO levels, with this effect being blunted by either L-NAME (10 μg·kg−1·min−1) or HOE-140 (0.5 ng·kg−1·min−1). Statistical analysis was performed by ANOVA followed by Bonferroni’s correction.

Figure 4. Changes in CPP (left) and CBF (right) with infusion and withdrawal of nifedipine during coronary hypoperfusion. Although reduced CPP was maintained at a constant level, nifedipine increased CBF, with this effect being blunted by either L-NAME (10 μg·kg−1·min−1) or HOE-140 (0.5 ng·kg−1·min−1). Statistical analysis was performed by ANOVA followed by Bonferroni’s correction.
not.5 This result may seem to be contradictory to our findings, although it is not. First, Zhang and Hintze5 observed NO production only by coronary arterial endothelial cells. NO is produced not only by endothelial cells13 but also by cardiac myocytes,14 erythrocytes,15 platelets,16 leukocytes,17 and fibroblasts18 in the heart. Therefore, it may be possible that nifedipine stimulates NO release from cells other than endothelial cells. Second, because nifedipine increases NO levels in the ischemic myocardium more than in the nonischemic myocardium, as revealed in the present study, nifedipine may have a less potent effect on NO production than amlodipine in the unstressed nonischemic myocardium.

In nonischemic hearts, because L-NAME partially inhibited nifedipine-induced coronary vasodilation in the present study, the contribution of NO/bradykinin to nifedipine-induced coronary vasodilation seemed to be ≈30% (Figure 2). The remainder of nifedipine-induced coronary vasodilation is attributable to the inhibition of Ca2+ entry into coronary smooth muscle. In contrast, nifedipine-induced coronary vasodilation was largely attenuated by L-NAME in ischemic hearts, suggesting that the effect of nifedipine on the ischemic myocardium was more attributable to NO than its effect on the nonischemic myocardium.

Mechanisms of the Nifedipine-Induced Increase in NO Levels
Because calcium channel blockers increase CBF via inhibition of Ca2+ entry into smooth muscle cells2 and the increase in shear stress due to an increase in CBF enhances NO production by endothelial cells, one may argue that the increase in NO levels due to nifedipine is secondary to the increase in shear stress after the increase in CBF. In the present study, however, L-NAME did not attenuate papaverine-induced coronary vasodilation, and even when CBF was kept constant at a low level during infusion of nifedipine, the cardiac NO level was increased. These results indicate that nifedipine directly affected the metabolism of NO.

Several stimuli exist that facilitate NO production. Acetylcholine, bradykinin, purines, and norepinephrine can all stimulate NO synthase.13 The receptors for one of these substances may already be stimulated because of ischemic stress, and nifedipine may increase the cardiac levels of one of these substances to stimulate the receptor. A calcium channel blocker is reported to activate kallikrein in the kidney,19 which may enhance the increase in bradykinin production in the ischemic heart. Indeed, we showed that nifedipine increases cardiac bradykinin levels, but in the present study we did not elucidate the cellular mechanisms by which nifedipine raises cardiac bradykinin levels.

Physiological and Clinical Relevance
Interestingly, the coronary hemodynamic and metabolic parameters did not completely return to the baseline level by 20 minutes after the withdrawal of nifedipine infusion during coronary hypoperfusion. We observed these parameters for
40 minutes after the discontinuation of nifedipine in the ischemic hearts of other dogs, and we observed only a slight decrease in CBF, but the parameters did not return to baseline, although nifedipine was not detected in the coronary venous blood (data not shown). Nifedipine may bind to the calcium channels or may directly or indirectly affect NO synthase for several hours to cause coronary vasodilation. NO is believed to attenuate the severity of myocardial ischemia; NO increases CBF, decreases myocardial anaerobic metabolism, inhibits platelet aggregation and leukocyte activation, and attenuates sympathetic nerve activity in ischemic hearts. Furthermore, NO is reported to mediate cardioprotection in the late phase of ischemic preconditioning, because at 24 or 48 hours after a brief period of ischemia, NO has an infarct size-limiting effect, which is blunted by L-NAME. The present results suggest that nifedipine may be beneficial for ischemic heart disease. However, nifedipine has not been found to be useful for myocardial salvage or reduction of myocardial ischemia in patients with acute myocardial infarction and patients with unstable angina. Indeed, in the presence of collateral vessels, nifedipine may cause the myocardial steal phenomenon and lead to worsening of ischemia in patients with ischemic heart disease. Therefore, we should be careful in extrapolating the present results to the clinical settings unless a large-scale clinical trial proves the utility of nifedipine.

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