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Cardiovascular Effects of and Interaction Between Calcium Blocking Drugs and Anesthetics in Chronically Instrumented Dogs. III. Nicardipine and Isoflurane

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To assess the interaction between isoflurane and the new calcium channel blocker, nicardipine, mongrel dogs were chronically instrumented to allow the following measurements: aortic, left ventricular and left atrial pressures; heart rate; cardiac output; and carotid, coronary, and renal blood flows. The hemodynamic effects of intravenous nicardipine 5, 10, 30, and 50 μg/kg were measured in awake dogs and during 1.6 and 3.0 per cent (end-tidal) isoflurane anesthesia. Nicardipine induced a dose-dependent fall in mean arterial pressure in both awake dogs and during 1.6 and 3.0 per cent isoflurane anesthesia. Heart rate and cardiac output were increased in proportion to the nicardipine dose in the awake dogs and, to a lesser degree, in the dogs anesthetized with 1.6 per cent isoflurane, but did not change during 3.0 per cent isoflurane anesthesia. Left atrial pressure was unchanged by nicardipine in awake dogs and during anesthesia. Left ventricular maximum rate of tension development (dP/dt) increased in awake dogs and decreased during anesthesia. Coronary blood flow increased dose dependently without anesthesia, and, to a smaller degree, during anesthesia. Nicardipine increased carotid blood flow without anesthesia, whereas it was unchanged during anesthesia. Renal blood flow was unchanged in awake dogs and decreased during anesthesia. The authors conclude that nicardipine is a potent vasodilator that minimally affects cardiac function and regional blood flow in the presence of isoflurane. The interactions between nicardipine and isoflurane are mainly the result of the isoflurane-induced inhibition of the reflex tachycardia elicited by nicardipine. (Key words: Anesthetics, volatile: isoflurane. Arteries: carotid. Heart: blood flow; ventricular function. Ions: calcium blockers, nicardipine (dihydropyridine derivative). Kidney: blood flow. Pharmacology: drug interactions.)

BECAUSE OF THEIR preferential vasodilator properties, dihydropyridine calcium channel blockers represent an interesting group of drugs for treatment of myocardial ischemia, hypertension, and coronary and cerebral vasospasm during anesthesia.[1] Most of the data related to the effects of dihydropyridine calcium channel blockers during inhalational anesthesia have been obtained using nifedipine and halothane. Marshall *et al.* have demonstrated that the negative inotropic properties of halothane and nifedipine are mostly additive *in vitro*.[2] However, it appears that cardiac function is better preserved in the presence of isoflurane than in the presence of halothane when nifedipine is administered.[3]

Clinical use of nifedipine in the acute situation has been limited mainly because the drug is photosensitive and unstable in its intravenous form. Nicardipine hydrochloride, a new dihydropyridine calcium channel blocker derivative,[4,5] is photoresistant and water soluble.[6] In addition, nicardipine has been demonstrated to cause less myocardial depression than nifedipine.[7] Therefore, intravenous nicardipine may be suitable as a treatment for hypertension, myocardial ischemia, or vasospasm during anesthesia.

This study was designed to assess the interactions between nicardipine and isoflurane in chronically instrumented dogs so that the effects of each drug and their combination could be studied separately.

Materials and Methods

INSTRUMENTATION

The basic model has been described previously.[8,9] Briefly, six healthy, mongrel dogs weighing 16.2–20.4 kg were instrumented with the following: Tygon® catheters (Tygon, Norton, Inc., Akron, OH) in the left atrium and thoracic aorta; pulsed Doppler flow probes (Baylor College of Medicine, Houston, TX) around the circumflex coronary, left common carotid and left renal arteries; an electromagnetic flow probe (Micron, Inc., Los Angeles, CA) around the pulmonary artery; and a high-fidelity pressure transducer (Konigsberg, Inc., Los Angeles, CA) in the left ventricular cavity. All animals were studied at least 10 days after surgery, when they were afebrile and trained to lie quietly. The details of the measurement techniques have also been previously published.[8,9] The Doppler flow probes were calibrated in terms of frequency shifts.[10] Aortic, left ventricular and left atrial blood pressures, cardiac output, and carotid, coronary, and renal blood flows were continuously recorded on a Gould®

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polygraph (Gould, Inc., Cleveland, OH) during the experiments. Cardiac output was measured using a Micron RC® 1000 electromagnetic flowmeter. Left ventricular maximum rate of tension development (dP/dt) was derived electronically. Vascular resistances were calculated as the quotient of mean aortic pressure and the respective organ blood flow.

Experimental Protocol

Each dog received nicardipine (5, 10, 30, and 50 μg/kg) as an intravenous bolus awake and during either 1.6 or 3.0 per cent end-tidal isoflurane. In conscious dogs, each dose was injected on separate days. In the presence of 1.6 per cent end-tidal isoflurane, nicardipine (30 μg/kg) was injected on one day and 5, 10, and 50 μg/kg on another day. The effects of all four nicardipine doses were studied during 3.0 per cent end-tidal isoflurane anesthesia on a separate day. All doses were given in random order. Hemodynamic measurements were performed prior to and 1, 3, 5, 10, 15, 20, and 30 min after each dose of nicardipine. Between each nicardipine injection, hemodynamic variables were allowed to return to baseline. The solvent of nicardipine (sorbitol 500 mg, HCl 0.1 N to *p*H 3.5, H_2O USP 10 ml) was also injected intravenously as a bolus both awake and during 1.6 and 3.0 per cent isoflurane anesthesia to verify that it did not produce any cardiac and regional hemodynamic changes.

Anesthesia was induced by mask with nitrous oxide/oxygen/isoflurane. When the animals were sufficiently anesthetized, the trachea was intubated and ventilation was controlled using a Harvard® ventilator (Harvard Apparatus, So. Natick, MA) at tidal volumes of 10–15 $ml \cdot kg^{-1}$ with the rate adjusted to maintain arterial oxygen and carbon dioxide tension as in the awake animal. Immediately after tracheal intubation, nitrous oxide was discontinued and nitrogen was substituted in a concentration that maintained arterial oxygen tension at approximately the same level as in the awake animal. Rectal temperature was maintained throughout the experiment by external heating if necessary. Studies performed during anesthesia were started after at least 20 min constant end-tidal anesthetic concentration.

During anesthesia, end-tidal isoflurane (Beckman LB-2®, Beckman, Inc., Schiller Park, IL) and carbon dioxide (Lifespan 100®, Biochem International, Inc., Waukesha, WI) concentrations were continuously monitored using infrared absorption techniques. Arterial blood gas determinations were made at intervals during anesthesia using a Radiometer ABL® electrode system (Radiometer, Inc., Denmark). Rectal temperature was measured with a thermocouple probe (Yellow Springs Instruments, Yellow Springs, OH). The animals were placed in a right lateral decubitus position (the same position as awake) and they received 3–5 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution during each experiment.

Statistical Analysis

Data were analyzed using a three-way analysis of variance (drug by anesthetic dose by time) for repeated-measures design. Alpha was set at a level of 0.05. When significant, multiple paired comparisons were applied. However, for each paired comparison, the appropriate level of alpha was determined according to the Bonferroni method.[11] Data are presented as mean ± SEM.

Results

There were no differences in baseline hemodynamics *within* each series of nicardipine injections in dogs studied awake and anesthetized with both 1.6 and 3.0 per cent isoflurane. The cardiac and regional hemodynamic values collected before the 50 μg/kg dose of nicardipine, as an example of baseline hemodynamics in awake and anesthetized dogs, are presented in table 1. Administration of isoflurane in a concentration of 1.6 per cent end-tidal resulted in a decrease in mean arterial pressure, stroke volume, and carotid, coronary, and systemic vascular resistances, and an increase in heart rate. The high (3.0 per cent end-tidal) isoflurane concentration produced similar but more pronounced hemodynamic changes. In addition, left atrial pressure was significantly increased, while left ventricular dP/dt and renal vascular resistance were significantly decreased by the high isoflurane concentration.

The nicardipine dose–effect relationship on cardiac and regional hemodynamics in the same awake and anesthetized dogs with 1.6 and 3.0 per cent end-tidal isoflurane anesthesia is presented in figures 1 and 2. In addition, the time–course effects of nicardipine in a dose of 50 μg/kg intravenously injected in the same dogs awake and during 1.6 and 3.0 per cent end-tidal isoflurane are presented in figure 3.

In conscious dogs, nicardipine 5, 10, 30, and 50 μg/kg injected intravenously as a bolus produced a dose-dependent decrease in mean arterial pressure and systemic and coronary vascular resistances, and a dose-dependent increase in heart rate, cardiac output, and left ventricular dP/dt. Simultaneously, a dose-dependent increase in coronary blood flow was recorded without any change in renal blood flow. Carotid blood flow increased, but the magnitude of change was not related to the dose administered. Nicardipine produced decreases in mean arterial pressure during anesthesia similar to those recorded awake. However, the effects of nicardipine on the other hemodynamic variables were less pronounced during anesthesia. Only a slight increase in cardiac output, heart rate, and coronary blood flow during 1.6 per cent isoflurane was recorded, while no changes occurred during 3.0

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TABLE 1. Cardiac and Regional Hemodynamic Values Recorded Awake and during 1.6 and 3.0 Per Cent Isoflurane Anesthesia before Nicardipine Injections (50 μg/kg, iv)

	n	Awake	1.6% isoflurane	3.0% isoflurane
HR beats/min	6	83 ± 6	131 ± 9*	126 ± 8*
MAP mmHg	6	93 ± 3	74 ± 5*	63 ± 2*
CO l/min	5	1.8 ± 0.2	2.0 ± 0.4	1.7 ± 0.2
LVdP/dt max	5	2806 ± 295	2306 ± 298	1614 ± 281*†
LAP mmHg	4	3.5 ± 1.5	6.0 ± 0.9	8.0 ± 1.6*†
CarBF ml · min^{-1}	5	110 ± 12	162 ± 20	156 ± 32
CorBF ml · min^{-1}	4	35 ± 8	35 ± 7	27 ± 5
RenBF ml · min^{-1}	4	98 ± 13	106 ± 18	107 ± 14
SV ml	5	22.3 ± 1.6	14.5 ± 2.0*	14.0 ± 0.6*
SVR units	5	53.7 ± 6.1	39.6 ± 4.2*	37.8 ± 2.9*
CarVR units	5	0.88 ± 0.08	0.47 ± 0.07*	0.45 ± 0.07*
CorVR units	4	3.31 ± 0.91	2.55 ± 0.52*	2.59 ± 0.34*
RenVR units	4	0.97 ± 0.09	0.79 ± 0.20	0.61 ± 0.08*

HR = heart rate; MAP = mean arterial pressure; CO = cardiac output; LVdP/dt = left ventricular dP/dt; LAP = left arterial pressure; CarBF = carotid blood flow; CorBF = coronary blood flow; RenBF = renal blood flow; SV = stroke volume; SVR = systemic vascular resistance; CarVR = carotid vascular resistance; CorVR = coronary vascular resistance; RenVR = renal vascular resistance.

* $P < 0.05$ *vs.* awake.

† $P < 0.05$ *vs.* 1.6% isoflurane.

per cent isoflurane. On the contrary, the effects of nicardipine on left ventricular dP/dt were reversed in the presence of isoflurane. A significant decrease was recorded after 30 μg/kg during both isoflurane concentrations and after 10 and 50 μg/kg during the high isoflurane concentration. During 1.6 per cent isoflurane, nicardipine did not affect left atrial pressure, stroke volume, renal blood flow, and vascular resistance, while a decrease in

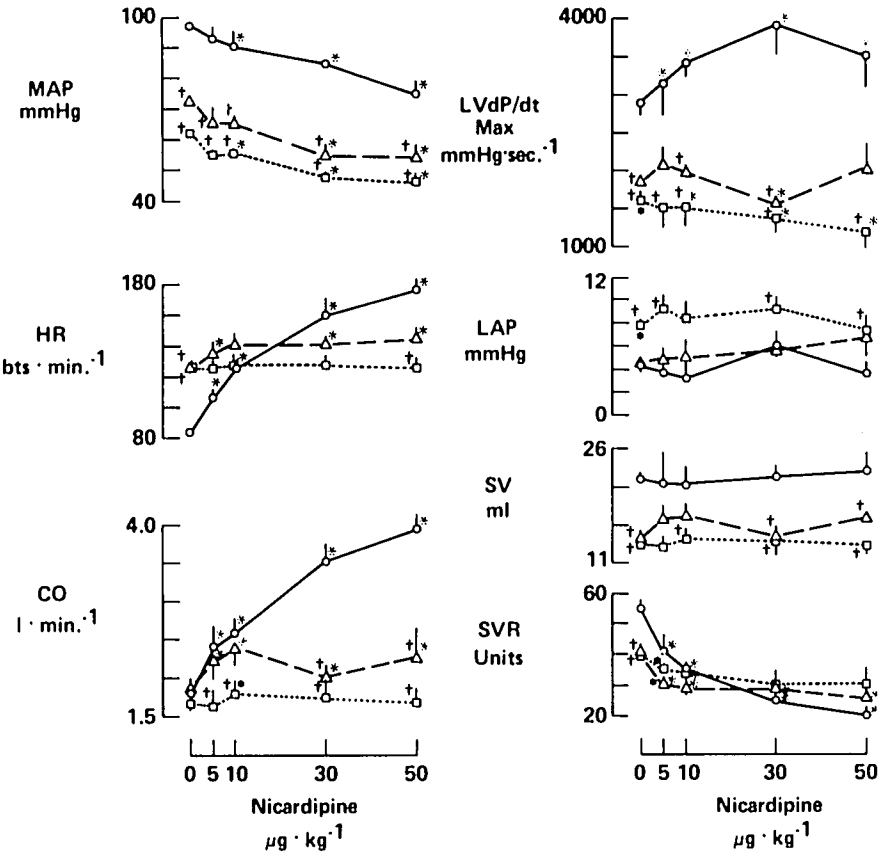

FIG. 1. Maximum changes produced by nicardipine (5, 10, 30, and 50 μg/kg, iv) on mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), left ventricular dP/dt (LVdP/dt), left arterial pressure (LAP), stroke volume (SV), and systemic vascular resistance (SVR) awake (○), and during 1.6 (△) and 3.0 per cent (□) end-tidal isoflurane anesthesia. 0 (control) represents the mean of control measurements before all four doses. * = $P < 0.05$ *vs.* respective control; † = $P < 0.05$ *vs.* awake; ✱ = $P < 0.05$ *vs.* 1.6 per cent end-tidal isoflurane anesthesia.

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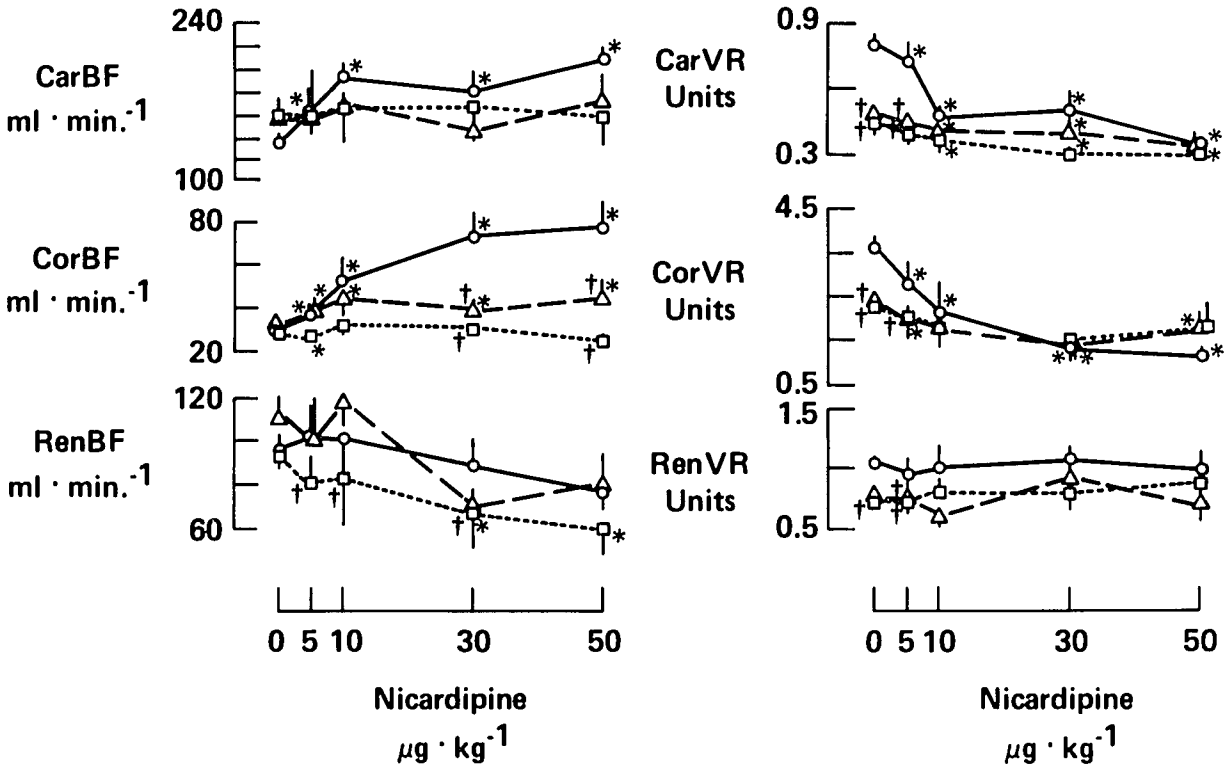

FIG. 2. Maximum changes produced by nicardipine (5, 10, 30, and 50 μg/kg, iv) on carotid (Car), coronary (Cor), and renal (Ren) blood flows (BF) and vascular resistances (VR) in awake dogs (○), and during 1.6 (△) and 3.0 per cent (□) end-tidal isoflurane anesthesia. 0 (control) represents the mean of control measurements before all four doses. * = $P < 0.05$ *vs.* respective control; † = $P < 0.05$ *vs.* awake.

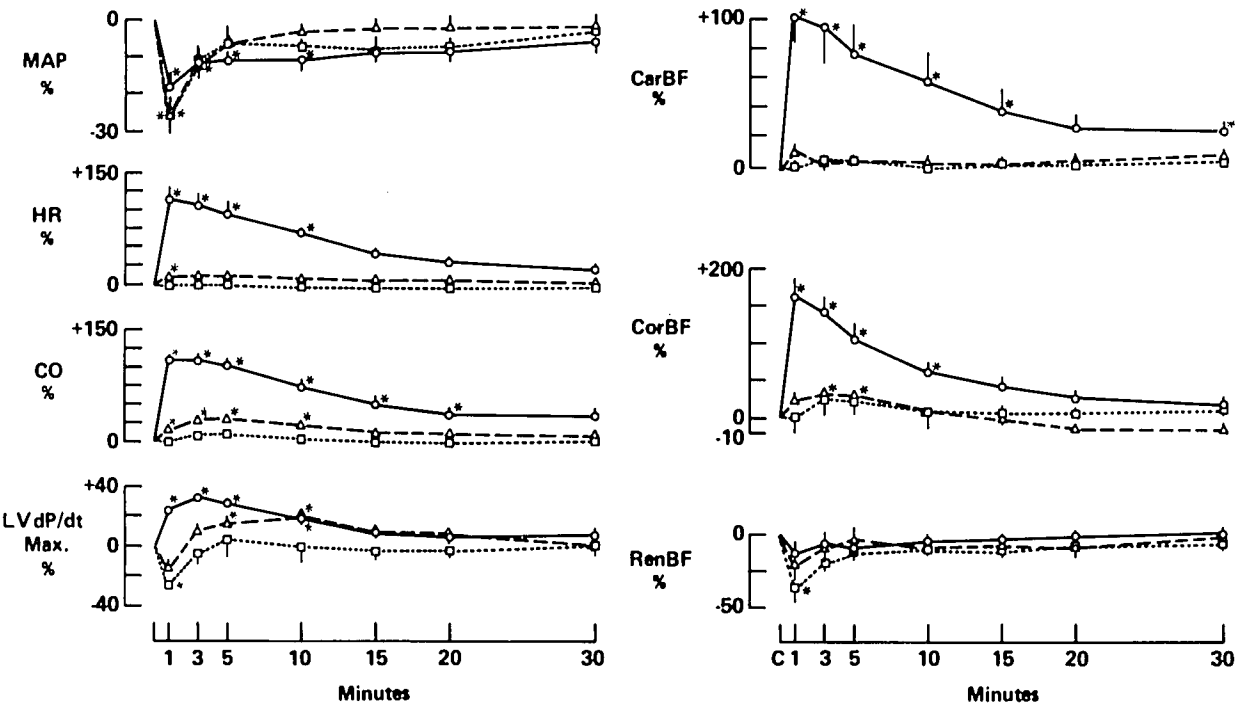

FIG. 3. Time course of changes in cardiac and regional hemodynamics after intravenous injection of nicardipine (50 μg/kg, iv) on awake (○), and during 1.6 (△) and 3.0 per cent (□) end-tidal isoflurane anesthesia presented as per cent of respective control values (mean ± SEM). * = $P < 0.05$ *vs.* control.

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renal blood flow was recorded for the two higher doses during 3.0 per cent isoflurane.

The maximum hemodynamic changes produced by nicardipine occurred within the first min after its injection and lasted 20–30 min in the awake dogs (fig. 3). The duration of nicardipine-induced hemodynamic changes was shorter during isoflurane anesthesia. Except for cardiac output, other hemodynamic variables returned to control within 3–5 min during 1.6 per cent isoflurane. In these experimental conditions, the effects of nicardipine on cardiac output lasted for 10 min. During high isoflurane anesthesia, the duration of hemodynamic changes was even shorter.

Discussion

Isoflurane 1.6 and 3.0 per cent end-tidal produced a decrease in baseline mean arterial pressure of 35% and 46%, respectively. Despite this effect, the magnitude of hypotension induced by nicardipine was similar in awake and anesthetized dogs. The hypotension induced by 3.0 per cent isoflurane was associated with a decrease in left ventricular dP/dt, stroke volume, and an increase in left atrial pressure, but nicardipine did not further decrease myocardial function. The hypotension associated with nicardipine was related to a peripheral vasodilation. Our data indicate that the hypotensive properties of nicardipine and isoflurane are additive. Similar additive interactions have been reported with halothane and nifedipine. Kates *et al.*[12] also demonstrated that in the presence of halothane, the hypotension elicited by nifedipine, like nitroprusside, is related to a decrease in systemic vascular resistance. Tosone *et al.*[13] demonstrated that the hypotensive properties of halothane and nifedipine are also additive. On the basis of these data, it seems that either nifedipine or nicardipine represents an alternative to the use of nitroprusside during surgery for treating hypertension.

In the presence of isoflurane, the tachycardic properties of nicardipine were blunted. The cardiac stimulation elicited by nicardipine in awake dogs was less pronounced and even absent during isoflurane 1.6 and 3.0 per cent end-tidal, respectively. The cardiac stimulation produced by dihydropyridine calcium channel blockers is known to be indirect and related to a baroreflex-mediated response initiated by the peripheral vasodilation.[14] In addition, depending on the drug, dihydropyridine calcium channel blockers can also directly enhance the response due to baroreflex stimulation, an effect that also contributes to the cardiac stimulation recorded.[15,16] Seagard *et al.*[17] have clearly demonstrated that isoflurane blocks the baroreflex pathway both peripherally and centrally. Thus, the inhibition of baroreflex function may play an important role in the reduction of the nicardipine-induced cardiac stimulation recorded in the presence of isoflurane. This hypothesis is supported further by the data reported by Tosone *et al.*,[13] indicating that halothane, which inhibits the baroreflex pathway,[18] also blunted the tachycardic properties of nifedipine. Morever, Kishi *et al.*[19] also reported that acutely injected nicardipine did not affect heart rate in patients anesthetized with high doses of fentanyl. In these experimental conditions, baseline heart rate was 75 ± 9 beats/min. On the basis of these data, the authors suggested that as opposed to the other dihydropyridine calcium channel blockers, nicardipine does not elicit any reflex tachycardia. It is well established that acutely injected nicardipine increases heart rate in conscious humans.[20] The absence of tachycardia recorded during fentanyl anesthesia was probably also the consequence of an alteration in baroreflex function, because fentanyl produces a parasympathetic stimulation *via* its direct effects on the ambiguus nucleus.[21] The anesthetic-induced inhibition of nicardipine and nifedipine reflex tachycardia must be considered to be beneficial, especially in patients with coronary artery disease. Otherwise, an increase in myocardial oxygen demand due to increased heart rate may constitute a limiting factor in the use of these drugs in these patients during anesthesia.

Our data confirm that nicardipine is a potent peripheral, coronary,[22] and carotid vasodilator.[23] In dogs awake and anesthetized with isoflurane, systemic, carotid, and coronary vascular resistances were progressively decreased by 5 and 10 μg/kg of nicardipine, but plateaued during higher doses. In addition, at the higher nicardipine concentrations, these resistances were the same in awake and anesthetized dogs. Nicardipine did not change renal vascular resistance at any dose in either awake or anesthetized dogs. Although inhalational anesthetics have been reported to interfere with transmembrane calcium flux in cardiac muscle,[24–26] their effects on vascular smooth muscle have not been established. In addition, the effects of isoflurane may be different even in the heart.[27] Tosone *et al.*[13] recorded potentiation of the vasodilatory properties of nifedipine with increasing concentrations of halothane. Nicardipine and nifedipine have been demonstrated to have similar vasodilator properties *in vitro*.[28,29] Therefore, the differences between our data and those reported by Tosone *et al.*[13] may be indicative of differences in the mechanism by which halothane and isoflurane interfere with transmembrane calcium movement. Because isoflurane is a more potent vasodilator than halothane,[30,31] it is also possible that the absence of potentiation of the peripheral vasodilator properties recorded in the presence of isoflurane is related to this reduced systemic vascular resistance baseline value. Indeed, the magnitude of dihydropyridine calcium channel blocker vasodilator properties has been demonstrated to be dependent on the degree of vasoconstriction prior to their administration.[32,33]

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Finally, the hypotension produced by isoflurane might be another mechanism contributing to the reduction of nicardipine's effects on carotid and coronary circulation, because arterial pressure is the main determinant of regional blood flow. In awake dogs, the hypotension produced by nicardipine remained within the range of regional autoregulation. Therefore, no decrease in regional blood flow should be expected as the result of the nicardipine-induced hypotension. Although isoflurane did not seem to affect the regional autoregulation mechanisms, the combination of high-dose isoflurane and nicardipine resulted in a decrease of mean arterial pressure below the threshold of autoregulation. In these conditions, a decrease in mean arterial pressure is expected to induce a parallel decrease in regional blood flow.[34] However, the direct carotid and coronary vasodilation produced by both nicardipine and isoflurane maintained carotid and coronary blood flow. Renal blood flow decreased after nicardipine (30 and 50 μg/kg) during 3.0 per cent isoflurane, suggesting a loss of autoregulation in renal circulation.

There is no intravenous form of nifedipine available or currently developed in this country. Rogers *et al.*[35] reported data in which intravenous nifedipine has been infused in the treatment of hypertension in anesthetized patients. The solution had to be prepared by collecting the capsule contents into amber-colored syringes packaged in aluminum envelopes. The sublingual as well as the intranasal routes have also been used in patients undergoing cardiac surgery, but such approaches can only be considered as an alternative. As opposed to nifedipine, nicardipine can be easily injected intravenously, and there is a stable intravenous form that is currently being developed in this country. The other dihydropyridine calcium channel blockers currently being developed, including nimodipine and nitrendipine, are also unstable like nifedipine. Therefore, nicardipine may represent the dihydropyridine calcium channel blocker of choice for use during anesthesia with isoflurane (present data) or fentanyl.[19]

In conclusion, our study indicates that nicardipine is a potent vasodilator that minimally affects cardiac function and regional blood flow in the presence of isoflurane.

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