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Effects of Nifedipine with Isoflurane, Halothane, or Enflurane on Automaticity, Conduction, and Contractility in Isolated Guinea Pig Hearts

Lori A. Gallenberg, Ph.D., David F. Stowe, M.D., Ph.D.,† John P. Kampine, M.D., Ph.D.,‡ Zeljko J. Bosnjak, Ph.D.§*

Background: **Calcium channel blockers and volatile anesthetics have depressant effects on cardiac function. Both groups of drugs appear to exert both qualitatively and quantitatively different effects on electrophysiologic and mechanical function. The aim of this study was to compare the direct cardiac effects of the calcium channel blocker nifedipine in the absence and presence of isoflurane, halothane, or enflurane.**

Methods: **Guinea pig hearts (N = 36) were isolated and perfused with oxygenated Krebs-Ringer solution (pH 7.4, 37° C). Recording electrodes were placed in the right atrium and ventricle to measure heart rate and atrioventricular (AV) conduction time. Isovolumetric left ventricular pressure (LVP) was measured *via* a latex balloon and transducer. Hearts were randomly assigned to one of three anesthetic groups at 0.7 and 1.4 minimum alveolar concentration (MAC) and treated with 15 and 30 nM nifedipine.**

Results: **Nifedipine alone significantly decreased atrial rate and left ventricular pressure, without prolonging AV conduction. Nifedipine plus isoflurane, halothane, or enflurane did not significantly prolong AV conduction compared with the respective anesthetic agent alone, but nifedipine plus isoflurane, halothane, or enflurane significantly decreased atrial rate compared with the effect of the anesthetic alone. Halothane or enflurane plus nifedipine significantly decreased atrial rate more than nifedipine alone or isoflurane plus nifedipine. Isoflurane, halothane, or enflurane plus nifedipine significantly depressed LVP more than the respective anesthetic agent alone. Halothane or enflurane plus nifedipine also significantly depressed LVP more than isoflurane plus nifedipine or nifedipine alone.**

Conclusions: **This study demonstrates that the combined treatment of nifedipine and volatile anesthetics, especially enflurane, additively depresses atrial rate and contractility, but not AV conduction *in vitro*. In comparison with results reported previously, these effects appear less pronounced than those of the combination of volatile agents with diltiazem and, especially, verapamil. (Key words: Animal: guinea pig. Heart: atrial rate; atrioventricular conduction; isolated; left ventricular pressure; perfused. Pharmacology: enflurane; halothane; isoflurane; nifedipine.)**

CALCIUM channel blockers are a group of drugs possessing disparate structures and electrophysiologic effects in humans and animal models.[1–3] Nifedipine, a dihydropyridine derivative, predominantly attenuates slow inward calcium current in vascular smooth muscle and cardiac muscle.[2] As do other calcium channel blockers, nifedipine also depresses automaticity and the maximal rate of rise of the action potential in isolated SA node preparations.[4,5] *In vivo,* nifedipine can increase heart rate, an effect related to the autonomic reflex response to decreased systemic blood pressure caused by peripheral vasodilation, rather than to any direct stimulatory effect on the SA node.[6,7] Nifedipine, unlike the calcium channel blockers diltiazem and verapamil, may also reflexly facilitate, rather than depress, AV conduction *in vivo*.[8] For these reasons, nifedipine has been employed as a vasodilatory agent having minimal negative dromotropic effects. Nifedipine is indicated for treatment and prevention of coronary artery spasm associated with ischemic heart disease. It has been used during anesthesia to treat vasospasm and hypertension and to protect the myocardium during ischemia.[6,7] Among other mechanisms,[9] volatile anesthetics nonspecifically alter cardiac sarcolemmal calcium flux[10–12] to produce quantitatively different negative chronotropic, dromotropic, and inotropic effects.[13–19]

Additive and synergistic direct depressant effects have been demonstrated between the several commonly used volatile anesthetics and several calcium channel blockers. We have previously reported the direct effects

* Assistant Professor, Departments of Anesthesiology and Pharmacology.

† Associate Professor, Departments of Anesthesiology and Physiology.

‡ Chairman, Department of Anesthesiology; Professor of Anesthesiology and Physiology.

§ Professor, Departments of Anesthesiology, Pharmacology, and Physiology.

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Address reprint requests to Dr. Gallenberg: Research Service 151, VA Medical Center, Milwaukee, Wisconsin 53295.

of verapamil[20,21] and diltiazem[22] with isoflurane, halothane, and enflurane on electrophysiologic and mechanical function in isolated guinea pig hearts. Knowledge of the direct cardiac effects of nifedipine in combination with volatile anesthetics would aid in prudent clinical drug use. The isolated guinea pig heart preparation was again utilized in these studies because it provides a functionally and metabolically stable model in which the direct cardiac effects can be examined. It also allows a comparison with our previous findings on the cardiac effects of diltiazem and verapamil in combination with isoflurane, halothane, or enflurane.

Materials and Methods

Hearts were isolated as previously described[17,22,23] from 52 Hartley English short-haired albino guinea pigs (250–500 g) of either sex that had been anesthetized with ketamine (20 mg/kg intraperitoneally). This protocol has been approved by the Animal Care and Use Committee of the Medical College of Wisconsin and the Zablocki VA Medical Center. Once the aorta was cannulated, nonrecirculating perfusion was quickly begun with oxygenated (97% O_2—3% CO_2) Krebs' bicarbonate solution modified[17,23] to include pyruvate, glucose, mannitol, insulin, and ethylenediaminetetraacetic acid (EDTA). Perfusate and organ bath temperatures were maintained at 36.9 ± 0.2° C throughout the experimental period with a thermostatically controlled recirculating water bath. Perfusion pressure was maintained constant at 55 mmHg *via* a 75-cm fluid column. Inflow perfusion pressure was measured at the level of the aorta with a pressure transducer and was monitored continuously on a Model 5 Grass polygraph (Quincy, MA). Inflow pH, P_{CO_2}, and P_{O_2}, measured with an automated blood gas analyzer, were 7.45 ± 0.01, 32 ± 3, and 550 ± 8 mmHg, respectively.

Silver Teflon®-coated bipolar electrodes (125 μm diameter) were placed at the inferior vena cava, right atrial appendage, and right ventricular conus. Spontaneous atrial rate was determined by the atrial electrode signal-to-signal interval and AV conduction time was determined from the atrial to right ventricular conus signal-to-signal interval. The electrode signals were amplified 1,000-fold, filtered at frequencies below 50 Hz and above 600 Hz, and continuously displayed on an image storage oscilloscope. Left ventricular pressure (LVP) was measured with a transducer connected to a saline-filled latex balloon inserted through the left atrium and mitral valve into the left ventricle. The balloon volume was adjusted by a screw-clamp syringe to maintain a diastolic pressure approximately equal to 0 mmHg. In the Langendorff preparation, contractions are isovolumetric, so that tension produced by the left ventricle contracting against the latex balloon can be measured as LVP and directly related to myocardial contractility. Measured variables were continuously recorded on a direct writing polygraph (Astromed® MT 9500R; Astro-Med, West Warwick, RI) and were FM tape recorded.

Stock solutions of nifedipine (Sigma Chemical, St. Louis, MO) were made by dissolving nifedipine in an absolute ethanol, polyethylene glycol (P-2263; Sigma Chemical), and saline vehicle (1:1:8, vol/vol). Serial dilutions of nifedipine stock were made in saline and aliquots were frozen for use throughout the study. In random experiments, equivalent volumes of vehicle alone were also tested and found to have no cardiac effects. Preparation and storage of nifedipine, and all experiments, were performed under minimal light conditions (no artificial light, windows shaded, all glassware and tubing foil-shielded, use of brown glass, reservoirs covered) to minimize photolysis. The effects of nifedipine were tested for a 10-min interval at final perfusate concentrations of 5 and 10 ng/ml (15 and 30 nM). These concentrations were selected because they approximate *in vivo* plasma levels that mimic cardiovascular effects observed for clinical use.[8] The specific protocol is similar to that described previously.[20,22] Three anesthetic treatment groups of 12 hearts each were designated. Each heart was exposed to two random concentrations of only one anesthetic and two random concentrations of nifedipine. With either concentration of nifedipine, steady state effects were achieved within 10 min; additional exposure time did not produce additional effects in the variables studied. An additional 16 hearts served as vehicle and time controls. The anesthetics isoflurane, halothane, and enflurane were administered by agent-specific vaporizers at clinically relevant delivered concentrations of 0.7 and 1.5 vol% isoflurane (Draeger®), 0.5 and 1.0 vol% halothane (Fluotec 3®), and 1.1 and 2.2 vol% enflurane (Ohio-Ohmeda®), alone and with 15 and 30 nM nifedipine over 10-min treatment intervals.

Delivered anesthetic concentrations, which are the same as used in the verapamil[20] and diltiazem[22] studies, were determined by gas chromatography from perfusate samples collected during each experimental period at the aortic inflow point and sealed in air-free glass vials as described previously.[20,22] Using measured bath con-

centrations, in mM, of 0.18 ± 0.01 and 0.37 ± 0.02 (isoflurane), 0.21 ± 0.01 and 0.45 ± 0.04 (halothane), and 0.35 ± 0.02 and 0.59 ± 0.03 (enflurane), and Krebs' solution gas partition coefficients for each anesthetic as described previously,[17] the following effective fractional concentrations were obtained: 0.8 and 1.7 vol% isoflurane; 0.7 and 1.5 vol% halothane; and 1.1 and 1.9 vol% enflurane. Using estimated minimum alveolar concentrations (MAC) of 1.0% for halothane, 2.2% for enflurane, and 1.2% for isoflurane for guinea pig, as noted previously,[17] gave approximately 0.7 and 1.4 MAC for each anesthetic. Perfusate samples taken at the conclusion of each wash-out period demonstrated that no detectable level of anesthetic remained in the perfusate.

All data are reported as mean ± SEM in all tables, figures, and text. Statistical differences were determined for values obtained at 0.7 and 1.4 MAC among the three anesthetic groups (intergroup comparisons) and within each anesthetic group for differences between controls (C1 and C2) and nifedipine concentration (intragroup comparisons). Differences for atrial rate, AV conduction time, and LVP as percent of control were determined by two-way analysis of variance (Statview®; Abacus Concepts, Calabasas, CA; and CLR Anova®; Clear Lake Research, Houston, TX) software programs. F tests were accepted as significantly different when the probability of no difference was less than 5%. Comparison among means were determined by Fischer's least significant difference (LSD) tests. The following comparisons were made: each anesthetic alone, or nifedipine alone, *versus* respective initial control (a); each anesthetic *plus* nifedipine *versus* respective initial drug-free controls (b); high *versus* low anesthetic with or without nifedipine (c); nifedipine *plus* anesthetic *versus* nifedipine alone (d); nifedipine *plus* anesthetic *versus* anesthetic alone (e); enflurane or halothane *versus* isoflurane, with or without nifedipine (f); and high nifedipine *versus* low nifedipine, with anesthetic (g). The above designations are used to denote significance in figures.

Results

Hearts were equally and randomly assigned to the three anesthetic groups for display in tables 1 and 2, and figures 1 and 2. Initial left ventricular pressure averaged 90 ± 5 mmHg for all groups during the initial control (C1) period; values for LVP are expressed as a percentage of these pre-control values normalized to 100%. Table 1 shows that nifedipine alone (*i.e.*, without anesthetic) did not significantly alter AV conduction time but decreased atrial rate and LVP (% of control) compared with the initial control values in a nonconcentration-dependent manner. Mean values following washout of nifedipine, postdrug control (C2), approached the initial control values.

Table 2 shows that neither isoflurane, halothane, nor enflurane alone at 0.7 MAC significantly altered AV conduction time, whereas each anesthetic significantly

Table 1. Effects of Nifedipine Alone for Each Preanesthetic Group

	Anesthetic Group	AVCT (ms)	Atrial Rate (beats/min)	LVP (% control)
Predrug control	Iso	60.2 ± 1.6	218 ± 4	100
	Hal	61.6 ± 1.3	218 ± 5	100
	Enf	63.6 ± 1.6	216 ± 3	100
Low nifedipine (15 nM)	Iso	62.9 ± 1.5	198 ± 5*	77.7 ± 8.5*
	Hal	62.5 ± 1.3	190 ± 6*	72.7 ± 4.4*
	Enf	62.9 ± 1.5	191 ± 4*	78.1 ± 8.6*
High nifedipine (30 nM)	Iso	64.4 ± 1.6	203 ± 6*	79.7 ± 3.5*
	Hal	65.8 ± 1.6	196 ± 8*	76.5 ± 5.3*
	Enf	66.0 ± 1.1	186 ± 6*	74.3 ± 6.2*
Postdrug control	Iso	65.5 ± 1.9	218 ± 4	88.7 ± 4.7
	Hal	64.8 ± 1.8	216 ± 5	91.5 ± 2.8
	Enf	62.3 ± 2.1	215 ± 3	86.9 ± 5.6

Effects of nifedipine alone (0 MAC) on AV conduction time (AVCT), atrial rate, and left ventricular pressure (LVP, percent of initial control, 100%). Values shown were derived from experimental groups subsequently treated with 0.7 and 1.4 MAC of isoflurane (Iso), halothane (Hal), and enflurane (Enf); N = 12 hearts/group. AVCT was not affected by nifedipine. Atrial rate and percent change in LVP were significantly decreased by both nifedipine concentrations compared with initial control values. Postdrug control values were not significantly different from pretreatment control values. Data represent mean ± SEM, N = 12 hearts per group.

* $P < 0.05$ for nifedipine alone or postdrug control *versus* initial control. All other comparisons are nonsignificant.

Table 2. Effects of Nifedipine Plus Anesthetics on AV Conduction Time

	Isoflurane		Halothane		Enflurane	
Nifedipine	0.7 MAC	1.4 MAC	0.7 MAC	1.4 MAC	0.7 MAC	1.4 MAC
C1	65.9 ± 1.3	60.6 ± 1.2	63.9 ± 1.9	61.1 ± 2.5	65.2 ± 1.5	64.9 ± 1.7
0 nM	62.8 ± 1.9	64.9 ± 1.4*	65.7 ± 1.7	66.8 ± 2.5*	63.9 ± 2.3	70.7 ± 2.0*‡§
15 nM	61.2 ± 2.8	63.6 ± 1.3†	63.3 ± 1.2	63.8 ± 1.8	63.3 ± 1.5	70.0 ± 1.0*†
30 nM	64.3 ± 1.8	65.1 ± 1.5†	61.6 ± 1.4	66.6 ± 2.8†	65.1 ± 1.3	71.2 ± 2.0*†
C2	65.9 ± 1.3	63.1 ± 1.8	63.8 ± 1.9	64.6 ± 2.9	65.2 ± 1.5	67.0 ± 1.9

Effects of nifedipine combined with 0.7 and 1.4 MAC of each anesthetic on AV conduction time (ms). At 0.7 MAC no anesthetic, alone or combined with nifedipine, significantly altered AV conduction time. At 1.4 MAC of each anesthetic AV conduction time was significantly increased compared with pretreatment control (C1) values. Generally, 1.4 MAC isoflurane and halothane plus either nifedipine concentration prolonged AV conduction compared with C1 values but not more than did nifedipine alone (table 1) or the anesthetic alone. Enflurane, 1.4 MAC, prolonged AV conduction more than 0.7 MAC enflurane, and more than 1.4 MAC isoflurane. Values are mean ± SEM; N = 12.

* Each anesthetic alone or nifedipine alone *versus* respective initial drug-free control.

† Each anesthetic plus nifedipine *versus* respective initial drug-free control.

‡ High *versus* low anesthetic, with or without nifedipine.

§ Halothane or enflurane *versus* isoflurane, with or without nifedipine.

prolonged AV conduction at 1.4 MAC. The high MAC of enflurane alone prolonged AV conduction more than the high MAC of isoflurane. With the addition of 15 or 30 nM nifedipine, there were no additional changes in AV conduction above effects caused by any given anesthetic alone at either concentration. Atrioventricular dissociation did not occur with any combination of nifedipine and volatile anesthetic or any agent alone.

Figure 1 shows that isoflurane, halothane, and enflurane alone, both at 0.7 (fig. 1A) and at 1.4 MAC (fig. 1B), significantly decreased spontaneous atrial rate compared with pretreatment control values (C1). Enflurane alone directly decreased atrial rate much more than isoflurane alone and also significantly more than halothane alone at the 1.4 MAC level. The effect of enflurane, but not isoflurane or halothane, was concentration dependent. In combination, 15 or 30 nM nifedipine and 0.7 MAC halothane or enflurane, but not isoflurane (fig. 1A), decreased atrial rate more than either agent alone. The effect of nifedipine was not concentration dependent at the molarities studied. Similarly, 30 nM nifedipine and 1.4 MAC halothane or enflurane, but not isoflurane (fig. 1B), decreased atrial rate more than either agent alone. For the 1.4-MAC enflurane group, the decrease in atrial rate was dependent on the concentrations of both enflurane (c) and nifedipine (g). Alone or in combination with nifedipine, atrial rate was depressed more by halothane and, es-

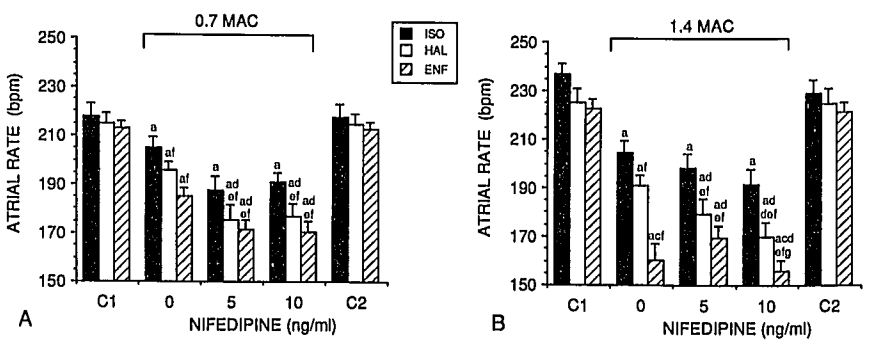

Fig. 1. Effects of nifedipine plus 0.7 MAC (*A*) and 1.4 MAC (*B*) of isoflurane (ISO), halothane (HAL), and enflurane (ENF) on atrial rate in beats per minute (bpm). Nifedipine at 5 and 10 ng/ml is equivalent to 15 and 30 nM, respectively. Data represent mean ± SEM, n = 12 for each anesthetic group. For $P < 0.05$ (a = each anesthetic alone or nifedipine alone *versus* respective initial drug-free controls; b = each anesthetic plus nifedipine *versus* respective initial drug-free control; c = high *versus* low anesthetic with or without nifedipine; d = nifedipine plus anesthetic *versus* nifedipine alone; e = nifedipine plus anesthetic *versus* anesthetic alone; f = halothane or enflurane *versus* isoflurane, with or without nifedipine; and g = high nifedipine *versus* low nifedipine, with anesthetic. The above designations are used to denote significance in tables and figures. Generally, nifedipine plus halothane or enflurane significantly decreased atrial rate more than the individual drugs alone.

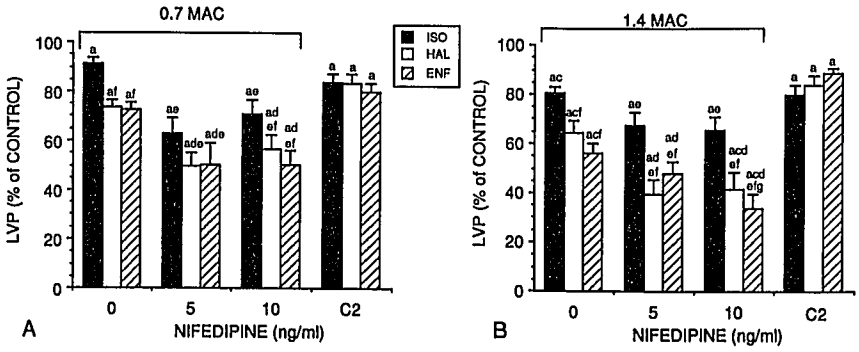

Fig. 2. Effects of nifedipine plus 0.7 MAC (*A*) and 1.4 MAC (*B*) isoflurane, halothane, or enflurane on left ventricular pressure (LVP) (percent of pretreatment control, 100%). Nifedipine at 5 and 10 ng/ml is equivalent to 15 and 30 nM, respectively. See figure 1 for abbreviations. Nifedipine plus each halothane and enflurane significantly decreased LVP more than the individual drugs alone.

pecially, by enflurane than by isoflurane. Sinus arrest did not occur with any treatment.

Figure 2 shows that each anesthetic alone significantly depressed LVP with greater depression at 1.4 MAC (c) when expressed as a percent of LVP control values normalized to 100%. Either concentration of nifedipine in the presence of each anesthetic decreased LVP more than did the anesthetic alone (e). Only for the enflurane group was the percent decrease in LVP dependent on the concentrations of both enflurane (c) and nifedipine (g). In the absence or presence of nifedipine, percent of LVP was decreased more in halothane and enflurane groups than in the isoflurane group.

Six additional hearts randomly exposed only to the vehicle for nifedipine for 10, 30, 45, and 60 min exhibited no change in any variable measured. Ten isolated hearts not subjected to any treatment protocol for 120 min also did not demonstrate any progressive time-related changes in atrial rate, AV interval, or LVP.

Discussion

In general, these results confirm other *in vitro* studies from this[17,20,22] and other laboratories[9,15,18,19,24] showing that enflurane and halothane have overall greater direct cardiac depressant effects than isoflurane. The results demonstrate that nifedipine alone has mild, but significant, effects to slow atrial rate and to depress contractility in isolated hearts without altering AV conduction time. Moreover, this study demonstrates that, compared with diltiazem[22] and verapamil,[20] nifedipine does not additionally depress AV conduction or produce AV block in the isolated heart exposed to isoflurane, halothane, or enflurane.

AV Conduction Effects

Atrioventricular conduction was not significantly prolonged either by 15 or 30 nM nifedipine, or by 0.7 MAC of isoflurane, halothane, or enflurane. The present results are similar to findings for these anesthetics alone in isolated guinea pig hearts[17,20,22] and in dogs.[8,25,26] We reported previously that 75 and 150 ng/ml diltiazem, like 5 and 10 ng/ml nifedipine (15 and 30 nM), did not alter AV conduction time,[22] whereas it was significantly prolonged by 75 and 150 ng/ml verapamil.[20] A higher dose of nifedipine, 100 ng/ml, has been shown to prolong the refractory period in the excised rabbit AV nodal preparation.[4] *In vivo,* however, the hypotensive effect of nifedipine often produces a reflex increase in atrial rate, causing a slowing of AV conduction.[27]

Administration of a volatile anesthetic in the presence of a calcium channel-blocking drug may be expected to enhance the negative dromotropic effect of the individual agents. Using the same preparation, protocol, and concentrations of anesthetics, we reported that verapamil in the presence of isoflurane or halothane additively prolonged AV conduction and, in the presence of enflurane, synergistically prolonged AV conduction leading to a high incidence of AV block.[20] We also demonstrated that diltiazem, given with the same concentrations of anesthetics, only additively, and less severely, prolonged AV conduction and produced a lower incidence of AV dissociation.[22] In the present study, nifedipine with any of the anesthetic agents neither prolonged AV conduction in an additive manner nor caused AV dissociation. The observed absence of AV dissociation with nifedipine, in contrast to other calcium channel blockers in combination with volatile anesthetics, may be an essential feature in its safe perioperative use in patients, especially those with conduction disturbances.[6,7] Lack of a significant effect on AV conduction by nifedipine is probably attributable either to its specificity of action compared with verapamil and diltiazem, to differences in the concentrations of these drugs to produce their desired clinical

effects, or both. Therefore, concentrations of nifedipine higher than therapeutic levels could prolong AV conduction, in the absence or presence of a volatile anesthetic. *In vivo* verapamil and diltiazem produce generally greater effects on cardiac conduction than nifedipine.[8] Ventricular dysrhythmias did not occur in the present study or in our previous studies with verapamil[20] or diltiazem.[22] Interestingly, *in vivo,* verapamil, the most potent negative inotropic agent of the available Ca^{2+} channel blockers, affords the most consistent protection against ventricular dysrhythmias in susceptible animal models.[28]

Atrial Rate Effects

Nifedipine, alone or in combination with isoflurane, halothane, or enflurane, had a more pronounced effect to decrease atrial rate than to prolong AV conduction. Administered alone, each anesthetic and nifedipine significantly decreased atrial rate. In combination, nifedipine caused a greater decrease in atrial rate than halothane or enflurane alone. This suggests a quantitative difference in the direct effects of combining nifedipine with specific volatile agents, because nifedipine in the presence of isoflurane did not further decrease atrial rate. *In vivo* nifedipine has been shown to reflexly increase heart rate compared with other calcium channel blockers administered at equivalent hypotensive doses.[29] This positive chronotropic effect is probably a result of peripheral vasodilation, rather than a direct effect on the SA node. Chronic administration of nifedipine at a therapeutic level is generally believed to have no significant effect on heart rate.[3] In humans, nifedipine also reflexly increases atrial rate, although with a sensitivity less than its vasodilatory effect.[7] However, in the isolated rabbit SA node, 10 nM nifedipine has been reported to decrease spontaneous activity,[5] thereby producing a negative chronotropic effect. Likewise, we demonstrate in this report that nifedipine directly decreases atrial rate when used alone and when combined with isoflurane, halothane, or enflurane. We previously reported that diltiazem[22] and verapamil[20] decrease atrial rate in isolated hearts and that verapamil in the presence of enflurane also caused sinus arrest.

Effects on Contractility

Nifedipine decreased left ventricular pressure in all anesthetic groups, but this effect was not concentration dependent. The effect of each anesthetic alone was to decrease left ventricular pressure in a concentration-dependent manner. There was an added effect of nifedipine with each volatile agent to decrease pressure, but this was not concentration dependent except for the high concentration of enflurane. Compared with our previous studies of volatile anesthetics with verapamil and diltiazem using the same isolated heart model, the current results with nifedipine are qualitatively more similar to those of the diltiazem plus anesthetic study than to the verapamil plus anesthetic study in that verapamil alone caused greater depression of left ventricular pressure, whereas diltiazem and nifedipine produced a similar depression. Cardiac depression by halothane and nifedipine have been reported in the isolated rat heart[30] and in swine[29] and dogs.[31] Nifedipine and volatile anesthetics may share common effects at the sarcolemma.[32]

Table 3. Relative Effects of Calcium Channel Blockers and Volatile Anesthetics on Isolated Hearts

	Atrial Rate				AV Conduction				LV Pressure		
	VER[2]	DIL[2]	NIF[1]		VER[2]	DIL[1]	NIF[0]		VER[3]	DIL[1]	NIF[2]
ISO[2]	↓	↓	↓	ISO[2]	↑↑	↑↑	—	ISO[1]	↓↓↓	↓↓	↓
HAL[2]	↓↓	↓↓	↓↓	HAL[2]	↑↑†	↑↑	—	HAL[3]	↓↓↓	↓↓↓	↓↓
ENF[3]	↓↓↓*	↓↓↓	↓↓	ENF[2]	↑↑↑‡	↑↑§	—	ENF[3]	↓↓↓	↓↓↓	↓↓

Qualitative effects based on data from references 20, 22, and the present study. Arrows refer to direction and degree of combined effects. Superscripts refer to degree of individual drug effects. VER = 150 ng/ml verapamil; DIL = 150 ng/ml diltiazem; NIF = 10 ng/ml nifedipine; ISO = 2.1% isoflurane; HAL = 1.5% halothane; ENF = 2.1% enflurane (effective measured concentrations).

* 17% incidence of sinoatrial block.

† 25% incidence of AV dissociation.

‡ 67% incidence of AV dissociation.

§ 31% incidence of AV dissociation.

Overall, our *in vitro* study indicates that nifedipine, alone or in combination with volatile agents, produces similar depressant effects on isolated hearts as diltiazem, and lesser effects than produced by verapamil. Prolongation of AV conduction by nifedipine appears to be less than that of diltiazem and much less than that of verapamil. The combined direct effects of nifedipine with halothane and, especially, enflurane are greater than those with isoflurane. This has been similarly noted for verapamil and diltiazem. Table 3 displays a qualitative summary of the direct combined effects of the commonly used calcium channel blockers and volatile anesthetics in the isolated heart. These *in vitro* comparisons indicate that verapamil plus enflurane causes the greatest cardiac depressant effect and that nifedipine produces the least cardiac effect with any of the volatile anesthetics. It should be noted that, *in vivo,* as compared with these direct *in vitro* cardiac effects, diltiazem and nifedipine are more potent vasodilators than verapamil; thus, they may produce greater tachycardic and positive inotropic effects through reflex mechanisms secondary to peripheral vasodilation. Although nifedipine appears to cause a smaller direct cardiac effect when given with volatile anesthetics, the peripheral vascular effects of these two classes of drugs must be considered in the clinical situation.

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