

## Effects and Interaction of Verapamil and Volatile Anesthetics on the Isolated Perfused Guinea Pig Heart

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The direct cardiac effects of volatile anesthetics and calcium channel blockers are obscured *in vivo* by autonomic reflexes and other extrinsic influences. The authors examined the direct *in vitro* effects of verapamil and the volatile anesthetics, halothane (HAL), enflurane (ENF), and isoflurane (ISO), in the isolated guinea pig heart. Each heart (N = 36) was perfused at constant pressure with an oxygenated Krebs-Ringer solution at 36° C. Recording electrodes were placed in the right atrium, septum, and right ventricular wall. Left ventricular pressure (LVP) and coronary flow were measured. The combination of 75 or 150 ng/ml verapamil and 0.7 or 1.4 minimum alveolar concentrations (MAC) of each of the three anesthetics dose-dependently depressed spontaneous atrial rate (HR) and peak LVP, and prolonged atrial-septal (AV) time and intraventricular conduction time (IVCT). ENF decreased HR and LVP and increased IVCT more than did HAL or ISO at each anesthetic level. The combination of either level of ENF and 150 ng/ml verapamil reduced HR more than did the same level of verapamil with HAL or ISO; 1.4 MAC ENF with 150 ng/ml verapamil also caused sinus arrest in 17% of hearts. Although ENF, HAL, and ISO alone similarly depressed AV time, 1.4 MAC ENF synergistically increased, and 1.4 HAL and ISO additively increased, the delay in AV time due to each level of verapamil. In addition, 1.4 MAC ENF caused significant 25% and 67% incidences of complete AV block with low and high verapamil levels, respectively. Both levels of ENF with verapamil also increased IVCT more than did HAL or ISO with verapamil. These *in vitro* findings show that ENF with verapamil, compared to equivalent levels of HAL and ISO with verapamil, synergistically depresses AV conduction and causes a higher incidence of AV block. The authors suggest that, in some clinical situations, administration of verapamil during enflurane anesthesia could result in deleterious cardiac depression. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Animal: guinea pig. Drugs: verapamil. Heart: atrioventricular conduction time; A-V block; coronary flow; electrophysiology; intraventricular conduction time; isolated; left ventricular pressure; perfused.)

VERAPAMIL<sup>1,2</sup> AND OTHER calcium channel blockers interfere with a calcium-dependent slow current across excitable cell membranes. In the heart, this effect is at least partly responsible for slowing heart rate<sup>3-6</sup> and atrioven-

tricular (AV) conduction,<sup>5,6</sup> reducing cardiac contractility,<sup>7</sup> and decreasing coronary vascular smooth muscle tone.<sup>8,9</sup> Many patients with rhythm disorders, coronary artery disease, or hypertension are given chronic oral verapamil treatment;<sup>10</sup> others may be given verapamil intravenously for acute treatment of supraventricular tachyarrhythmias, myocardial ischemia, or hypertension during anesthesia.<sup>11,12</sup>

Volatile anesthetics decrease free calcium availability for contraction<sup>1</sup> and probably interfere with several other steps in the excitation-contraction coupling process.<sup>13,14</sup> Like verapamil, the direct effects of volatile anesthetics are to decrease heart rate<sup>3</sup> and contractility,<sup>1,14</sup> to slow AV conduction,<sup>15</sup> and to decrease coronary vascular smooth muscle tone.<sup>16</sup> The direct effects of calcium channel blockers and anesthetics on depressing the heart and reducing vascular smooth muscle tone elicit indirect reflex cardiac effects *in vivo*. Indirect cardiac effects are triggered by the depressive actions of these agents on reducing preload, afterload, and cardiac function and are mediated by humoral substances and by cardiopulmonary and arterial baroreflexes through changes in sympathetic and parasympathetic nerve activity.<sup>17,18</sup>

The general cardiovascular effects of calcium channel blocking drugs during inhalational anesthesia have been reported in intact animals.<sup>19-23</sup> *In vivo* studies have provided generally useful clinical information, but have not always furnished reproducible results. The many responses which cannot be measured or well controlled in intact animals may account for some of the differences; others may be due to differences in preparations and techniques. It is important to differentiate the direct and interactive cardiac effects of these agents from the indirect effects obtained *in vivo*. We knew of no other study of the direct effects of volatile anesthetics and of their interaction with calcium channel blockers on the isolated heart. Our aim was to investigate the direct cardiac effects of verapamil with each of the three most commonly used volatile anesthetics, *i.e.*, halothane, enflurane, and isoflurane, in the isolated, Langendorff heart preparation. Our hypothesis was that cardiac chronotropic, dromotropic, and inotropic effects of verapamil are different in the presence of equivalent concentrations of these volatile anesthetics.

### Materials and Methods

Thirty-six albino English short-haired guinea pigs (400-600 g) were injected intraperitoneally with 10 mg of keta-

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mine and 1000 units of heparin and were decapitated when unresponsive to noxious stimulation. After thoracotomy, the inferior and superior vena cava were cut and the aorta was cannulated distal to the aortic valve. The heart was immediately perfused retrograde to the aorta and was excised. The perfusate, a modified Krebs-Ringer solution, had the following composition (in mM): Na<sup>+</sup> 137, K<sup>+</sup> 5.9, Mg<sup>++</sup> 1.2, Ca<sup>++</sup>, 2.5, Cl<sup>-</sup> 134, HCO<sub>3</sub><sup>-</sup> 15.5, H<sub>2</sub>PO<sub>4</sub><sup>-</sup> 1.2, glucose 11.5, mannitol 16, and EDTA (ethylenediaminetetraacetic acid 99%) 0.05. The solution was equilibrated with a 97% O<sub>2</sub>-3% CO<sub>2</sub> gas mixture, pH 7.42 ± 0.005 (SEM). pH, P<sub>CO<sub>2</sub></sub>, and P<sub>O<sub>2</sub></sub> were determined at the beginning and end of each exposure to control and treatment solutions with a blood-gas analyzer (Radiometer® ABL-2). Hearts were perfused with a nonrecirculating perfusate and were submerged in a bath of perfusate solution. Perfusate and bath temperature were maintained at 36.3 ± 0.1° C using a thermostatically controlled water circulating system. The perfusion pressure was maintained at 55 mmHg with a 75 cm high fluid column maintained with an overflow pump (Masterflex® 7520) that returned excess solution to the reservoir. Perfusion pressure was measured at the aortic root with a pressure transducer (Gould-Statham P23).

Left ventricular pressure (LVP) was measured with a transducer connected to a thin, saline-filled latex balloon (Hugo Sachs Electronic KG, FRG) inserted into the left ventricle through the mitral valve from a cut in the left atrium. Balloon volume was adjusted to maintain a diastolic pressure of zero.

In studies using isoflurane and enflurane, but not halothane, coronary flow was measured with an electromagnetic flowmeter (Micron Instruments, Series 1000) and a 1.5 mm extracorporeal flow probe (Micron Instruments, Series 1000) placed into the aortic inflow line. Zero flow was periodically established by temporarily bypassing the flow probe. The flow probe was calibrated by timed collections into a volumetric cylinder over the range of measured flow.

Three pairs of bipolar electrodes (Teflon® coated silver, diameter 125 μm, Cooner Wire Company, Chatsworth, CA) were placed in each heart to monitor intracardiac electrograms from which spontaneous sinoatrial rate and conduction times were measured as reported previously.<sup>24</sup> Sinus cycle length (SCL) was measured and heart rate was calculated from the superior right atrial beat-to-beat interval; atrial-septal (AV) conduction time was determined from the superior right atrial to the left ventricular septal beat-to-beat interval. Electrode pairs placed in the superior left ventricular septum and in the pulmonary conus of the right ventricle were used to measure intraventricular conduction time (IVCT).

The three electrode signals were amplified 100–1000-fold, were filtered at frequencies below 1 Hz and above

10 KHz, and were displayed continuously on a polygraph (Astromed MT 9500R) and on an image storing oscilloscope (Tektronix 5A26, 5113). One atrial and one ventricular electrogram were audibly amplified. Electrograms, LVP, perfusion pressure, and a calibrated 50 ms square wave pulse signal were intermittently tape recorded (Vetter D1) at 38 cm/s for later playback at 5.4 cm/s. Electrogram intervals were measured from polygraph tracings recorded at paper speeds of 10 or 100 mm/s by an observer blinded to the treatments or automatically by digital timer systems that allowed instantaneous beat-to-beat interval and rate analyses. Bradycardia was defined arbitrarily by an atrial or ventricular rate below 170 beats/min. Sinus arrest was defined as the absence of electrical activity recorded by the atrial electrode. AV dissociation was defined by asynchrony in atrial and septal electrogram activity that persisted at least 1 min. Junctional bradycardia was defined by the presence of AV dissociation, and by the absence of any morphologic or temporal changes in septal and ventricular electrogram waveforms from those observed during sinus bradycardia.

Anesthetics were introduced by switching to perfusate equilibrated with one of three anesthetics at vaporizer settings corresponding to approximately 0.7 and 1.4 minimum alveolar concentration (MAC): 0.5 and 1.0 volume % halothane ( Draeger® vaporizer); 1.1 and 2.2 volume % enflurane (Ohio® vaporizer); and 0.7 and 1.5 volume % isoflurane (Fluotec® 3 vaporizer). Delivered anesthetic fractions were periodically checked for accuracy by mass spectrometry (Perkin-Elmer, Medical Gas Analyzer 1100A). Perfusate was collected at an aortic inflow side port into sealed, air-free, 1-ml vials for measurement of anesthetic concentrations by gas chromatography as described previously.<sup>3</sup> Measured mean concentrations (±SEM) corresponding to vaporizer settings for 0.7 and 1.4 MAC were (in mM): halothane (0.5 and 1.0%), 0.20 ± 0.01 and 0.40 ± 0.01; enflurane (1.1 and 2.2%), 0.41 ± 0.01 and 0.71 ± 0.02; and isoflurane (0.7 and 1.5%), 0.23 ± 0.02 and 0.49 ± 0.03. Verapamil was prepared to two final perfusate concentrations, 75 and 150 ng/ml, by adding aliquot concentrations of verapamil to a known volume of perfusate. Verapamil stock was prepared by dissolving verapamil hydrochloride USP (Sigma) in Krebs-Ringer solution, dividing it into aliquots, and freezing the stock for subsequent daily use. Adenosine (200 μM in 0.2 ml) was injected before and at the end of each experiment with isoflurane and enflurane to establish peak coronary flow.

#### PROTOCOL

Drug-free control measurements were recorded after a 30-min period of stabilization. Only hearts with no more than two single premature atrial or ventricular beats per

TABLE 1. Control Values for Each of the Three Anesthetic Groups

	Groups		
	HALOTHANE	ENFLURANE	ISOFLURANE
N	12	12	12
Atrial rate (beats/min)	193 ± 6	201 ± 6	193 ± 6
AVCT (ms)	62.9 ± 1.8	62.5 ± 1.8	58.4 ± 2.1
IVCT (ms)	3.8 ± 0.6	4.6 ± 0.7	3.6 ± 0.3
Peak LVP (mmHg)	86 ± 4	89 ± 3	84 ± 3
CF (ml · g <sup>-1</sup> · min <sup>-3</sup> )	—	2.9 ± 0.4	2.9 ± 0.2

N = number of hearts; AVCT = atrioventricular conduction time; IVCT = intraventricular conduction time; LVP = left ventricular pressure; CF = coronary flow. Data are averages (mean ± SEM) of three controls; before "CONTROL" and before 0.7 and 1.4 MAC anesthetic levels. There were no significant ( $P > 0.05$ ) mean differences among controls for the three anesthetic groups.

min were used in this study. Each of the three anesthetic groups was composed of 12 hearts. Following a 10-min control, or a 10-min exposure to either a low (0.7 MAC) or a high (1.4 MAC) level of anesthetic, each heart was perfused for 15 min with a solution containing 75 ng/ml verapamil, and then for 15 min with a solution containing 150 ng/ml verapamil. The order of exposure to control, low, or high anesthetic levels, before each of the two increasing concentrations of verapamil, was randomized. Variables recorded in the last 3 min of each maneuver were: spontaneous atrial rate, atrial-septal (AV), and intraventricular conduction (IVC) times; coronary flow; and left ventricular pressure. Verapamil-free and anesthetic-free controls followed exposure to drugs for a period of approximately 60 min. The values of all variables returned to control levels except peak left ventricular pressure,

which remained about 10% lower than the baseline control. This small and nonsignificant decrease in pressure also occurred in hearts not exposed to any drugs over this time period (90 min).

### STATISTICS

Each heart served as its own control for treatment effects. All data were expressed as mean ± standard errors of the mean (SEM). Mean data from verapamil treatments alone (N = 12) for three anesthetic groups were not significantly different ( $P > 0.05$ ) and were pooled (N = 36) for presentation in figures 2–6. Statistical comparisons, however, were made individually for each group. All data were evaluated by appropriate one or two-way analysis of variance; means were compared by least significant difference (LSD) tests. Significance is designated at the  $P < .05$  level unless noted otherwise. AV time as a function of verapamil concentration, in the presence and absence of each anesthetic, was examined by linear regression analysis. Linear regression slopes (AV-verapamil relationship) ± 95% confidence intervals, in the presence and absence of anesthetics, were constructed from individual data points and their means were compared for parallelism by Student's *t* tests. The incidences of sinus arrest and AV dissociation were analyzed by Chi-square tests.

Multiple comparisons were made: 1) on the effect of any given treatment and the final control *versus* the initial drug-free control ("C" on figs. 2–6); 2) on low *versus* high levels of each anesthetic with and without verapamil; 3) on each anesthetic with and without verapamil *versus* the anesthetic-free control for verapamil alone ("CONTROL" on figs. 2–6); and 4) on each anesthetic *versus* the other two anesthetics with and without verapamil.

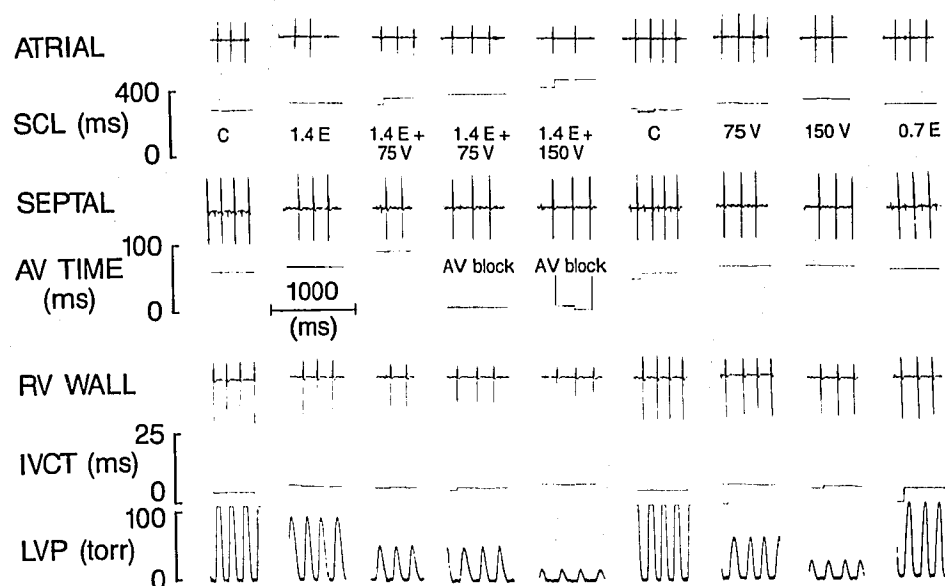


FIG. 1. Selected polygraph tracings of cardiac electrical activity and left ventricular pressure from one enflurane, verapamil study. Electrogram intervals were determined electronically on a beat-to-beat basis and displayed simultaneously. SCL = sinus cycle length (atrial beat-to-beat interval); atrioventricular (AV) time = atrial to septal interval; intraventricular conduction time (IVCT) = septal to right ventricular (RV) wall interval; LVP = left ventricular pressure; E = enflurane (MAC); V = verapamil.

Statistical symbols for 3) and 4) only are shown on the figures. Statistical analyses were performed on either a Hewlett-Packard® (HP) 98820A or on an Apple Macintosh® T4SE computer using the HP Statistical Library® and Apple Statview 512+® software programs.

### Results

Table 1 shows average pre-anesthetic control values of all variables examined for each of the three anesthetic groups. There were no significant differences among the three groups for a given variable. Figure 1 shows polygraph tracings of LVP and cardiac electrical activity measured with electrodes placed in the atrium, septum, and ventricular wall. Post-anesthetic control values (figs. 2-6) were not significantly different from the preanesthetic control values, except for AV conduction time (AVCT) in the isoflurane group, which was lower than in the halothane group after 0.7 MAC and 150 verapamil.

The steady-state individual and interactive effects of verapamil and anesthetics on atrial rate are shown in figure 2. Verapamil alone (CONTROL line) and each anesthetic alone (0 verapamil) caused significant ( $P < 0.01$ ) dose-dependent additive decreases in atrial rate (statistics not shown). Enflurane depressed rate significantly more than did halothane or isoflurane. The combination of 0.7 MAC enflurane and 150 ng/ml verapamil caused a greater depression in atrial rate than did halothane or isoflurane with verapamil. Also, the combination of 1.4 MAC enflurane and 150 ng/ml verapamil caused significantly greater depression of rate than did isoflurane. This combination also caused sinus arrest in 17% of 12 experiments. The septal (AV nodal) rate was 114 and 124 beats/min in the two hearts during sinus arrest. Halothane and isoflurane, with or without verapamil, did not cause sinus arrest.

For each anesthetic group, verapamil alone dose-dependently increased AVCT (fig. 3). All three anesthetics alone increased AVCT at the high MAC levels but not at the low MAC levels. At 0.7 MAC of isoflurane or halothane, the addition of 75 or 150 ng/ml verapamil did not further accentuate the increase in AVCT observed with these concentrations of verapamil alone. At 0.7 MAC, enflurane AVCT increased significantly with 150 ng/ml verapamil compared with verapamil alone; the difference with 75 ng/ml verapamil was not significant. At 0.7 MAC, enflurane also caused a greater increase in AVCT with 150 ng/ml verapamil than did halothane or isoflurane with 150 ng/ml verapamil. At 1.4 MAC of isoflurane, halothane, or enflurane, the addition of 75 or 150 ng/ml verapamil significantly enhanced the increases in AVCT observed with the corresponding concentrations of verapamil alone. Enflurane at 1.4 MAC in the presence of 75 or 150 ng/ml verapamil significantly increased

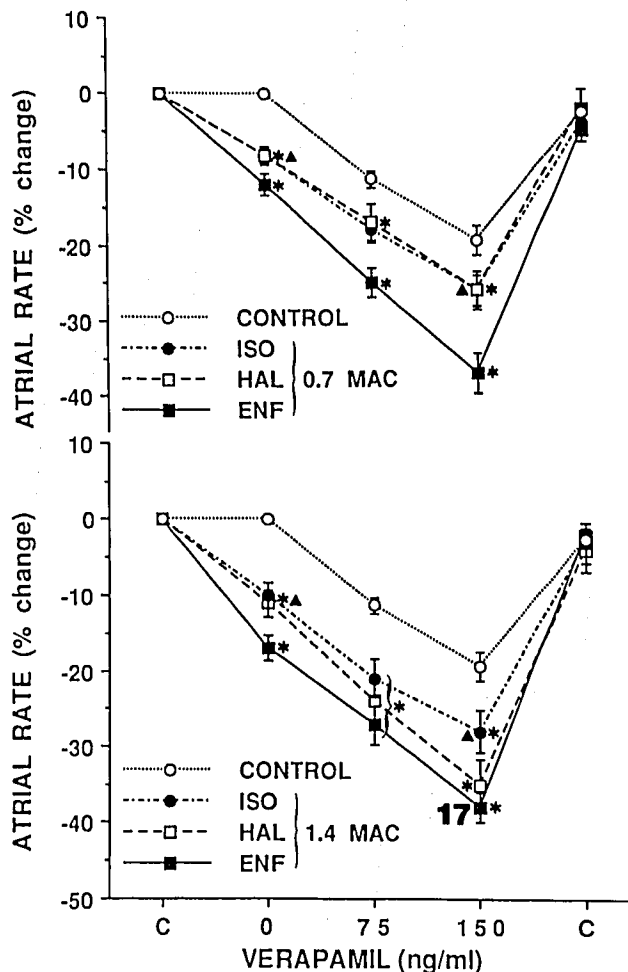


FIG. 2. Steady-state individual and interactive effects of verapamil and anesthetics on atrial rate. The number (17) is the incidence (%) of sinus arrest. For figures 2-6:  $N = 12$  for each anesthetic group at both anesthetic levels; the "CONTROL" group represents pooled data ( $N = 36$ ) on effects of verapamil alone for all three anesthetic groups; ISO = isoflurane; ENF = enflurane; HAL = halothane; MAC = minimum alveolar concentration; \* =  $P < 0.05$  versus verapamil alone;  $\Delta$  =  $P < 0.05$  versus enflurane group; + =  $P < 0.05$  isoflurane versus halothane; "C" = control; "O" = anesthetic alone.

AVCT compared with verapamil alone; moreover, 1.4 MAC enflurane increased AVCT more than did 1.4 MAC halothane or isoflurane in the presence of 75 or 150 ng/ml verapamil.

The verapamil-AVCT slopes,  $m (\pm 95\%$  confidence intervals), in the absence of anesthetics were:  $0.080 \pm 0.03$ ,  $0.075 \pm 0.04$ , and  $0.068 \pm 0.04$  for isoflurane, halothane, and enflurane groups, respectively, which were not significantly (ns) different. Verapamil-AVCT slopes in the presence of anesthetics were (in  $\text{ms} \cdot \text{ng}^{-1} \cdot \text{ml}^{-1}$ ):  $0.116 \pm 0.02$ ,  $0.098 \pm 0.04$ , and  $0.280 \pm 0.10$  for 1.4 MAC isoflurane, halothane, and enflurane, respectively. Comparisons of these slopes showed that the slopes for vera-

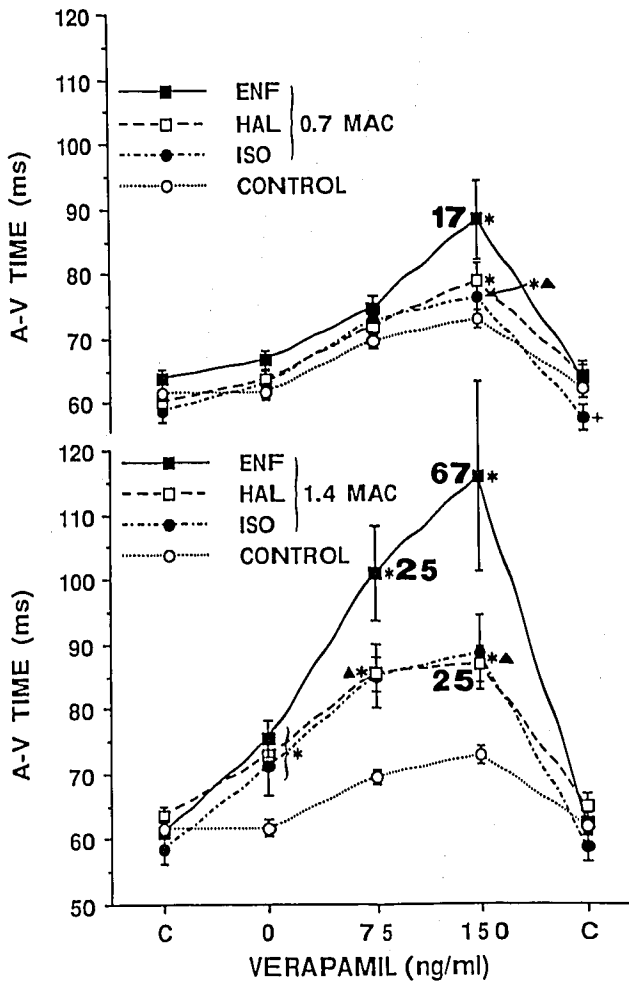


FIG. 3. Steady-state individual and interactive effects of verapamil and anesthetics on atrioventricular (AV) conduction time. Numbers indicate the percent incidence of AV block. Refer to figure 2 for legend.

pamil alone, and those for verapamil plus isoflurane or halothane, were statistically parallel. The slope of the verapamil-AVCT relationship for 1.4 MAC enflurane, however, was about 2.5 times steeper ( $P < 0.001$ ) than the slopes for verapamil with or without 1.4 MAC halothane or isoflurane.

The combination of 150 ng/ml verapamil and 0.7 MAC enflurane caused a 17% (ns) incidence of complete AV block with ventricular (AV nodal) rhythm. The high dose of verapamil with 1.4 MAC enflurane caused a significant ( $P < 0.001$ ) 67% incidence of AV block. Enflurane at 1.4 MAC and 75 ng/ml verapamil and 1.4 MAC halothane in combination with 150 ng/ml verapamil also caused the same (25%) significant incidence of AV block. The mean atrial and ventricular rates with these agents during AV dissociation were  $125.8 \pm 6.4$ , and  $133.3 \pm 4.2$  beats/min, respectively. Verapamil plus isoflurane did not produce AV block. Other than sinus and junc-

tional bradycardia, there were no other dysrhythmias observed.

Intraventricular conduction time (IVCT) increased dose-dependently with both concentrations of verapamil and with each level of anesthetic, except 0.7 MAC isoflurane alone (ns) (fig. 4). The high level of each anesthetic, with or without verapamil, did not increase IVCT more than did the low level of each anesthetic. Enflurane alone increased IVCT more than did isoflurane. Only enflurane in combination with verapamil increased IVCT compared with verapamil alone.

Peak left ventricular systolic pressure was significantly reduced by each of the two levels of anesthetic and verapamil (fig. 5). The decrease in pressure produced by 0.7 and 1.4 MAC enflurane alone was greater than that produced by the same MAC levels of isoflurane and halo-

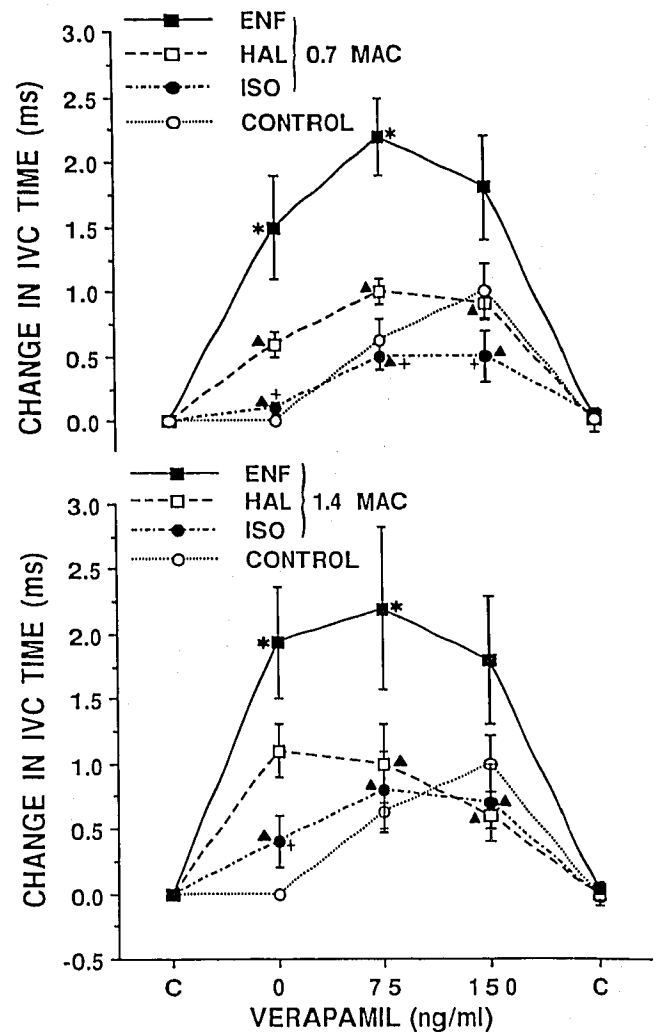


FIG. 4. Steady-state individual and interactive effects of verapamil and anesthetics on intraventricular conduction time (IVCT). Data are shown as change from control. Refer to figure 2 for legend.

thane. Also, 0.7 MAC halothane produced a greater decrease in peak LVP than did 0.7 MAC isoflurane. The addition of 75 or 150 ng/ml verapamil significantly enhanced the decreases in pressure produced by 0.7 and 1.4 MAC isoflurane, halothane, and enflurane. There were no differences in the decreases in peak LVP among the anesthetics in the presence of verapamil.

Each level of anesthetic alone and verapamil alone increased coronary flow (fig. 6). The high MAC levels of enflurane and isoflurane with 75 ng/ml verapamil significantly increased coronary flow over that observed with 75 ng/ml verapamil alone. There were no significant differences between the two concentrations of verapamil or levels of anesthetics on coronary flow. The maximal increase in coronary flow by these agents (approximately 40%) was significantly lower than the averaged (pre- and

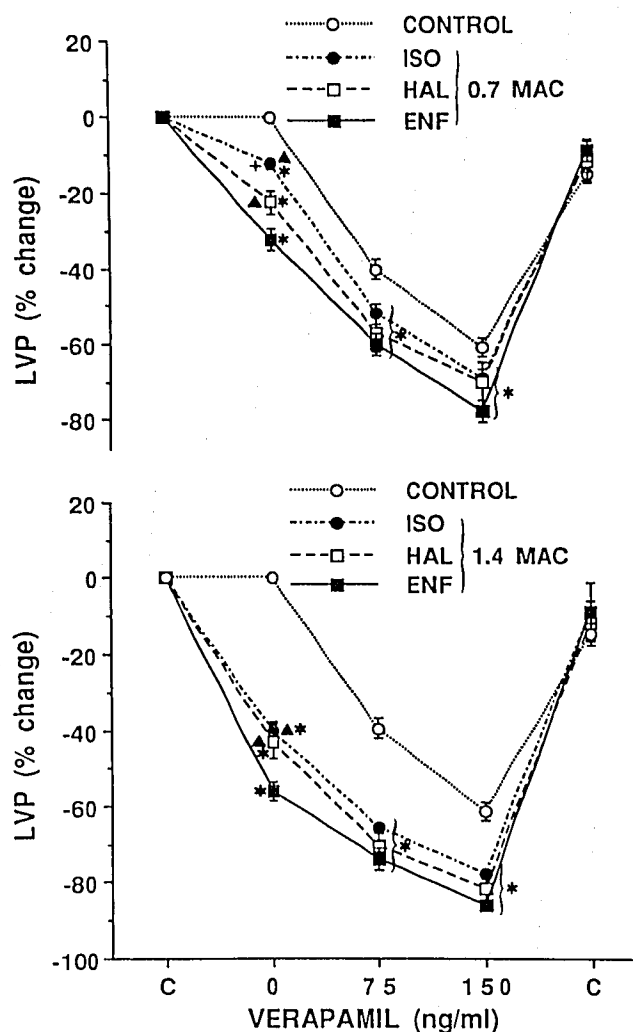


FIG. 5. Steady-state individual and interactive effects of verapamil and anesthetics on peak left ventricular pressure (LVP). Data are shown as % change from control. Refer to figure 2 for legend.

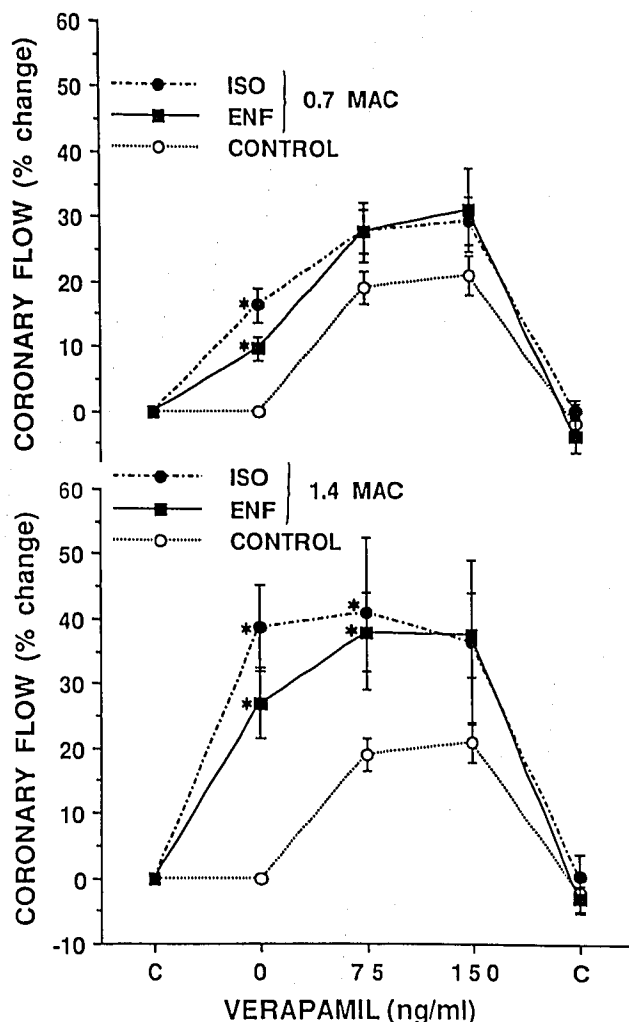


FIG. 6. Steady-state individual and interactive effects of verapamil and isoflurane and enflurane on coronary flow. Data are shown as % change from control. Refer to figure 2 for legend.

post-control) maximal increase in coronary flow obtained by bolus injection of adenosine ( $70.1 \pm 14.2\%$ ).

### Discussion

There are several *in vivo* reports<sup>19-23</sup> on the cardiovascular effects of and interaction between verapamil and inhalational anesthetics. These studies, carried out in the dog, have furnished clinically useful information on the overall cardiovascular effects of these drugs but have not allowed examination of their interactive effects directly on the heart. We have examined the effect of several of these agents in our previous electrophysiological studies in isolated cardiac tissue.<sup>1,3</sup> We chose the isolated, retrogradely perfused guinea pig heart because we wanted: 1) to avoid the indirect cardiac effects of these drugs resulting from hypotension and activation of reflex

mechanisms; 2) to avoid anesthetic effects on altering distribution of verapamil<sup>23</sup> and decreasing verapamil clearance<sup>21</sup> by the liver due to decrease in hepatic blood flow; and, foremost, 3) to examine direct and interactive effects of these drugs in a preparation found useful for eliciting consistent and reversible responses.<sup>24</sup> Ketamine, which has an indirect sympathomimetic effect, but a small, direct, negative inotropic effect,<sup>25</sup> was used to induce anesthesia prior to decapitation of animals. We have found that prior treatment with ketamine does not alter cardiac performance compared to treatment with halothane for anesthesia.<sup>24</sup>

In summary, our findings are as follows. First, verapamil accentuated the decreases in spontaneous atrial rate produced by all three anesthetics, but enflurane depressed the atrial rate more than did halothane or isoflurane in the presence or absence of verapamil. The combination of high MAC enflurane and high-dose verapamil produced a 17% incidence of sinus arrest with junctional bradycardia, whereas verapamil plus isoflurane or halothane produced no sinus arrest. Second, verapamil alone and each of the three anesthetics caused dose-dependent increases in AV conduction time, but the combinations of verapamil and 1.4 MAC enflurane produced a greater slowing of conduction and caused 25 and 67% incidences of complete AV block with the low and high doses of verapamil, respectively. Third, verapamil alone and each of three anesthetics caused increases in intraventricular conduction time, but verapamil with enflurane caused greater ventricular conduction delay than did halothane or isoflurane with verapamil. Fourth, verapamil alone and each of the three anesthetics caused dose-dependent decreases in left ventricular pressure, but enflurane depressed LVP more than did halothane or isoflurane in the absence, but not in the presence, of verapamil. Fifth, verapamil, enflurane, and isoflurane similarly increased coronary flow but not to the maximal peak increase produced by bolus injection of adenosine.

#### SINUS RATE EFFECTS

Although some authors have reported positive chronotropic responses to inhalational anesthetics,<sup>26</sup> results from our study confirm the many other *in vitro* studies, *e.g.*, those in the isolated SA node,<sup>3</sup> guinea pig atria,<sup>27</sup> isolated guinea pig heart,<sup>24</sup> isolated rabbit heart,<sup>28</sup> and dog heart-lung<sup>29</sup> preparations, in which anesthetics have been shown to decrease heart rate as anesthetic concentration is increased. The direct negative chronotropic effects of volatile anesthetics can be variably altered in intact animals<sup>15,22,30</sup> and in humans<sup>18</sup> by a variable change in sympathetic efferent nerve activity so that a decrease, no change, or an increase in heart rate can be observed. Verapamil alone can also produce a reflex increase in heart rate in intact animals and humans,<sup>31</sup> but in intact dogs<sup>19,20</sup>

the combination of verapamil and volatile anesthetics, particularly enflurane, causes bradycardia and can even cause sinus arrest.<sup>19,20</sup> Our *in vitro* study shows that enflurane and verapamil can directly interact to cause sinus arrest.

#### INTRACARDIAC CONDUCTION EFFECTS

The AV node, as well as the SA node, is dependent in large part on Ca<sup>++</sup> influx for phase 4 and 0 depolarization; therefore, any changes in Ca<sup>++</sup> influx by calcium channel blocking drugs or volatile anesthetics will have profound effects on AV conduction. Greater impaired AV conduction by enflurane than with halothane or isoflurane has been reported in intact dogs.<sup>32</sup> Our results indicate that volatile anesthetics and verapamil prolong AV nodal and intraventricular conduction times in the spontaneously beating heart. Although there were no significant differences among the three anesthetics when tested alone on slowing AV conduction, the combination of enflurane and verapamil clearly increased AV conduction time more than did isoflurane or halothane with verapamil. Indeed, we found that the slope of 1.4 MAC enflurane plus verapamil was significantly greater than the slopes of isoflurane or halothane with verapamil. If we had paced hearts at control rates during exposure to these agents, we would have expected a more exaggerated prolongation of AV time because of the rate dependency of AV conduction; *e.g.*, an increase in sinus rate with pacing causes an increase in AV conduction time.<sup>24</sup> Therefore, with a decrease in sinus rate, the expected AV nodal response would be a decrease, or no change, in AV conduction time. Moreover, the incidence of complete AV conduction block in the enflurane group with 150 ng/ml of verapamil was higher than that observed in the halothane or isoflurane groups with verapamil. If hearts had been paced, we might have expected a higher incidence of AV dissociation with AV nodal rhythm with these volatile agents. Our finding that ventricular rate was higher than atrial rate during AV dissociation suggests that the sinoatrial nodal pacemaker is more sensitive than ventricular pacemakers to the combination of volatile anesthetics, especially enflurane, and verapamil. Indeed, conduction block with enflurane and verapamil has also been observed *in vivo*.<sup>19,33</sup> Our *in vitro* study, in which responses to verapamil and volatile anesthetics were not affected by verapamil pharmacokinetics or by autonomic reflexes, directly demonstrates a pronounced interaction between verapamil and enflurane, but not between verapamil and halothane or isoflurane, on AV conduction.

#### EFFECTS ON LEFT VENTRICULAR PRESSURE AND CORONARY FLOW

Our study demonstrates that peak isovolumetric LVP is depressed dose-dependently by verapamil and by each

of the three anesthetics in ranges of concentration used clinically. The combination of verapamil and each anesthetic additively depressed LVP, which, in this preparation, is unaffected by changes in preload, afterload, or neural influences. Additive depression of developed tension in isolated papillary muscle by verapamil and halothane has also been reported.<sup>7</sup> In addition, we found that LVP is not equally reduced by each anesthetic in the absence of verapamil; peak LVP was reduced most by enflurane and least by isoflurane. Others have reported that halothane depresses tension in isolated guinea pig<sup>34</sup> and rabbit<sup>35</sup> papillary muscle more than does isoflurane. There are a number of cellular and subcellular sites at which anesthetics might act to depress cardiac contractility. These sites include the sarcolemma, sarcoplasmic reticulum, mitochondria, and contractile proteins.<sup>14</sup> A possible mechanism for differences among these anesthetics is our recent finding that for the same decrease in papillary muscle tension isoflurane depresses intracellular calcium ion concentration much less than does halothane or enflurane.<sup>36</sup> Verapamil also decreases contractility by decreasing calcium availability to the contractile proteins as demonstrated by a decrease in intracellular  $Ca^{2+}$  concentration.<sup>1</sup> Part of the negative inotropic effect of these agents might be caused indirectly by a decreased heart rate.

Our results show that in the isolated, perfused heart, volatile anesthetics produce submaximal coronary vasodilatation despite decreases in oxygen demand. The submaximal coronary vasodilatation by volatile anesthetics has also been shown in isolated coronary vessels<sup>16</sup> and in awake, instrumented dogs.<sup>37</sup> Moreover, we found no difference between enflurane and isoflurane on increasing coronary flow. Although verapamil alone produced significant coronary vasodilatation, as also shown by others in open chest dogs,<sup>9</sup> the addition of verapamil in the presence of isoflurane or enflurane did not additionally increase coronary flow. It is likely that the added decrease in cardiac work afforded by verapamil effected a compensatory vasoconstriction by autoregulatory mechanisms.

We cannot extrapolate our *in vitro* results to indicate clinical relevance, but our results do aid in understanding the direct actions of volatile anesthetics and verapamil and their interactions in the isolated heart. In the intact animal and in humans, baroreceptor reflex activation and cardiogenic hormones probably reduce the negative chronotropic, dromotropic, and inotropic effects of verapamil and volatile anesthetics on the heart and this may attenuate the degree of dysfunction noted in our studies. Our *in vitro* and *in vivo* studies by others should alert anesthesiologists to the higher probabilities of AV block and of depressed cardiac function during intravenous bolus administration of verapamil in patients undergoing general anesthesia, especially with enflurane. Moreover, patients with conduction system defects and patients with

autonomic system dysfunction may experience deleterious effects of these agents. Patients chronically treated with verapamil might also be at increased risk for depression of cardiac function and development of AV block during enflurane anesthesia.

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