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Combined Effects of Verapamil and Isoflurane on Coronary Blood Flow and Myocardial Metabolism in the Dog

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The effects of three different plasma levels of verapamil on coronary hemodynamics and myocardial metabolism in the presence of 1.61 ± 0.05% end-tidal concentration of isoflurane (mean ± SEM) were studied in a canine model, using a thermodilution coronary sinus catheter to measure coronary sinus blood flow and pressure and to provide coronary sinus plasma samples. A control group receiving only isoflurane was also studied (n = 6). Plasma arterial verapamil levels of 55 ± 7 (n = 6); 134 ± 7 (n = 10); and 301 ± 37 ng · ml^{-1} (n = 5), were achieved by a loading dose followed by a continuous infusion for 30 min. The only changes with time in the isoflurane group were decreases in left ventricular maximum rate of tension development (dP/dt) and left ventricular stroke work index compared with control after 90 min without changes in myocardial oxygen balance. The low plasma verapamil level caused reductions in heart rate, mean and diastolic arterial pressure, and left ventricular dP/dt without changes in myocardial oxygen supply or myocardial metabolism. Intermediate verapamil concentrations produced a transient initial increase in heart rate and a reduction in stroke volume index. With the intermediate and the highest levels of verapamil, mean and diastolic arterial pressure, left ventricular dP/dt, and cardiac index were decreased. An increase in arterial norepinephrine plasma levels was seen in the intermediate and the highest levels of verapamil; however, a transient coronary vasodilation occurred without changes in myocardial oxygen balance. Significant prolongation of the PR interval was observed in all verapamil groups, with second or third degree heart block in some of the higher-dose animals. Despite no adverse effects on myocardial oxygen balance when these concentrations of isoflurane and verapamil were combined, conduction block at moderate plasma levels may limit the usefulness of verapamil during isoflurane anesthesia. (Key words: Anesthetics, volatile: isoflurane. Heart: coronary blood flow; myocardial metabolism. Ions: calcium. Pharmacology: verapamil.)

VERAPAMIL, A CALCIUM channel blocker with multiple effects on the cardiovascular system, is used as an antiarrhythmic agent for the treatment of paroxysmal supraventricular tachycardias.[1] Other uses include the relief of myocardial ischemia in the treatment of angina pectoris[2] and coronary vasospasm.[3] In addition to possibly improving coronary blood flow (CBF) by coronary vasodilation, verapamil may potentially improve myocardial oxygen balance by reducing oxygen demand. However, profound coronary and systemic vasodilation may cause further changes in coronary perfusion pressure and changes in CBF. The effects of verapamil on myocardial oxygen balance in the presence of volatile anesthetics has not been thoroughly investigated.

The effects of intravenous verapamil 0.2 mg · kg^{-1} on CBF in the morphine–pentobarbital-anesthetized dog were studied by Rowe *et al.*,[4] who found an increase in the CBF with a decrease in coronary vascular resistance (CVR) and systemic vascular resistance (SVR) and no change in mean arterial pressure (MAP). Similar observations were made by Neugebauer[5] in the dog; however, a decrease in MAP was present with no change in left ventricular (LV) maximum rate of tension development (dP/dt). In conscious dogs intravenous verapamil has resulted in a dose-dependent reduction in the LV dP/dt.[6] In a right heart bypass preparation in the thiopental-anesthetized dog, Nayler and Szeto[7] found a reduction in myocardial oxygen demand and in myocardial oxygen consumption ($M\dot{V}_{O_2}$). In healthy, middle-aged men, intravenous verapamil caused an increase in heart rate (HR), with a decrease in systolic arterial pressure (SAP) and no changes in LV dP/dt.[8]

Isoflurane is a volatile anesthetic that has been reported to cause decreased $M\dot{V}_{O_2}$ and CVR, with an increase in coronary sinus oxygen content (Ccs_{O_2}) and no change in CBF in dogs.[9] Increases in end-expired concentration have resulted in a reduction in whole body oxygen uptake ($\dot{V}_{O_2}$) and myocardial blood flow.[10,11]

The combination of verapamil and isoflurane in a canine right heart bypass model resulted in significant myocardial depression at relatively low plasma levels of verapamil (<80 ng · ml^{-1}).[12] In the intact dog, this combination resulted in dose-dependent cardiovascular depression that was significant at plasma verapamil levels of greater than 100 ng · ml^{-1}.[13]

The present study was designed to investigate the effects of different plasma levels of verapamil on global myocardial oxygenation, coronary hemodynamics, and myocardial metabolism in the presence of one concentration of isoflurane in the intact dog to determine the effects of the combination of these two agents on myocardial oxygen balance.

Methods

Twenty-seven mongrel dogs of either sex weighing 22 ± 1 kg (mean ± SEM) with chronic tracheostomies[14] were studied. An 8 Fr Portex® tracheostomy tube was placed under topical anesthesia with lidocaine 2%. The animals were then anesthetized with isoflurane in 40% oxygen in

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air. Ventilation was controlled at a mean end-tidal P_{CO_2} of 31 ± 1 mmHg as measured continuously by a mass spectrometer (model MGA-1100®, Perkin Elmer Corp., Pomona, CA) and corroborated by serial arterial blood samples analyzed by an Instrumentation Laboratory *p*H/Blood Gas Analyzer 813®. The dogs were placed on a temperature-controlled water mattress, and a heat lamp was used to maintain blood temperature between 37° to 39° C. NaCl 0.9% was infused at 5 $ml \cdot kg^{-1} \cdot h^{-1}$. Maintenance of anesthesia was by isoflurane 1.61 ± .05% end tidal concentration measured by mass spectrometry (blood anesthetic levels 1.32 ± .04%[15]). A femoral arterial catheter was inserted percutaneously or by dissection for measurements of systolic, mean, and diastolic arterial pressure (DAP). The tip of the arterial catheter was situated in the abdominal aorta.

A balloon-tipped, flow-directed catheter was positioned in a pulmonary artery *via* the left external jugular vein for measurement of right atrial (RA), mean (MPAP) and diastolic (PAD) pulmonary artery, and pulmonary capillary wedge (PCWP) pressures and for sampling of mixed venous blood. A micromanometer-tipped catheter (Millar Instruments, Inc., Houston, TX) was positioned in the left ventricle *via* the femoral artery for measurement of LV pressure. The first derivative, LV dP/dt, was electronically differentiated. All pressures and HR were recorded continuously on a Hewlett-Packard® oscillograph, Model 7758A. The electrocardiogram (ECG) (limb lead II) was intermittently recorded at high paper speed (100 $mm \cdot s^{-1}$) for measurement of PR interval. Cardiac output (CO) was determined by the Fick principle using the mass spectrometer to measure inspired and expired gas concentrations, and a modified electronic volume displacement spirometer (Model 220, Cardiopulmonary Instruments, Inc., Houston, TX). Computations of $\dot{V}_{O_2}$ were performed in real time at approximately 1-min intervals using a general-purpose laboratory minicomputer (Data General Corp., Framingham, MA)[16] and the formula:

$$\dot{V}_{O_2} = V_e\{[F_{I_{O_2}}(F_{E_{N_2}}/F_{I_{N_2}})] - F_{E_{O_2}}\}$$

where V_e is the expired volume and FE and FI are the expired and inspired fractions of the specific gases. SVR, left ventricular stroke work index (LVSWI), stroke volume index (SVI), and cardiac index (CI = CO/body surface area) were calculated.

A 7 Fr woven Dacron® thermodilution coronary sinus catheter (Model CCS-7U-90B, Webster Laboratories, Inc., P.O. Box 237, Altadena, CA) was introduced into the coronary sinus (CS) *via* the right external jugular vein, under fluoroscopic control. The proper position of the catheter was checked every 20 min using small amounts of contrast dye (Renografin®), diluted 1:2 with 0.9% NaCl prior to injection, separated from the next sampling time by at least 5 min. The proper catheter position was confirmed by measurements of the CS P_{O_2} and observation of the pressure wave form. Total coronary sinus blood flow (CSBF) measurements were performed in duplicate, as described by Ganz *et al.*,[17] using a thermodilution technique during continuous infusion of the indicator (0.9% NaCl) at room temperature with a Harvard® infusion pump at 24 $ml \cdot min^{-1}$. A continuous infusion is necessary in order to achieve optimal mixing and equilibration of blood and the indicator. At least 1 min was allowed to elapse after beginning the infusion before CSBF determinations were made. In addition, ventilation was transiently stopped for 15–30 s. The temperature curves for CSBF were recorded on a Hewlett-Packard® 7402A polygraph. The following equation was then used to calculate CSBF:

$$\text{CSBF } (ml \cdot min^{-1}) = \left(\frac{TB - TI}{TB - TM} - 1\right)K$$

where TB = temperature of the blood (° C); TI = temperature of injected indicator (° C); TM = temperature of mixed indicator and blood (° C); and K is a constant factor for the specific heat and densities of blood and of the saline indicator.

CVR was calculated using the following formula:

$$\text{CVR } (mmHg \cdot ml^{-1} \cdot min^{-1}) \frac{DAP - PCWP}{CSBF}$$

Arterial, mixed venous, and CS blood samples were obtained simultaneously for determination of blood gases and oxygen content. Blood gas tensions and *p*H were measured with an Instrumentation Laboratories Model 813 analyzer. Blood oxygen content was measured with an LEX O_2 Con-TL® (Lexington Instruments Corp., Waltham, MA). $M\dot{V}_{O_2}$ equals arterial oxygen content (Ca_{O_2}) minus Ccs_{O_2}, all multiplied by CSBF. Arterial and CS plasma samples were also analyzed for lactate and pyruvate;[18] free fatty acid (FFA);[19] glucose; electrolytes Na^+, Cl^-, and K^+; Ca^{++}; hematocrit; verapamil;[20] and epinephrine (E) and norepinephrine (NE)[21] levels.

The per cent of myocardial lactate extraction was defined as the difference of the arterial lactate minus CS lactate, divided by arterial lactate, all multiplied by 100. Blood-sample losses were replaced from a typed and cross-matched donor dog to keep hematocrit greater than 30%.

Following hemodynamic stabilization for approximately 1 h on isoflurane, control values were recorded and plasma samples were taken. Six dogs served as a control group and received isoflurane only for 90 min after complete instrumentation. The remainder of the dogs received one of four possible infusions of verapamil, which consisted of either a loading dose of verapamil of 75 $\mu g \cdot kg^{-1}$ over 2 min followed by infusion of 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min (n = 3), or a loading dose of 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over 2 min followed by infusion of 5 (n = 6), 10 (n = 7), or 20 (n = 5) $\mu g \cdot kg^{-1} \cdot min^{-1}$ for

TABLE 1. Range of Arterial Plasma Verapamil Concentrations (V_{art}) after 20 Min of Infusion for Each Infusion Rate

Infusion Rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	n	V_{art} ($ng \cdot ml^{-1}$)
2.5	3	38–71
5.0	6	34–164
10.0	7	108–160
20.0	5	202–371

30 min. Previous studies had indicated that verapamil plasma levels had already plateaued by 30 min.[13] Measurements and plasma samples were repeated at 30, 60, and 90 min for the control group of dogs (n = 6); at 2, 10, 20, and 30 min after starting verapamil; and 15, 30 and 60 min of recovery after turning off the verapamil infusion. Effects of isoflurane only or of adding verapamil were evaluated by analysis of variance for repeated measures with Bonferroni *t* tests. Analysis of variance with weighted *t* tests was used to compare control values among the four groups. A *P* value less than 0.05 was considered statistically significant.

Results

Each infusion rate of verapamil resulted in a range of plasma levels (table 1), presumably because of individual pharmacokinetic variation among the animals. The pharmacodynamic effects of verapamil are well known to be related to its plasma concentrations[22,23]; thus, rather than analyze the data by infusion rate, the results for the animals that received verapamil were divided into three groups according to the verapamil levels achieved in the arterial sample (V_{art}): Group 2 (n = 6) = 55 ± 7 $ng \cdot ml^{-1}$; Group 3 (n = 10) = 134 ± 7 $ng \cdot ml^{-1}$; and Group 4 (n = 5) = 301 ± 37 $ng \cdot ml^{-1}$. Mean arterial and CS verapamil levels are presented in figure 1, showing the close correlation at these measurement periods.

Mean values for hemodynamic variables and $\dot{V}_{O_2}$ for isoflurane alone (Group 1) and for the three verapamil groups during and after the infusion are given in table 2. Mean values for arterial and CS NE and E are given for the four groups in table 3. Coronary hemodynamics (CSBF, CVR); myocardial metabolic factors ($M\dot{V}_{O_2}$, myocardial lactate extraction, Ccs_{O_2}), and PR interval of the ECG are plotted as a function of time for the four groups in figure 2.

No significant changes were observed in temperature, plasma electrolytes, glucose, or calcium levels throughout the study in any of the four groups. There was no significant change in hematocrit, comparing control with subsequent times in the four groups. There was no statistical difference in control values among the four groups for

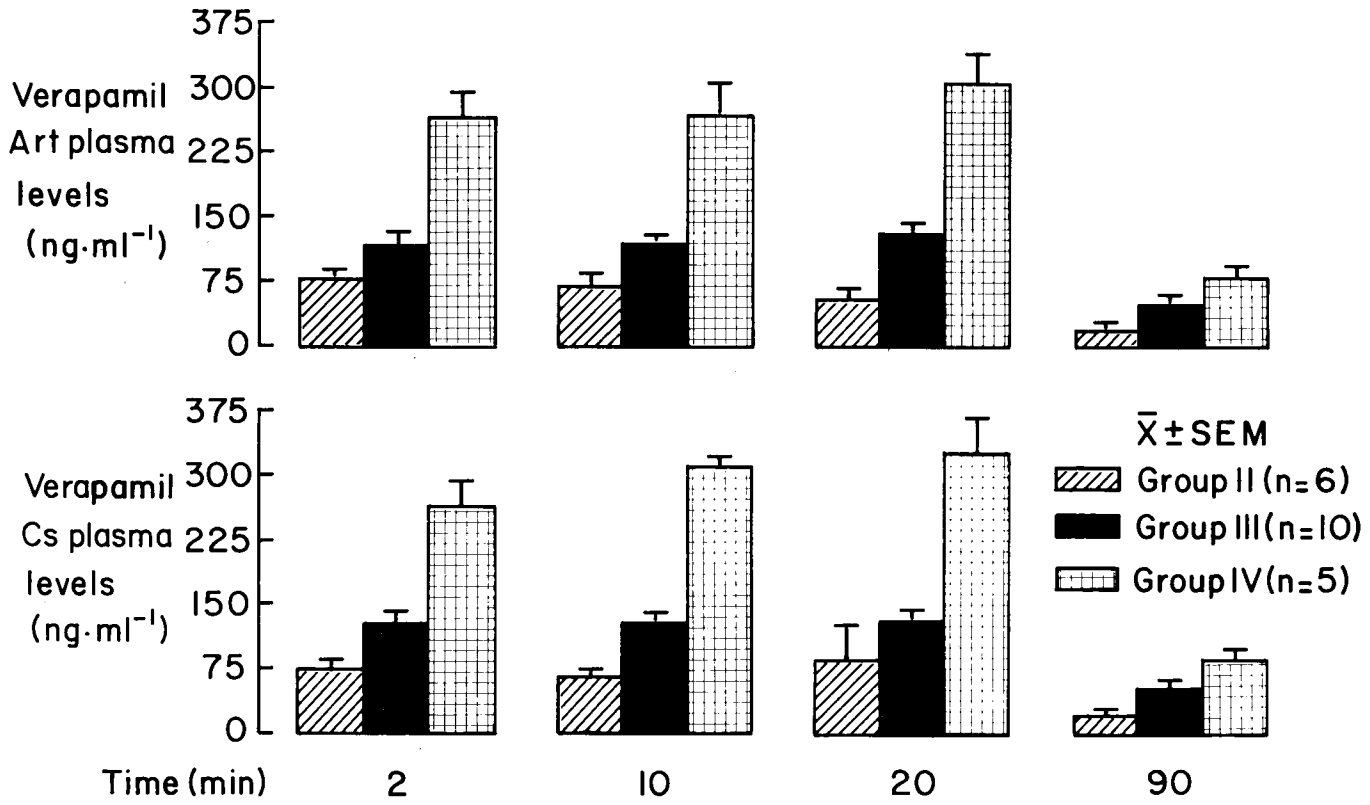

FIG. 1. Verapamil levels in arterial (art) and coronary sinus (cs) plasma for the three groups of animals at 2, 10, 20, and 90 min after starting the 30-min verapamil infusions. Mean ± SEM.

TABLE 2. Hemodynamic Values

	Group	n	Control	Verapamil Infusion 2 min	Verapamil Infusion 10 min	Verapamil Infusion 20 min	Verapamil Infusion 30 min	Recovery 60 min	Recovery 90 min
HR	1	6	134 ± 6				135 ± 6	135 ± 4	132 ± 4
(beats/min)	2	6	126 ± 7	125 ± 9	115 ± 6	115 ± 5*		102 ± 7*	110 ± 7*
	3	10	146 ± 6	158 ± 5*	144 ± 4	138 ± 5	138 ± 5	135 ± 5	139 ± 4
	4	5	148 ± 9	142 ± 7	122 ± 9*	116 ± 10*	115 ± 11*	118 ± 9*	120 ± 9*
MAP	1	6	111 ± 7				97 ± 5	101 ± 5	93 ± 8
(mmHg)	2	6	89 ± 8	74 ± 9*	84 ± 6	85 ± 9		97 ± 7‡	103 ± 5‡
	3	10	96 ± 4	76 ± 3*	87 ± 3*	89 ± 5	89 ± 4	98 ± 5†	103 ± 5†
	4	5	106 ± 2	72 ± 5*	84 ± 6*	92 ± 5*	92 ± 5*	103 ± 3	109 ± 4†
DAP	1	6	87 ± 7				80 ± 5	80 ± 5	78 ± 6
(mmHg)	2	6	68 ± 7	57 ± 8*	68 ± 5	75 ± 4		81 ± 7	86 ± 5‡
	3	10	78 ± 4	57 ± 4*	71 ± 3	73 ± 5	76 ± 6	81 ± 4	86 ± 4†
	4	5	86 ± 3	55 ± 5*	67 ± 5*	72 ± 4*	72 ± 3*	85 ± 2	90 ± 3†
LV dP/dt	1	6	2538 ± 196				2367 ± 183	2290 ± 105	1982 ± 79*
($mmHg \cdot s^{-1}$)	2	6	2004 ± 133	1629 ± 147*	1658 ± 160*	1613 ± 93*		1683 ± 108	1725 ± 146
	3	10	2628 ± 295	2360 ± 270	2155 ± 264*	2115 ± 256*	1968 ± 251*	1980 ± 182*	1950 ± 158*
	4	5	1930 ± 180	1460 ± 51*	1415 ± 204*	1430 ± 198*	1600 ± 235	1440 ± 227*	1450 ± 244*
CI	1	6	4.7 ± 0.9				3.9 ± 0.5	4.1 ± 0.6	3.3 ± 0.4
($l \cdot min^{-1} \cdot m^{-2}$)	2	6	4.9 ± 0.4	4.4 ± 0.6	4.4 ± 0.8	3.9 ± 0.4		3.7 ± 0.3	3.7 ± 0.2
	3	8	5.7 ± 0.9	5.0 ± 0.4	4.1 ± 0.2*	4.2 ± 0.4*	4.4 ± 0.4*	4.9 ± 0.8	4.1 ± 0.3
	4	5	5.4 ± 0.7	4.3 ± 0.4	3.4 ± 0.3*	3.2 ± 0.3*	3.4 ± 0.3*	3.1 ± 0.3*	3.3 ± 0.2*
SVR	1	6	2193 ± 328				2266 ± 394	2360 ± 407	2619 ± 422
($dyn \cdot s \cdot cm^{-5}$)	2	6	1745 ± 268	1869 ± 535	2116 ± 412	2266 ± 524		2480 ± 335	2529 ± 216
	3	8	1745 ± 192	1366 ± 91	1917 ± 95	2004 ± 149	1894 ± 129	2044 ± 247	2325 ± 195†
	4	5	1862 ± 301	1402 ± 138	2025 ± 98	2446 ± 195	2263 ± 156	2826 ± 208	2798 ± 183
SVI	1	6	36 ± 8				29 ± 4	31 ± 5	26 ± 4
($ml \cdot m^{-2}$)	2	6	40 ± 3	34 ± 3	38 ± 6	34 ± 3		37 ± 4	34 ± 2
	3	8	38 ± 5	32 ± 2*	29 ± 1*	30 ± 2*	32 ± 2*	36 ± 5	30 ± 2
	4	5	37 ± 6	30 ± 3	28 ± 2	27 ± 1	29 ± 1	26 ± 1	28 ± 2
LVSWI	1	6	50 ± 10				36 ± 4	39 ± 6	30 ± 5*
($g \cdot m \cdot m^{-2}$)	2	6	43 ± 5	30 ± 4	37 ± 4	34 ± 4		44 ± 4	43 ± 3
	3	8	49 ± 8	31 ± 4	32 ± 2	35 ± 4	37 ± 4	46 ± 7	39 ± 3*
	4	5	49 ± 7	26 ± 3*	29 ± 3*	30 ± 1*	32 ± 3*	33 ± 1*	37 ± 3
PCWP	1	6	8 ± 2				7 ± 1	6 ± 1	6 ± 0
(mmHg)	2	6	8 ± 2	7 ± 2	9 ± 2	8 ± 2		8 ± 1	10 ± 2
	3	10	9 ± 1	9 ± 1	9 ± 1	9 ± 1	9 ± 1	9 ± 1	11 ± 1
	4	5	8 ± 2	9 ± 3	10 ± 3	11 ± 3*	12 ± 3*	11 ± 3*	11 ± 3
$\dot{V}_{O_2}$	1	6	139 ± 13				134 ± 9	150 ± 17	137 ± 13
($ml \cdot min^{-1}$)	2	6	119 ± 5	114 ± 8	116 ± 8	114 ± 9		117 ± 8	118 ± 10
	3	8	139 ± 7	134 ± 6	131 ± 6	134 ± 6	134 ± 7	135 ± 7	131 ± 7
	4	5	136 ± 11	131 ± 10	129 ± 12	130 ± 8	129 ± 9	129 ± 8	138 ± 10

See text for abbreviations.
Mean ± SEM (for all the groups).
* $P < 0.05$ compared with control for 2, 10, 20, 30, 60, and 90 min.
† $P < 0.05$ compared with 30-min values for recovery.
‡ $P < 0.05$ compared with 20-min values for recovery.

any variable except for PR interval, where Group 1 was significantly higher than Groups 3 and 4; and for arterial and CS lactates, where Group 2 was significantly lower than Group 3.

There was no statistical difference between the 20-min and 30-min values for any variable for Groups 1, 3, and 4. Thirty-minute data were incomplete for Group 2 and are not presented.

In the isoflurane only group (Group 1) a decrease in LV dP/dt and LVSWI occurred compared with control values at 90 min. There were no changes compared with control in the other hemodynamic variables or in $M\dot{V}_{O_2}$, myocardial lactate extraction, Ccs_{O_2}, and $\dot{V}_{O_2}$ for the duration of the study in Group 1. Arterial and CS lactates were decreased from control values and remained decreased throughout the study (data not shown). A decrease in arterial pyruvates and arterial E from control was also present at 90 min.

The administration of different dosages of verapamil during anesthesia with one concentration of isoflurane resulted in significant hemodynamic and catecholamine effects. Transient, loading-dose-related reductions in MAP and DAP occurred in the three groups, which persisted for the duration of the infusion at the highest ver-

TABLE 3. Catecholamine Values

	Group	n	Control	Verapamil Infusion 2 min	10 min	20 min	30 min	Recovery 60 min	90 min
NE (art)	1	6	206 ± 67				169 ± 39	162 ± 41	110 ± 32
(pg · ml^{-1})	2	6	81 ± 37	163 ± 42	148 ± 36	144 ± 46		139 ± 55	106 ± 43
	3	10	122 ± 15	221 ± 38*	167 ± 25	183 ± 25*	174 ± 18	117 ± 13	91 ± 17†
	4	5	128 ± 34	299 ± 75*	313 ± 76*	385 ± 98*	426 ± 107*	237 ± 72†	170 ± 55†
E (art)	1	6	630 ± 124				597 ± 178	480 ± 199	281 ± 105*†
(pg · ml^{-1})	2	6	391 ± 144	346 ± 79	319 ± 64	224 ± 70		89 ± 29*	100 ± 33*
	3	10	557 ± 105	764 ± 156	753 ± 168	749 ± 133	650 ± 128	395 ± 93	283 ± 95†
	4	5	572 ± 193	816 ± 220	752 ± 235	947 ± 307	1047 ± 344*	610 ± 204	457 ± 149
NE (cs)	1	5	76 ± 25				59 ± 7	63 ± 13	45 ± 7
(pg · ml^{-1})	2	6	142 ± 57	144 ± 51	124 ± 51	110 ± 49		156 ± 68	174 ± 78
	3	10	65 ± 11	114 ± 19*	102 ± 16*	111 ± 18*	120 ± 20*	85 ± 15†	81 ± 20†
	4	5	117 ± 34	180 ± 49	206 ± 26	242 ± 62	298 ± 47*	153 ± 38†	142 ± 38†
E (cs)	1	5	165 ± 18				178 ± 64	122 ± 51	84 ± 37
(pg · ml^{-1})	2	6	74 ± 14	80 ± 26	64 ± 21	61 ± 17		37 ± 12	30 ± 10*
	3	10	176 ± 35	220 ± 52	216 ± 48	204 ± 40	166 ± 31	107 ± 30	84 ± 37†
	4	5	227 ± 59	205 ± 62	238 ± 63	246 ± 61	280 ± 111	169 ± 62	169 ± 83

See text for abbreviations.
Mean ± SEM (for all the groups).
* $P < 0.05$ compared with control for 2, 10, 20, 30, 60, and 90 min.
† $P < 0.05$ compared with 30-min values for 60 and 90.

apamil plasma level (table 2). A decrease in LV dP/dt was observed in the three groups. CI was decreased in the intermediate and the highest verapamil level groups by 10 min after the infusion was begun. LVSWI was decreased in the highest verapamil plasma level group. SVI was decreased in Group 3 after the loading dose of verapamil and remained decreased during the 30 min of infusion. An increase in PCWP occurred in the highest group. A transient coronary vasodilation occurred immediately after the loading dose of verapamil in the intermediate and highest plasma level groups (fig. 2). The significant catecholamine effects observed were increases in arterial and CS NE levels in Groups 3 and 4, and arterial E in Group 4 (table 3).

The changes observed in HR were variable: in Groups 2 and 4 reductions in HR were seen; however, in Group 3 there was an increase in HR immediately after the loading dose of verapamil (table 2). Prolongation of the PR interval occurred immediately after the loading dose of verapamil in all three groups and persisted into the recovery period (fig. 2). Conduction disturbances were seen in four dogs. Two of the ten dogs in Group 3 developed second degree heart block of the Wenckebach type: one at 10 min into the verapamil infusion that converted to sinus rhythm 15 min after the verapamil infusion was stopped; the other at 20 min of the drug infusion that converted to sinus rhythm after the verapamil infusion was stopped. Two of the five dogs in Group 4 had conduction disturbances: one had a junctional rhythm and the other had second degree heart block of the Wenckebach type after the loading dose that persisted until the end of the study.

The only statistically significant metabolic changes were changes in arterial pyruvate levels observed in Groups 2 and 3. In Group 2, the arterial pyruvate levels decreased from control by 10 min after the drug infusion was begun and remained decreased for 30 min. In Group 3 arterial pyruvate levels were decreased from control after 30 min of verapamil infusion and remained decreased through the recovery period (1.95 ± 0.20 [control]; 1.60 ± 0.16 [30 min]; and 0.94 ± 0.17 [60 min of recovery] mg · dl^{-1}) (data not shown).

In the recovery period the significant changes compared with the 20- or 30-min verapamil infusion values were an increase in MAP and DAP 30 or 60 min after the verapamil infusion was turned off for the three groups and a decrease of both arterial and CS NE levels. There were no changes in RA, CSBF, $M\dot{V}_{O_2}$, myocardial lactate extraction, Ccs_{O_2}, $\dot{V}_{O_2}$, arterial and CS FFA at any time in the three groups that received verapamil.

Discussion

The objective of this study was to compare the interactions between verapamil at different arterial plasma levels and one concentration of isoflurane on determinants of myocardial oxygen supply and demand. Other than a transient decrease in CVR after the loading dose, no changes were observed in global coronary blood flow or myocardial metabolism when these plasma levels of verapamil were added to isoflurane. The transient coronary vasodilation observed in Groups 3 and 4 after the loading dose may have resulted from a decrease in myocardial oxygen supply (decreased DAP). The lack of any change

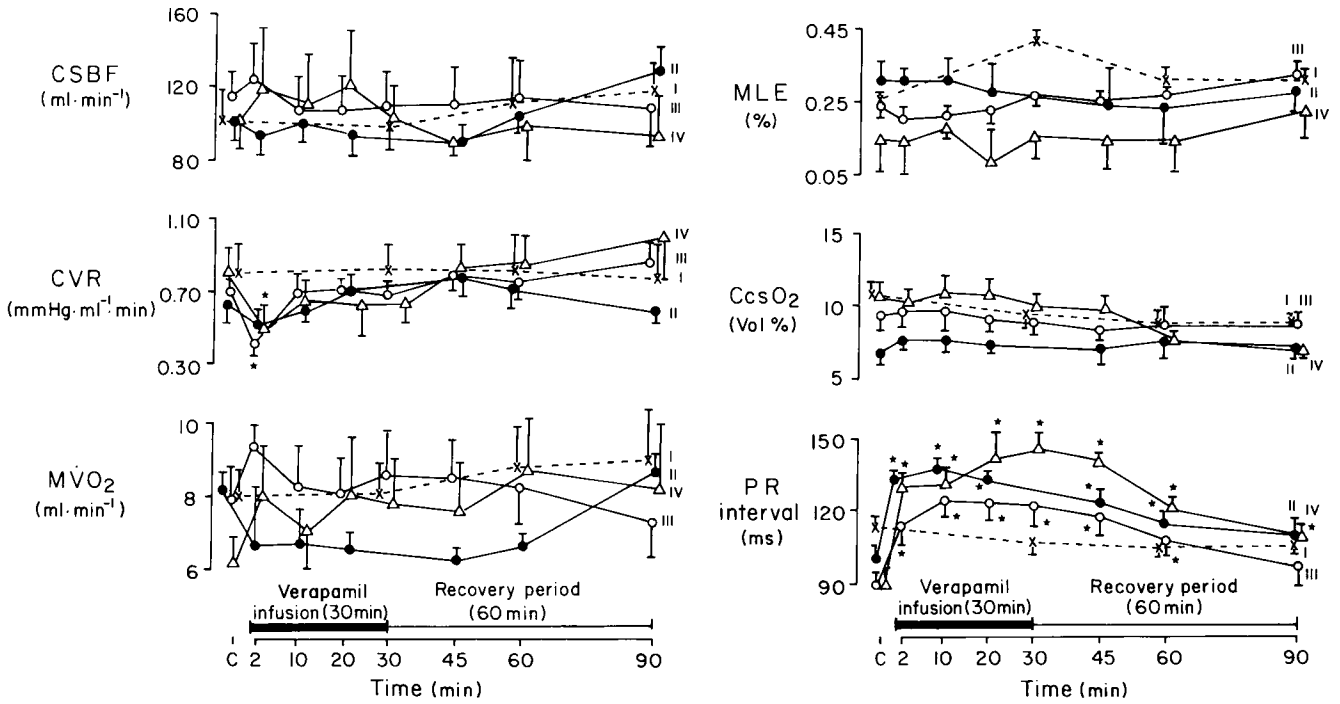

FIG. 2. Changes in coronary hemodynamics, $M\dot{V}_{O_2}$, myocardial lactate extraction (MLE), Ccs_{O_2}, and PR interval (mean ± SEM) as a function of time after starting the 30-min verapamil infusions. Values shown for the isoflurane only group (n = 6), at control (c), 30, 60, and 90 min (× --- ×); and at control (c), 2, 10, 20, 30, 45, 60, and 90 min after starting the 30-min verapamil infusions for the three groups that received verapamil. Verapamil arterial plasma levels at 20 min were: Group 2 (n = 6) = 55 ± 7 ng·ml^{-1} (● --- ●); Group 3 (n = 10) = 134 ± 7 ng·ml^{-1} (O --- O); and Group 4 (n = 5) = 301 ± 37 ng·ml^{-1} (Δ --- Δ). * = $P < 0.05$ from the control values.

in CSBF, Ccs_{O_2}, $M\dot{V}_{O_2}$, and myocardial lactate extraction represents a favorable myocardial oxygen balance.

Certain limitations are inherent in the thermodilution technique for estimating CSBF.[24] All precautions were taken in this study to assure proper catheter position, uniform delivery and mixing of the indicator, and avoidance of the effects of positive pressure ventilation as detailed earlier in "Methods." The Renografin® used for checking the catheter position was diluted to minimize any hemodynamic effects. During this procedure no changes were noted in the hemodynamic variables being continuously recorded at slow paper speeds. Higgins *et al.* injected undiluted Renografin® into the coronary arteries of dogs and found that the transient hemodynamic effects were dissipated by 20 s after the injection, even in the presence of verapamil.[25] Only global measures of myocardial oxygenation can be evaluated because the CS drains 95% of the LV mass. In the intact dog this technique has an advantage over others by avoidance of the effects of an open-chest preparation and surgical manipulation.

In this study, prolongation of atrioventricular conduction was seen even at plasma levels of 55 ± 7 ng·ml^{-1} and conduction block was seen when plasma verapamil levels increased. These findings are consistent with those of other investigations that showed that atrioventricular conduction may be prolonged at low plasma levels.[13,26] In conscious dogs, McAllister *et al.*[27] observed Wenckebach heart block only when verapamil plasma concentrations were between 250–400 ng·ml^{-1}. In this study second degree heart block was seen in four dogs, at plasma verapamil levels of 107, 126, 167, and 254 ng·ml^{-1}.

The decreases in blood pressure and LV dP/dt observed in Groups 2, 3, and 4 are known consequences of the infusion of verapamil during isoflurane anesthesia in dogs.[13] An unchanged $M\dot{V}_{O_2}$ with decreased LVSWI may indicate decreased myocardial efficiency after verapamil.

In this study, even verapamil levels of 134 ± 7 ng·ml^{-1} (Group 3) during 1.6% end-tidal isoflurane anesthesia in dogs resulted in a decrease in both MAP and CI. This is in contrast to the observations of Hamann *et al.*[22] in the pentobarbital-anesthetized dog where verapamil plasma concentration less than 250 ng·ml^{-1} caused an increase in CO. At plasma verapamil levels greater than 250 ng·ml^{-1} in their study, a progressive depression of CO occurred. In the morphine–pentobarbital-anesthetized dog, Rowe *et al.*[4] reported a decrease in SVR and CVR after verapamil associated with an increase in CO and CBF. Probably the decrease in CI in groups 3 and 4 in the present study was due to a reduction in LV contractility in so far as reflected in LV dP/dt associated with a reduction in HR in Group 4 because SVR and SVI were unchanged.

The lack of sustained decreases in SVR when verapamil was administered by a continuous infusion in any of the

three groups during isoflurane is also consistent with the other studies.[12,13] Perhaps our animals were maximally vasodilated by the isoflurane.[9-11] Dose–response effects for isoflurane were not evaluated. The 1.6% end-tidal concentration was chosen because the dogs did not move and slept throughout the study.

Catecholamine changes (arterial and CS NE) seen in this study were presumably in response to the decreases in blood pressure observed in Groups 3 and 4. Despite this increase in NE levels, $M\dot{V}_{O_2}$ was unaffected.

When verapamil was added to isoflurane in this study, myocardial oxygen balance and myocardial metabolism were unchanged. However, extrapolation of these findings from the canine model to the clinical setting is limited. Despite the adequate myocardial oxygen balance seen in this study, caution must be taken when verapamil in high doses is administered during isoflurane anesthesia because conduction disturbances may arise with no changes in CSBF. In an ischemic heart, the presence of conduction disturbances may contribute to the development of pump failure or extension of ischemia. Further study is needed in the presence of regional myocardial ischemia and in the presence of other anesthetics in varied concentrations.

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