Title: COMBINED EFFECTS OF VERAPAMIL AND ISOFLURANE ON CORONARY BLOOD FLOW AND MYOCARDIAL METABOLISM

Authors: J.H. Campos, M.D., and P.A. Kapur, M.D.

Affiliation: Department of Anesthesiology, UCLA School of Medicine, Center for the Health Sciences, Los Angeles, California 90024

Introduction: Verapamil (V) is a calcium channel blocker used to treat angina pectoris and dysrhythmias. Studies of myocardial lactate extraction ratio (MLE) have demonstrated that V decreases myocardial lactate consumption and coronary sinus blood flow (CBF) (1). Isoflurane (F) causes coronary vasodilation with no changes in CBF in patients with coronary artery disease (2). This study was designed to investigate the interactions of V with F on CBF and myocardial metabolism in the intact dog.

Methods: Ten dogs (17-25 kg) with chronic tracheostomies were induced with F in oxygen. Mechanical ventilation controlled end-tidal CO_2 at 28-35 mmHg (arterial pH 7.38 $\pm$ 0.02). Maintenance of anesthesia was by F 1.70 $\pm$ 0.20% end-tidal (mass spectrometry), vol % in blood F 1.42 $\pm$ 0.18%. EKG lead II at fast paper speed for measurement of PR interval, femoral arterial pressure for mean blood pressure (MAP), left ventricular dP/dt (Millar catheter), pulmonary artery (PA) and wedge pressures (PCWP) (PA catheter) were continuously recorded. Cardiac outputs (CO) were determined by the Fick method. Systemic vascular resistance (SVR) was calculated. A Webster thermodilution coronary sinus catheter was introduced, aided by fluoroscopy. Total CBF was measured by thermodilution in duplicate, and coronary vascular resistance (CVR) was calculated. Arterial, mixed-venous and coronary sinus (cs) blood samples were obtained simultaneously for blood gases and oxygen content ($CcsO_2$). Arterial and cs samples were also drawn for lactate and plasma levels of epinephrine (E), norepinephrine (NE), and V. Blood sample losses were replaced. Myocardial oxygen consumption ($M\dot{V}O_2$) and MLE were computed. Following hemodynamic stabilization for 1 hour on F and measurement of control values, the animals were divided into 2 groups. Group I received: V bolus 75 ug/kg over 2 min followed by V 2.5 ug/kg/min for 30 min. Group II: V 150 ug/kg/2 min followed by 5.0 ug/kg/min for 30 min. Measurements were then made 2, 10, 20, 30, 45, 60 and 90 min post bolus. All data were evaluated by analysis of variance for repeated measures with Bonferroni t-test. $P < 0.05$ was considered statistically significant.

Results: Control cardiovascular and catecholamine values are shown in the table. Coronary and metabolic values, PR interval, and V levels are shown in the figure. There were no significant changes in MAP, SVR, dP/dt, CVR, CBF, $CcsO_2$ or $M\dot{V}O_2$ in either group, except for a transient decrease in MAP and dP/dt immediately after the bolus dose in Group II that returned to control by the 10 min measurement. HR rose above control at 2 min in Group II and was decreased below control thereafter. MLE decreased in Group I but remained within normal values for the intact dog. NE increased to 222 $\pm$ 62 pg/ml ($P < 0.05$) after V in Group I and remained elevated for 90 min. PR interval was significantly prolonged up to 15-60 min after cessation of V.

Discussion: The mechanism by which V is effective in the treatment of patients with angina pectoris is not clear. Possibilities include relief of vasospasm, increased myocardial blood flow, reduced $M\dot{V}O_2$, and improved ventricular compliance. One study did not show any increase in collateral blood flow to ischemic tissue by V (3). In this study during F anesthesia, V levels were similar in both groups, and no clinically significant effects on hemodynamics, CBF, or $M\dot{V}O_2$ were observed except immediately after the larger bolus in Group II, though PR intervals were significantly prolonged. We conclude that in combination with F, the effect of low levels of V remains interference with slow channel sensitive conduction. Higher V levels, at which hemodynamic depression is also encountered, may have different coronary and myocardial metabolic effects.

References:

1. Ferlinz J. and Turbow M.E. Antianginal and myocardial metabolic properties of verapamil in coronary artery disease. Am J Cardiol 46:1019, 1980
2. Reiz S., Balfors E., Sorensen M.G., et al. Isoflurane a powerful vasodilator in patients with coronary artery disease. Anesthesiology 59:91, 1983
3. Forman R., Eng C., Kirk E.S. Comparative effect of verapamil and nitroglycerin on collateral blood flow. Circulation 67:1200, 1983

TABLE. Control Values $\bar{X} \pm$ SEM

	HR (bpm)	MAP (mmHg)	PCWP (mmHg)	dP/dt (torr/s)
Group I	122 $\pm$ 7	91 $\pm$ 6	3 $\pm$ 1	2390 $\pm$ 307
Group II	137 $\pm$ 4	87 $\pm$ 10	10 $\pm$ 2	2800 $\pm$ 348

	SVR (dynes·s·cm^{-5})	CO (l/min)	NE (pg/ml)	E (pg/ml)
Group I	1684 $\pm$ 259	4.7 $\pm$ 0.9	107 $\pm$ 51	724 $\pm$ 173
Group II	1372 $\pm$ 296	4.7 $\pm$ 0.3	101 $\pm$ 31	313 $\pm$ 79

FIGURE.