

Cardiovascular effects of romifidine in dogs

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Objective—To characterize the cardiovascular effects of romifidine at doses ranging from 5 to 100 $\mu\text{g}/\text{kg}$ of body weight, IV.

Animals—25 clinically normal male Beagles.

Procedure—Romifidine was administered IV at a dose of 5, 10, 25, 50, or 100 $\mu\text{g}/\text{kg}$ ($n = 5/\text{group}$). Heart rate, arterial pressure, central venous pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, body temperature, cardiac output, and PCV were measured immediately prior to and at selected times after romifidine administration. Cardiac index, stroke index, rate-pressure product, systemic and pulmonary vascular resistance indices, and left and right ventricular stroke work indices were calculated. Degree of sedation was assessed by an observer who was blinded to the dose administered.

Results—Romifidine induced a decrease in heart rate, pulmonary arterial pressure, rate-pressure product, cardiac index, and right ventricular stroke work index and an increase in central venous pressure, pulmonary capillary wedge pressure, and systemic vascular resistance index. In dogs given romifidine at a dose of 25, 50, or 100 $\mu\text{g}/\text{kg}$, an initial increase followed by a prolonged decrease in arterial pressure was observed. Arterial pressure immediately decreased in dogs given romifidine at a dose of 5 or 10 $\mu\text{g}/\text{kg}$.

Conclusions and Clinical Relevance—Results suggest that IV administration of romifidine induces dose-dependent cardiovascular changes in dogs. However, the 2 lowest doses (5 and 10 $\mu\text{g}/\text{kg}$) induced less cardiovascular depression, and doses ≥ 25 $\mu\text{g}/\text{kg}$ induced similar cardiovascular changes, suggesting that there may be a ceiling on the cardiovascular effects of romifidine. (*Am J Vet Res* 2001; 62:490–495)

Various α_2 -adrenoceptor agonists, particularly xylazine hydrochloride and medetomidine, are used to induce sedation and analgesia in dogs.^{1,2} Romifidine is another α_2 -adrenoceptor agonist that has been used in horses for several years. Recently, its use in dogs was proposed, and preliminary studies have shown that romifidine could be useful for sedation or premedication of dogs before general anesthesia.^{3,4} According to these studies, the dose of romifidine rec-

ommended for sedation and premedication varies from 40 to 120 $\mu\text{g}/\text{kg}$ of body weight, IV. However, a recent study indicated that sedative effects were still observed at doses as low as 10 $\mu\text{g}/\text{kg}$, IM.⁴ Like other α_2 -adrenoceptor agonists, romifidine seems to have important anesthetic-sparing effects.^{5,6}

Similarly to other agents in its class, romifidine induces adverse cardiovascular effects, mainly a reduction in cardiac index related to bradycardia.³ Moreover, α_2 -adrenoceptor agonists usually induce an increase in systemic vascular resistance accompanied by an initial hypertension, at least when administered IV.^{2,7,8} All of these effects are thought to be dose dependent.^{8–11} One method of reducing the adverse cardiovascular effects associated with the use of α_2 -adrenoceptor agonists is, therefore, to decrease the dose administered.^{1,4,8} However, to our knowledge, the cardiovascular effects of only 2 doses of romifidine (40 and 120 $\mu\text{g}/\text{kg}$) have been characterized.³

The purposes of the study reported here were to characterize the cardiovascular effects of romifidine at doses ranging from 5 to 100 $\mu\text{g}/\text{kg}$ in dogs and determine whether these effects were dose dependent. We hypothesized that IV administration of romifidine induces dose-dependent cardiovascular changes.

Materials and Methods

Animals—All procedures were performed according to the Belgian regulations for animal research and experimentation and the *NIH Guide for the Care and Use of Laboratory Animals*. Twenty-five healthy male Beagles between 1 and 4 years old and weighing between 10 and 15 kg (mean \pm SD, 12.8 \pm 1.5 kg) were used. Food and water were withheld for 12 hours prior to the experiment. Before the study, ECG and thoracic radiography were performed to exclude any detectable cardiac abnormalities. Dogs were trained to lie in lateral recumbency.

Experimental protocol—Dogs were randomly allotted to 1 of 5 groups ($n = 5/\text{group}$). Dogs in each group were assigned to receive romifidine^b administered IV as a bolus in the right jugular vein at a dose of 5, 10, 25, 50, or 100 $\mu\text{g}/\text{kg}$.

The day prior to the study, dogs were instrumented, as described.⁹ Briefly, dogs were anesthetized with isoflurane in oxygen administered with a face mask. A cuffed endotracheal tube was placed, and the dogs were positioned in dorsal recumbency. Anesthesia was maintained with a semiclosed circle system. Under aseptic conditions, a 6-F introducer was placed in the right jugular vein, and a 20-gauge 16-cm arterial catheter was inserted into the right carotid artery. The catheters were protected with a light bandage, and the dogs were allowed to recover from anesthesia. Dogs were housed separately until the day of the study.

On the day of the study, a thermodilution catheter was inserted through the introducer into the right jugular vein. This catheter was positioned with the proximal port in the right atrium and the distal port and thermistor in the pulmonary artery and was used to record pulmonary arterial pressure (PAP) and measure cardiac output (CO). Correct

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placement of the catheter was confirmed by use of fluoroscopy. Pressures were continuously measured by use of pressure transducers calibrated with a water manometer before the study, with a pressure of 0 set at the level of the thoracic inlet in laterally recumbent dogs. A lead-II ECG was continuously monitored throughout the study to detect any arrhythmias.

Determination of cardiovascular variables—During the procedure, dogs were positioned in right lateral recumbency. All variables were measured 15 minutes before (baseline) and 3, 7, 10, 20, 30, 40, 50, and 60 minutes after romifidine administration. Additional measurements were obtained 90 minutes after administration of romifidine at a dose of 50 $\mu\text{g}/\text{kg}$ and 90 and 120 minutes after administration of romifidine at a dose of 120 $\mu\text{g}/\text{kg}$ because of the longer duration of sedation observed with these doses in preliminary trials.

The following variables were measured: heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), central venous pressure (CVP), mean PAP, mean pulmonary capillary wedge pressure (PCWP), core body temperature (determined by use of the thermodilution catheter thermistor), CO, and PCV. Packed cell volume was measured to check for any hemodilution related to the cumulative effects of the fluid injected for measurement of CO. Cardiac output was measured by rapidly injecting ice-cold isotonic dextrose solution (5 ml) into the right atrium at end expiration. All CO measurements were performed in triplicate and averaged. Venous blood samples for determination of PCV were collected through the proximal port of the thermodilution catheter in the right atrium.

Cardiac index (CI) was calculated by dividing CO by body surface area (BSA). Body surface area was calculated as $(\text{body weight}^{2/3} \times 10.1)/10$. Stroke index was calculated as stroke volume (SV) divided by CO. Stroke volume was calculated as CO divided by HR. The rate-pressure product (RPP) was calculated as $\text{HR} \times \text{SAP}$. Systemic vascular resistance index was calculated as systemic vascular resistance (SVR) divided by BSA. Systemic vascular resistance was calculated as $[(\text{MAP} - \text{CVP})/\text{CO}] \times 80$. Pulmonary vascular resistance index was calculated as pulmonary vascular resistance divided by BSA. Pulmonary vascular resistance was calculated as $[(\text{PAP} - \text{PCWP})/\text{CO}] \times 80$. Left ventricular stroke work index (LVSWI) was calculated as $[(1.36 \text{ MAP} - \text{PCWP})/100] \times \text{SI}$. Right ventricular stroke work index (RVSWI) was calculated as $[(1.36 \text{ PAP} - \text{CVP})/100] \times \text{SI}$.

Determination of sedative effects—Seven minutes after romifidine was administered (ie, the expected time of maximal sedative effect), an individual blinded to the dose of romifidine assigned a score for degree of sedation. Sedation scores ranged from 0 to 3, with 0 = no sedation; 1 = mild sedation, with the dog still responsive to environmental stimuli; 2 = moderate sedation, with the dog unresponsive to most environmental stimuli; and 3 = profound sedation, with the dog unresponsive to environmental stimuli.

Statistical analysis—To test for differences over time, data for each group were analyzed by use of a repeated-measures ANOVA followed by the Bonferroni test for 2×2 comparisons.¹² To test for differences among romifidine doses, data for each time point were analyzed by use of 1-way ANOVA and the Bonferroni test for 2×2 comparisons.¹² Data are reported as mean \pm SD. For all analyses, values of $P < 0.05$ were considered significant.

Results

Heart rate, blood pressure, and body temperature—Baseline heart rate ranged from 88 to 155 beats/min. Heart rate decreased to approximately 60% of the baseline value following administration of romi-

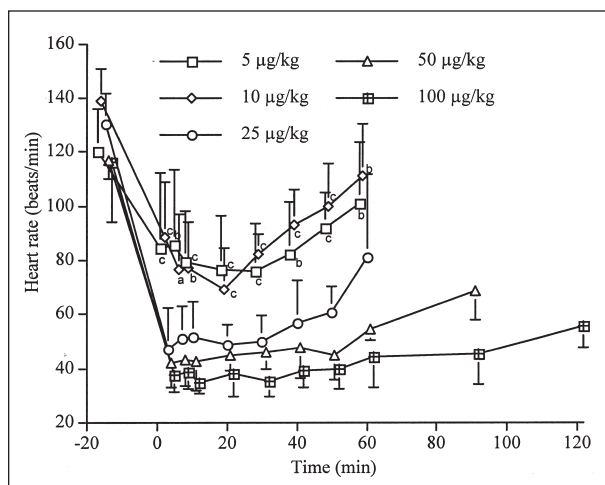


Figure 1—Mean heart rate in dogs ($n = 5/\text{group}$) given romifidine IV at various doses. Error bars represent SD. ^aSignificantly ($P < 0.05$) different from value for dogs given romifidine at a dose of 100 $\mu\text{g}/\text{kg}$. ^bSignificantly ($P < 0.05$) different from values for dogs given romifidine at a dose of 50 or 100 $\mu\text{g}/\text{kg}$. ^cSignificantly ($P < 0.05$) different from values for dogs given romifidine at a dose of 25, 50, or 100 $\mu\text{g}/\text{kg}$.

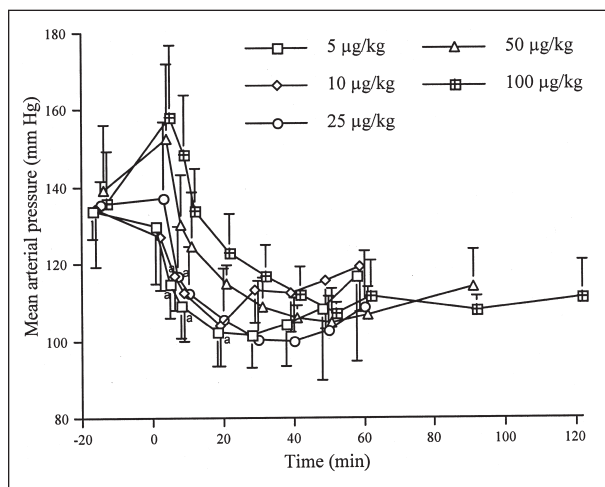


Figure 2—Mean arterial pressure in dogs given romifidine IV at various doses. See Figure 1 for key.

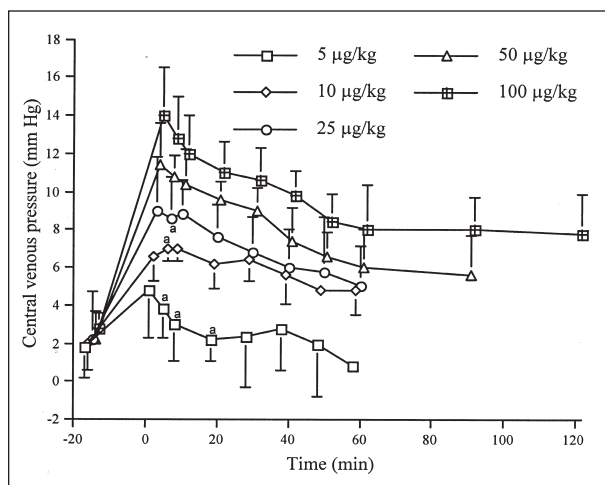


Figure 3—Mean central venous pressure in dogs given romifidine IV at various doses. See Figure 1 for key.

Table 1—Cardiovascular effects of romifidine administered IV in dogs

Variable	Dose (µg/kg)	Time after romifidine administration (min)					
		Baseline	3	7	10	20	30
Pulmonary arterial pressure (mm Hg)	5	21.6 ± 3.2	19.0 ± 3.7	16.8 ± 2.2	16.2 ± 2.6	14.4 ± 3.5	14.0 ± 3.5
	10	19.2 ± 1.8	17.6 ± 3.1	16.6 ± 2.1	15.4 ± 2.3	14.4 ± 2.2	14.6 ± 1.8
	25	20.4 ± 3.9	20.0 ± 2.8	17.8 ± 2.4	18.0 ± 2.8	16.0 ± 1.4	14.0 ± 1.6
	50	23.4 ± 2.5	22.8 ± 2.3	20.8 ± 4.4	20.6 ± 3.3	17.6 ± 3.2	17.0 ± 3.1
	100	20.6 ± 5.3	22.8 ± 1.8	20.4 ± 2.6	19.2 ± 2.2	17.2 ± 1.9	16.2 ± 2.6
Pulmonary capillary wedge pressure (mm Hg)	5	10.2 ± 4.0	11.0 ± 2.2†	10.8 ± 1.5†	10.8 ± 2.2§	9.4 ± 2.8	9.0 ± 3.2
	10	12.2 ± 2.8	11.6 ± 3.2†	12.4 ± 1.5†	10.8 ± 1.1§	10.4 ± .9	10.2 ± 2.2
	25	12.8 ± 2.9	16.0 ± 3.1	13.8 ± 1.3	14.6 ± 2.9	13.0 ± 1.9	11.0 ± 1.6
	50	13.2 ± 3.3	18.6 ± 1.5	15.4 ± 3.1	16.6 ± 1.7	13.0 ± 2.3	12.2 ± 2.6
	100	11.8 ± 5.4	17.8 ± 3.6	16.6 ± 2.3	15.6 ± .9	13.2 ± 1.9	12.6 ± 1.8
Body temperature (C)	5	38.7 ± 0.2	38.6 ± 0.2	38.5 ± 0.2	38.4 ± 0.2	38.3 ± 0.2	38.3 ± 0.2
	10	39.0 ± 0.4	39 ± 0.6	38.8 ± 0.5	38.7 ± 0.6	38.6 ± 0.7	38.7 ± 0.7
	25	39.0 ± 0.4	39.0 ± 0.5	38.7 ± 0.6	38.5 ± 0.6	38.3 ± 0.6	38.2 ± 0.7
	50	38.8 ± 0.6	38.9 ± 0.6	38.7 ± 0.7	38.6 ± 0.7	38.5 ± 0.6	38.3 ± 0.6
	100	38.9 ± 0.5	39.0 ± 0.6	38.9 ± 0.6	38.8 ± 0.6	38.9 ± 0.6	38.7 ± 0.6
Rate-pressure product (beats • min ⁻¹ • mm Hg)	5	19,050 ± 3202	13,263 ± 5201†	11,766 ± 4370	10,490 ± 2,835*†	9,664 ± 2,816*†	9,278 ± 2,376*§
	10	20,575 ± 3453	13,069 ± 3345*	10,269 ± 2,899*	9,989 ± 2,634*†	8,433 ± 1,850*	10,612 ± 1,035*§
	25	19,899 ± 1189	7,832 ± 1006*	7,713 ± 1,296*	7,151 ± 1,427*	6,513 ± 1,197*	6,027 ± 1,174*
	50	17,187 ± 2320	7,407 ± 1158*	6,944 ± 1,317*	6,263 ± 1,433*	6,176 ± 996*	6,236 ± 1,044*
	100	17,866 ± 4001	7,281 ± 1311*	6,959 ± 1,198*	5,688 ± 787*	5,648 ± 1,072*	5,095 ± 1,142*
Right ventricular stroke work index (g • m • m ⁻²)	5	11.6 ± 3.3	6.9 ± 1.9	6.4 ± 1.2*	6.6 ± 1.8*	6.4 ± 2.0*	6.1 ± 2.3*
	10	9.3 ± 2.1	5.4 ± 1.7*	5.7 ± 1.5*	5.1 ± 0.9*	5.1 ± 1.3*	5.1 ± 0.4*
	25	11.7 ± 3.2	7.7 ± 1.3	6.0 ± 1.2*	6.6 ± 2.0*	6.1 ± 1.4*	5.0 ± 1.5*
	50	13 ± 3.2	7.5 ± 2.3*	6.2 ± 1.7*	7.7 ± 1.1*	4.8 ± 1.8*	5.3 ± 1.8*
	100	11 ± 1.6	6.4 ± 2	5.5 ± 2.5	6.4 ± 3.9	4.8 ± 2.0*	5.6 ± 3.7

Variable	Dose (µg/kg)	Time after romifidine administration (min)				
		40	50	60	90	120
Pulmonary arterial pressure (mm Hg)	5	14.2 ± 4.1	14.0 ± 3.4	14.8 ± 3.7	—	—
	10	15.2 ± 2.4	15.2 ± 1.5	15.6 ± 1.1	—	—
	25	15.4 ± 3.0	15.4 ± 4.2	16.4 ± 4.7	—	—
	50	15.2 ± 2.6*	14.8 ± 2.8*	14.6 ± 1.3*	15.4 ± 1.5*	—
	100	15.6 ± 3.0	15.0 ± 2.3	16.4 ± 4.7	14.6 ± 2.9	13.2 ± 3.6
Pulmonary capillary wedge pressure (mm Hg)	5	8.8 ± 3.0	8.6 ± 4.4	7.6 ± 2.7	—	—
	10	10.2 ± 1.3	10.0 ± 1.0	9.2 ± .8	—	—
	25	12.2 ± 2.5	11.4 ± 3.5	12.0 ± 2.9	—	—
	50	11.4 ± 3.2	9.2 ± 3.9	11.4 ± .5	10.8 ± 1.9	—
	100	12.0 ± 2.6	11.0 ± 2.0	12.4 ± 5.1	11.2 ± 2.3	10.5 ± 1.7
Body temperature (C)	5	38.2 ± 0.2	38.1 ± 0.2	38.2 ± 0.2	—	—
	10	38.7 ± 0.8	38.7 ± 0.9	38.7 ± 1.0	—	—
	25	38.0 ± 0.8	37.8 ± 0.8	37.7 ± 0.8	—	—
	50	38.0 ± 0.7	37.9 ± 0.7	37.7 ± 0.7	37.6 ± 0.8	—
	100	38.6 ± 0.6	38.3 ± 0.6	38.1 ± 0.6	37.8 ± 0.6	37.7 ± 0.5
Rate-pressure product (beats • min ⁻¹ • mm Hg)	5	10,327 ± 2,899*†	12,064 ± 3,148 §	14,292 ± 4,423†	—	—
	10	11,613 ± 2,205*§	12,875 ± 3,026*§	15,088 ± 3,717 †	—	—
	25	6,633 ± 1,737*	7,460 ± 776*	10,482 ± 3,544*	—	—
	50	6,099 ± 1,462*	5,763 ± 1,479*	7,241 ± 733*	9,196 ± 1,546*	—
	100	5,295 ± 1,281*	5,197 ± 1,201*	6,102 ± 2,148*	5,971 ± 1,776*	7,307 ± 1,903*
Right ventricular stroke work index (g • m • m ⁻²)	5	6.1 ± 1.9*	6.7 ± 2.3*	7.7 ± 2.6	—	—
	10	5.9 ± 1.4*	5.8 ± 1.1*	5.9 ± 1.0*	—	—
	25	6.6 ± 1.2*	7.2 ± 2.6	7.6 ± 2.1	—	—
	50	4.5 ± 1.1*	5.8 ± 0.5*	5.2 ± 1.5*	6.9 ± 0.7*	—
	100	5.2 ± 1.9*	6.1 ± 1.2	6.4 ± 2.9	4.8 ± 1.8*	4.3 ± 2.2*

*Significantly ($P < 0.05$) different from baseline value. †Significantly ($P < 0.05$) different from value for dogs given romifidine at a dose of 100 µg/kg. ‡Significantly ($P < 0.05$) different from values for dogs given romifidine at a dose of 50 or 100 µg/kg. §Significantly ($P < 0.05$) different from values for dogs given romifidine at a dose of 25, 50 or 100 µg/kg.

fidine at a dose of 5 or 10 µg/kg and to approximately 35% of the baseline value following administration at a dose of 25, 50, or 100 µg/kg (Fig 1). Significant differences among groups were detected between 3 and 60 minutes after romifidine administration.

Changes in SAP, DAP, and MAP were similar to each other. Baseline MAP ranged from 112 to 160 mm Hg, and MAP decreased to approximately 80% of the baseline value in all groups. During the first 3 minutes after administration of romifidine at a dose of 25, 50,

or 100 $\mu\text{g}/\text{kg}$, arterial pressure increased to approximately 110% of the baseline value but was significantly less than the baseline value thereafter. An initial increase in arterial pressure was not detected after administration of romifidine at a dose of 5 or 10 $\mu\text{g}/\text{kg}$. Mean arterial pressure was significantly higher 3 minutes after administration of romifidine at a dose of 25, 50, or 100 $\mu\text{g}/\text{kg}$ than after administration at a dose of 5 or 10 $\mu\text{g}/\text{kg}$ (Fig 2).

Baseline CVP ranged from 0 to 6 mm Hg. Central venous pressure did not change significantly after administration of romifidine at a dose of 5 $\mu\text{g}/\text{kg}$ (Fig 3) but increased to approximately 3.5 times the baseline value immediately following administration of romifidine at a dose of 10 $\mu\text{g}/\text{kg}$, 4 times the baseline value after administration at a dose of 25 $\mu\text{g}/\text{kg}$, and 5 times the baseline value after administration at a dose of 50 or 100 $\mu\text{g}/\text{kg}$; CVP then decreased. At various times, CVP was significantly higher after administration of romifidine at a dose of 100 $\mu\text{g}/\text{kg}$ than after administration at a dose of 5, 10, or 25 $\mu\text{g}/\text{kg}$.

Baseline PAP ranged from 14 to 28 mm Hg. Pulmonary arterial pressure decreased to 70 to 80% of the baseline value in all groups (Table 1). Baseline PCWP ranged from 4 to 21 mm Hg. Pulmonary capillary wedge pressure increased to 1.2 times the baseline value immediately following administration at a dose of 25 $\mu\text{g}/\text{kg}$, and increased to approximately 1.5 times the baseline value following administration at a dose of 50 or 100 $\mu\text{g}/\text{kg}$, and then decreased. Significant differences were found among groups during the first 10 minutes after administration of romifidine.

Baseline body temperature ranged from 38.3 to 39.7 C. Body temperature decreased significantly by 0.5 to 1.3 C after administration of romifidine, except after administration at a dose of 10 $\mu\text{g}/\text{kg}$. We did not detect any significant differences in regard to body temperature among groups (Table 1).

Cardiac index, stroke index, and rate-pressure product—Baseline CI ranged from 3.6 to 7.5 $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^2$. Cardiac index decreased significantly in all groups after administration of romifidine; CI decreased to approximately 50% of the baseline value following administration at a dose of 5 or 10 $\mu\text{g}/\text{kg}$ and to approximately 30% of the baseline value following administration at a dose of 25, 50, or 100 $\mu\text{g}/\text{kg}$ (Fig 4). No significant changes in PCV were detected, indicating that the amount of fluid administered for measurement of CO did not result in hemodilution. Baseline SI were 41.7 ± 4.3 , 38.3 ± 4.5 , 45.4 ± 7.5 , 43.6 ± 7.9 , and $46.1 \pm 12.2 \text{ ml}\cdot\text{beat}^{-1}\cdot\text{m}^2$ following administration of romifidine at doses of 5, 10, 25, 50, and 100 $\mu\text{g}/\text{kg}$, respectively. Stroke index was unchanged in all groups throughout the study.

Baseline RPP ranged from 13,464 to 29,655 $\text{beats}\cdot\text{min}^{-1}\cdot\text{mm Hg}$. Rate-pressure product significantly decreased to approximately 45% of the baseline value following administration of romifidine at a dose of 5 or 10 $\mu\text{g}/\text{kg}$ and to 30% of the baseline value following administration at a dose of 25, 50, or 100 $\mu\text{g}/\text{kg}$. Significant differences among groups were detected (Table 1).

Vascular resistance—Baseline SVRI ranged from 5,017 to 12,178 $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}\cdot\text{m}^2$. Systemic vascular resistance index increased significantly to 184% of the baseline value after administration of romifidine at a dose of 10 $\mu\text{g}/\text{kg}$, 304% of the baseline value after administration at a dose of 25 $\mu\text{g}/\text{kg}$, 345% of the baseline value after administration at a dose of 50 $\mu\text{g}/\text{kg}$, and 443% of the baseline value after administration at a dose of 100 $\mu\text{g}/\text{kg}$. Significant changes in SVRI were not detected after administration of romifidine at a dose of 5 $\mu\text{g}/\text{kg}$, and SVRI was significantly higher after administration at a dose of 100 $\mu\text{g}/\text{kg}$ than after administration at a dose of 5 or 10 $\mu\text{g}/\text{kg}$. After 10 minutes, SVRI began to decrease (Fig 5). Baseline PVRI were 646.2 ± 216.6 , 367.4 ± 198.8 , 374.2 ± 186.4 , 522.9 ± 296.7 , and $447.8 \pm 159.2 \text{ dynes}\cdot\text{sec}\cdot\text{cm}^{-5}\cdot\text{m}^2$ following administration of romifidine at doses of 5, 10, 25, 50, and 100 $\mu\text{g}/\text{kg}$, respectively. Significant changes in PVRI were not detected.

Ventricular stroke work—Baseline LVSWI were 71.6 ± 9.4 , 65.8 ± 14.9 , 78.0 ± 15.5 , 77.0 ± 20.8 , and $80.6 \pm 25.8 \text{ g}\cdot\text{m}\cdot\text{m}^2$ following administration of romi-

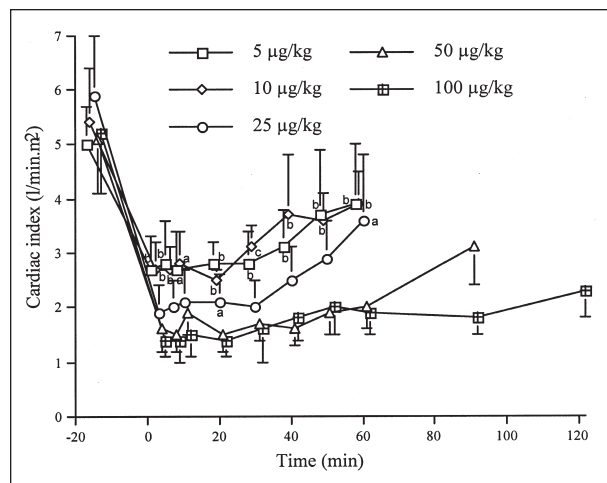


Figure 4—Mean cardiac index in dogs given romifidine IV at various doses. See Figure 1 for key.

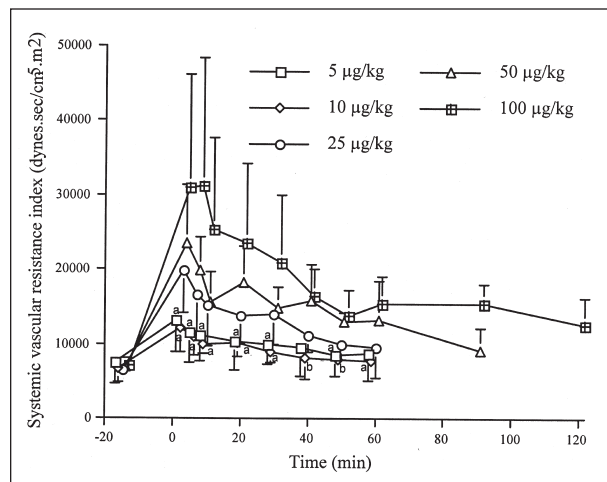


Figure 5—Mean systemic vascular resistance index in dogs given romifidine IV at various doses. See Figure 1 for key.

fidine at doses of 5, 10, 25, 50, and 100 $\mu\text{g}/\text{kg}$, respectively. Significant changes in LVSWI were not detected. Baseline RVSWI ranged from 7.0 to 17.2 $\text{g}\cdot\text{m}\cdot\text{m}^{-2}$. Right ventricular stroke work index decreased significantly to approximately 50% of the baseline value in all groups following administration of romifidine (Table 1).

Degree of sedation—Mean sedation scores were 1.0 ± 0.7 , 1.0 ± 0.6 , 2.2 ± 0.8 , 1.5 ± 0.4 , and 2.3 ± 0.7 7 minutes following administration of romifidine at doses of 5, 10, 25, 50, and 100 $\mu\text{g}/\text{kg}$, respectively.

Discussion

Results of the present study suggest that romifidine administered IV at doses ranging from 5 to 100 $\mu\text{g}/\text{kg}$ induces dose-dependent cardiovascular changes in dogs. Those changes are mainly characterized by a decrease in HR and CI and an increase in SVR.

α_2 -Adrenoceptor agonists induce bradycardia partially through a baroreflex related to the increase in arterial pressure usually observed after the administration of these drugs and partially through an effect on central sympathetic mechanisms regulating HR.¹³ In the present study, HR decreased regardless of the dose of romifidine administered. However, this effect was moderate with administration at a dose of 5 or 10 $\mu\text{g}/\text{kg}$, and HR for dogs in these groups was in the physiologic range for medium-size dogs (ie, 70 to 140 beats/min¹⁴). The effects on HR seemed dose dependent; however, HR decreased similarly following administration of romifidine at a dose of 25, 50, or 100 $\mu\text{g}/\text{kg}$, suggesting that there may be a ceiling on this effect of romifidine.

Following administration of an α_2 -adrenoceptor agonist, arterial pressure shows a biphasic response: an initial transient increase followed by a more prolonged decrease.^{7,8} Such a pattern was observed in the present study with administration at a dose of 25 $\mu\text{g}/\text{kg}$ or greater. At lower doses, arterial pressure decreased without first increasing. This suggests that at low doses, romifidine could have predominantly central effects, whereas at higher doses, it stimulates peripheral adrenoceptors, including those on the vascular smooth muscle, thereby inducing vasoconstriction. Similar findings have been reported for medetomidine, another α_2 -adrenoceptor agonist.⁸ The effects on arterial pressure seemed dose dependent in the present study, with the 3 lowest doses inducing larger decreases than the 2 higher doses.

Except in dogs that received the lowest dose, CVP increased in response to romifidine administration. α_2 -Adrenoceptor agonists have been reported to induce such increases in CVP secondary to a reduction in venous capacitance and CO.¹⁵ This effect seems dose related, with higher doses inducing higher increases.

Pulmonary arterial pressure decreased significantly in all groups in this study. This effect remains unexplained, because α_2 -adrenoceptor agonists are reported not to affect PAP, probably because of the lower density of α_2 -adrenoceptors in the pulmonary vasculature, compared with the systemic vasculature.¹⁶ A decrease in CI without a compensatory increase in pulmonary vascular resistance seems an unlikely explanation,

because PAP decreased progressively, whereas CI decreased abruptly.

Pulmonary capillary wedge pressure increased transiently in response to administration of romifidine at doses higher than 10 $\mu\text{g}/\text{kg}$. Again, α_2 -adrenoceptor agonists have not been reported to have any direct effects on PCWP. It is possible that this increase is a transient response to circulatory stasis related to bradycardia and to an acute increase in left ventricular afterload, resulting in blood stasis in the pulmonary capillaries. Moreover, the shift of blood from the venous capacitance vessels induced by venoconstriction, as illustrated by the increase in CVP, could also have resulted in a relative overload of pulmonary vessels. Such effects were indeed more important following administration at a dose of 25, 50, or 100 $\mu\text{g}/\text{kg}$ than following administration at a dose of 5 or 10 $\mu\text{g}/\text{kg}$, similar to the increases in SVRI and CVP. Another possible explanation is decreased myocardial compliance secondary to, for example, decreased myocardial perfusion.¹⁷

A significant decrease in body temperature was detected in all groups in the present study except dogs that received romifidine at a dose of 10 $\mu\text{g}/\text{kg}$. α_2 -Adrenoceptor agonists have been reported to induce hypothermia by decreasing heat production related to muscular activity and by having direct effects on noradrenergic hypothalamic mechanisms implicated in thermoregulation.¹⁸ The degree of hypothermia observed, however, was slight, with mean core temperature > 37.5 C. Moreover, the injection of ice-cold fluids for determination of CO may have participated in this effect.

Dose-dependent decreases in CI were detected following romifidine administration. For dogs that received romifidine at a dose of 5 or 10 $\mu\text{g}/\text{kg}$, CI was near the lower limit of the reference range for healthy awake dogs; for dogs in the other 3 groups, CI was less than the reference range.¹⁹ As SI remained stable, this decrease in CI appeared to be mainly related to bradycardia. Except among dogs that received romifidine at a dose of 100 $\mu\text{g}/\text{kg}$, CI had returned to reference values by the end of the observation period.

Rate-pressure product has been used to estimate myocardial oxygen consumption. Rate-pressure product decreased in response to romifidine administration in relation to the degree of bradycardia induced. Thus, the decrease in RPP was lower for dogs that received romifidine at a dose of 5 or 10 $\mu\text{g}/\text{kg}$, compared with the other groups, because bradycardia was less pronounced. Bradycardia decreases myocardial oxygen demand and myocardial work.²

Systemic vascular resistance index increased in response to romifidine administration. The magnitude of this effect was the least among dogs that received romifidine at a dose of 5 or 10 $\mu\text{g}/\text{kg}$, intermediate among dogs that received romifidine at a dose of 25 or 50 $\mu\text{g}/\text{kg}$, and highest among dogs that received romifidine at a dose of 100 $\mu\text{g}/\text{kg}$, indicating that this response was dose dependent. This probably reflects the direct effect of the drug on α_2 -adrenoceptors on the vascular smooth muscle, inducing vasoconstriction.^{15,20,21} This is also compatible with the hypothesis that at lower doses, romifidine exhibits less peripheral

than central effects, because the increase in SVRI was less pronounced with the 2 lowest doses studied.

The effects on RVSWI were mainly related to the increase in preload, which is illustrated by the increase in CVP.

Sedation scores indicated that romifidine induced sedation at all doses tested. Degree of sedation ranged from mild (5 and 10 µg/kg) to moderate (25 and 100 µg/kg). Dogs that received romifidine at a dose of 50 µg/kg seemed less sedated than those that received a dose of 25 µg/kg. The reason for this remains unclear, but it may be related to the small number of dogs used in the study.

Whatever the dose administered, IV administration of romifidine induced cardiovascular effects, which were mainly characterized by bradycardia resulting in a decrease in CI and by vasoconstriction. Most of the hemodynamic effects induced appeared to be dose dependent, although the 5 and 10 µg/kg doses and the 25, 50, and 100 µg/kg doses induced comparable effects, suggesting that there may be a ceiling on the cardiovascular effects of romifidine. Moreover, values observed for dogs that received romifidine at a dose of 5 or 10 µg/kg were mostly within reference ranges.

The effects induced by romifidine were similar to those observed after medetomidine administration.⁸ In an unpublished study, we observed that, based on the thiopental-sparing effect, romifidine was roughly 5 times less potent than medetomidine (on a µg/kg basis), and this is also compatible with the level of sedation observed here and in the previous study on medetomidine. However, lower doses of romifidine seem to induce less severe hemodynamic effects than the lower doses of medetomidine.

In conclusion, it appears possible to limit the cardiovascular effects of romifidine by using a dose of 10 µg/kg or less. However, at these doses, the sedation induced is mild. Moreover, this study did not determine what effects romifidine would have when combined with other cardiovascular depressants such as inhalant anesthetics. Further studies are warranted to determine other effects of low doses of romifidine, such as its anesthetic-sparing or analgesic effects.

⁸England GCW, Alibhai HIK. Cardiopulmonary effects of romifidine in dogs (abstr), in *Proceedings*. 6th Int Congress Vet Anaesthesiol 1997;98.

^bRomifidine (1 mg/ml), Boehringer Ingelheim Vetmedica GmbH, Ingelheim, Germany.

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