Cardiovascular effects of a high dose of romifidine in propofol-anesthetized cats

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Objective—To determine the hemodynamic effects of IM administration of romifidine hydrochloride in propofol-anesthetized cats.

Animals—15 adult domestic shorthair cats.

Procedure—Cats were randomly assigned to receive romifidine (0, 400, or 2,000 µg/kg, IM). Cats were anesthetized with propofol and mechanically ventilated with oxygen. The right jugular vein, left carotid artery, and right femoral artery and vein were surgically isolated and catheterized. Heart rate; duration of the PR, QRS, and QT intervals; mean pulmonary artery pressure; mean right atrial pressure; systolic, diastolic, and mean arterial pressures; left ventricular systolic pressure; left ventricular end-diastolic pressure; and cardiac output were monitored. Systemic vascular resistance, rate of change of left ventricular pressure, and rate pressure product were calculated. Arterial and venous blood samples were collected anaerobically for determination of pH and blood gas tensions (P_{O_2} and P_{CO_2}).

Results—Administration of romifidine at 400 and 2,000 µg/kg, IM, decreased heart rate, cardiac output, rate of change of left ventricular pressure, rate pressure product, and pH. Arterial and pulmonary artery pressures, left ventricular pressure, left ventricular end-diastolic pressure, and right atrial pressure increased and then gradually returned to baseline values. Arterial blood gas values did not change, whereas venous P_{CO_2} increased and venous P_{O_2} decreased. Significant differences between low and high dosages were rare, suggesting that the dosages investigated produced maximal hemodynamic effects.

Conclusions and Clinical Relevance—Romifidine produces cardiovascular effects that are similar to those of other α_2-agonists. High dosages of romifidine should be used with caution in cats with cardiovascular compromise. (*Am J Vet Res* 2002;63:1241–1246)

The α_2-agonists are commonly used to produce sedation, analgesia, and muscle relaxation in dogs, cats, and horses and are adjuncts administered during general anesthesia to reduce the amount of injectable and inhalant anesthetic required.[1-5] Although recognized for their relatively predictable sedative and analgesic properties, α_2-agonists, including xylazine hydrochloride, detomidine hydrochloride, and medetomidine hydrochloride, are also known for their cardiovascular effects including bradycardia, decreases in cardiac output, and increases in systemic vascular resistance.[6-10] Arterial blood pressure remains unchanged, or increases initially, followed by a longer period of reduced pressure below baseline values. Interestingly, indices of cardiac contractility and myocardial oxygen consumption (ie, pressure rate product) remain relatively unchanged or decrease only minimally with time.[7,9-13] These hemodynamic effects may not be dose-dependent throughout the clinical range, and a plateau or ceiling effect has been reported for cardiovascular effects when medetomidine is administered at high dosages to cats and dogs (> 150 µg/kg in cats[8] and > 120 µg/kg in dogs[9]).

Sedative and analgesic effects of α_2-agonists are attributed to the activation of presynaptic α_2-agonist receptors in the CNS, whereas cardiovascular effects are attributed to a decrease in CNS sympathetic outflow and activation of peripheral vascular α_2-agnoist receptors.[14,15] Activation of peripheral vascular α_2-agonist receptors causes vasoconstriction, increasing arterial blood pressure and decreasing vascular (particularly venous) capacitance, which thereby increases baroreflex activity to produce bradycardia.[14,16] Similar to other members of this class of drugs, romifidine, which is estimated to be one-fifth as potent as medetomidine, can cause sedation in dogs, cats, and horses.[3,5,10,17] In dogs, heart rate, cardiac index, and stroke work index decrease following romifidine administration, whereas central venous pressure, pulmonary capillary wedge pressure, and systemic vascular resistance increase.[10] Furthermore, arterial blood pressure initially increases, followed by a prolonged decrease, and **rate pressure product (RPP)** decreases.[10] Analysis of results of those studies[9,10] suggests that relatively low dosages of romifidine produce effects that are not dose-dependent and produce less severe hemodynamic effects than medetomidine, although the authors admitted that the degree of sedation was also diminished.

Propofol is an ultra-short acting, nonbarbiturate, hypnotic, injectable anesthetic used to produce and maintain general anesthesia in dogs and cats.[18-22] In contrast to thiopental, propofol does not accumulate because of its rapid clearance and large volume of distribution.[22] Propofol often is used to induce general anesthesia in dogs and cats prior to the administration of inhalant anesthetics (isoflurane, sevoflurane) and has been used in combination with α_2-agonists in dogs as part of a total intravenous anesthetic protocol.[18,23]

The objective of the study reported here was to determine the cardiovascular effects for 2 dosages of romifidine when administered to propofol-anesthetized cats. We selected a dosage of romifidine that

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was at the upper limit of the clinically recommended dosage range (400 µg/kg) for cats and another dosage that was 5 times that value to determine whether administration of these doses would produce dose-dependent effects.

Materials and Methods

Animals—Fifteen purpose-bred domestic shorthair cats that were > 1 year old and weighed between 3.9 and 5.5 kg were used in the study. Cats were judged to be healthy on the basis of results of physical examination and analysis of an ECG and hemogram. This study was approved by the Laboratory Animal Care and Use Committee of The Ohio State University and was conducted in compliance with good laboratory practices.

Surgical procedures—Propofol was administered for the induction (6 mg/kg, IV) and maintenance (10 mg/kg/h, IV) of anesthesia. Cats were endotracheally intubated with a cuffed endotracheal tube, which was then attached to a ventilator that was set to deliver 100% oxygen at a rate of 6 to 10 breaths/min and volume of 12 to 15 ml/kg. The Pa_{CO_2} was maintained between 35 and 40 mm Hg. A small amount (0.1 ml) of 2% lidocaine hydrochloride was diluted to a volume of 1 ml by the addition of saline (0.9% NaCl) solution and injected into the right and left jugular furrow and right inguinal area prior to surgical isolation of the right jugular vein, left carotid artery, and right femoral vein and artery, respectively.

A 4-F flow-directed thermodilution catheter[a] was introduced into the right jugular vein and advanced until the distal tip was positioned in the pulmonary artery. This catheter was used to determine core (pulmonary artery) temperature, pulmonary artery pressure, and cardiac output.[b] Cardiac output was measured by injecting 1 ml of ice-cold saline solution into the proximal port of the catheter. Mean value for 3 injections was used to calculate cardiac output for each recording period. A 4-F catheter[c] that contained 2 pressure-sensing micromanometers located at the tip was advanced into the left carotid artery and positioned so that the distal pressure sensor was located in the left ventricle and the proximal pressure sensor was located in the ascending aorta. The right femoral artery and vein were catheterized by use of polyethylene 90 tubing[d] and polyethylene 160 tubing,[e] respectively. Tips of those catheters were advanced to the level of the diaphragm. A lead-II ECG was continuously recorded. A circulating hot-water blanket and heat lamp were used to maintain body temperature between 37 and 39 C. All cats were administered warmed, lactated Ringer's solution (5 ml/kg/h) throughout the procedure.

Procedure—The procedures facilitated measurement of heart rate, duration of the PR, QRS, and QT intervals, **mean pulmonary artery pressure (mPAP)**, mean **right atrial pressure (RAP)**, **systolic arterial pressure (SAP)**, **diastolic arterial pressure (DAP)**, **mean arterial pressure (MAP)**, **left ventricular systolic pressure (LVSP)**, **left ventricular end-diastolic pressure (LVEDP)**, and cardiac output. These hemodynamic variables were used to calculate **systemic vascular resistance (SVR)**, left ventricular **rate of change of pressure (+dP/dt)**, and RPP. The RPP was calculated as the product of heart rate times MAP. All data were continuously monitored and periodically recorded by use of a computer-based data acquisition system[f] for physiologic measurements. Blood samples collected anaerobically from the right femoral vein and artery were used to determine venous and arterial pH and blood gas tensions (P_{O_2} and P_{CO_2}),[g] respectively. All cats were euthanized at the end of the study by IV administration of an overdose of sodium pentobarbital (120 mg/kg).

Experimental design—Cats were allowed to stabilize for 15 minutes after insertion of all catheters and recording instruments. Baseline data for heart rate, duration of the PR, QRS, and QT intervals, mPAP, RAP, SAP, DAP, MAP, LVSP, LVEDP, cardiac output, SVR, left ventricular +dP/dt, and RPP were obtained 15 and 5 minutes before drug administration (time 0), and data were also obtained 5, 15, 30, 60, 90, 120, and 240 minutes after drug administration. The cats were randomly assigned into 3 groups and administered romifidine IM as follows: group 1 (3 cats), 0.0 µg/kg; group 2 (6), 400 µg/kg; and group 3 (6), 2,000 µg/kg.

Statistical analysis—Data within and among groups were compared by use of an ANOVA for repeated measures. Pairwise comparisons within and among groups were performed by use of the Dunnet and Tukey post hoc tests, respectively. A value of $P < 0.05$ was considered significant.

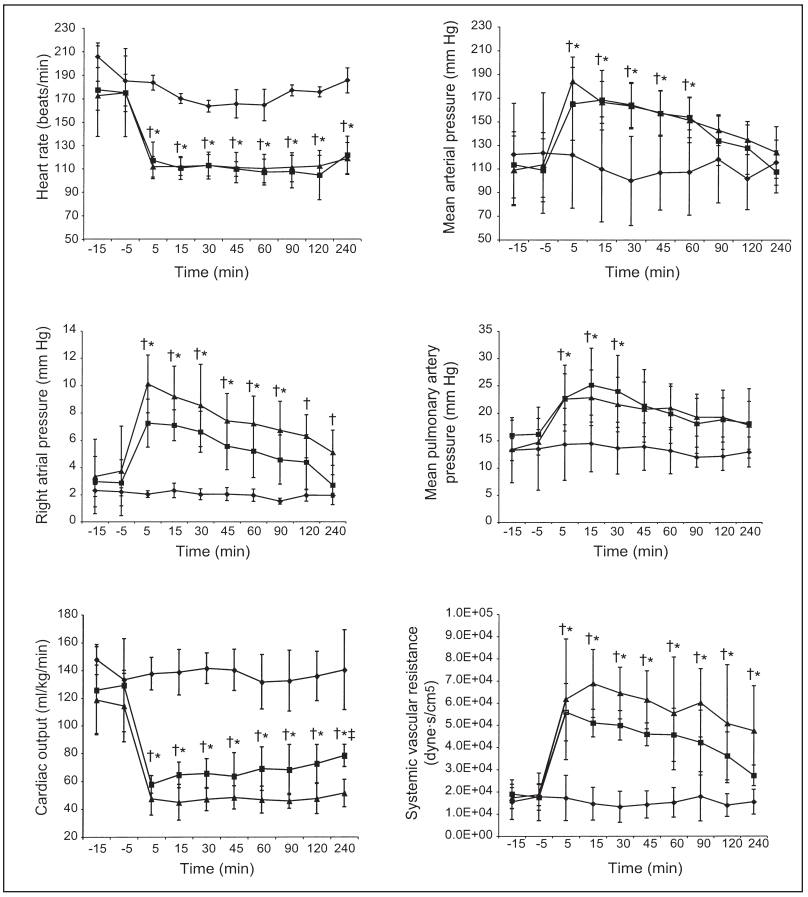

Figure 1—Mean ± SD hemodynamic effects after IM administration of romifidine (0 µg/kg [circle], 400 µg/kg [square], and 2,000 µg/kg [triangle]) to 3 groups of propofol-anesthetized cats. Time 0 = Time of romifidine administration. *Within a time point, value differs significantly ($P < 0.05$) from value for 0 µg/kg. †Within a treatment group, value differs significantly ($P < 0.05$) from value for –5 minutes. ‡Within a time point, value for 400 µg/kg differs significantly ($P < 0.05$) from value for 2,000 µg/kg.

Results

All measured and calculated hemodynamic variables remained unchanged from baseline values in cats of group 1. Heart rate decreased from baseline values in cats of groups 2 and 3 after IM administration of romifidine. Heart rate remained decreased for approximately 120 minutes and then began to return toward baseline values. The decrease in heart rate was similar after administration of romifidine at 400 and 2,000 µg/kg (**Fig 1**). The QRS interval did not change from baseline values after administration of romifidine at 400 or 2,000 µg/kg, whereas the PR and QT intervals increased from baseline values 5 minutes after IM administration of romifidine; however, those values were within reference ranges for cats (data not shown). The increases in PR and QT intervals paralleled changes in heart rate. Cardiac arrhythmias were not observed, and changes in intervals for the ECG variables were similar after administration of romifidine at 400 and 2,000 µg/kg.

The SAP, DAP, and MAP increased from baseline values in both groups of cats that received romifidine. The MAP remained increased for approximately 60 minutes and then gradually returned to baseline values by 90 minutes after drug administration (Fig 1). Changes in MAP were similar after administration of romifidine at 400 and 2,000 µg/kg. The LVSP increased from baseline values in cats administered romifidine

Table 1—Mean ± SD hemodynamic and metabolic effects after IM administration of various doses of romifidine to 3 groups of propofol-anesthetized cats

Variable	Romifidine (µg/kg)	Time (min) –15	–5	5	15	30	45	60	90	120	240
Systolic arterial pressure (mm Hg)											
	0	133 ± 49	136 ± 57	134 ± 50	121 ± 49	110 ± 40	118 ± 33	118 ± 39	132 ± 42	113 ± 28	129 ± 20
	400	127 ± 29	123 ± 28	199 ± 37*†	204 ± 31*†	200 ± 25*†	190 ± 24*†	185 ± 21*†	160 ± 26*†	153 ± 25*†	130 ± 21
	2,000	124 ± 32	128 ± 31	219 ± 26*†	195 ± 22*†	192 ± 22*†	185 ± 20*†	178 ± 17*†	169 ± 13*†	161 ± 12*†	148 ± 24
Diastolic arterial pressure (mm Hg)											
	0	110 ± 4	109 ± 47	106 ± 41	96 ± 41	87 ± 35	92 ± 30	94 ± 35	102 ± 33	89 ± 24	99 ± 18
	400	97 ± 27	92 ± 27	138 ± 26*†	142 ± 23*†	138 ± 19*†	132 ± 19*†	129 ± 17*†	112 ± 21	106 ± 24	86 ± 17
	2,000	93 ± 27	96 ± 26	162 ± 21*†	144 ± 17*†	141 ± 19*†	136 ± 21*†	130 ± 23*†	121 ± 14†	113 ± 13	103 ± 21
Left ventricular systolic pressure (mm Hg)											
	0	133 ± 47	137 ± 54	136 ± 48	123 ± 47	112 ± 38	121 ± 31	120 ± 38	132 ± 37	126 ± 25	134 ± 17
	400	129 ± 28	124 ± 27	200 ± 37*†	205 ± 32*†	202 ± 28*†	192 ± 27*†	186 ± 25*†	160 ± 28*†	154 ± 29*†	131 ± 19
	2,000	113 ± 20	118 ± 20	202 ± 26*†	192 ± 20*†	191 ± 17*†	183 ± 19*†	176 ± 20*†	172 ± 14*†	162 ± 9*†	147 ± 25
Left ventricular end-diastolic pressure (mm Hg)											
	0	5 ± 3	6 ± 4	6 ± 3	5 ± 2	5 ± 2	5 ± 1	5 ± 2	5 ± 2	5 ± 1	5 ± 1
	400	7 ± 3	6 ± 2	17 ± 6*†	20 ± 5*†	19 ± 4*†	17 ± 5*†	15 ± 4*†	13 ± 6*†	11 ± 5*†	9 ± 4
	2,000	5 ± 1	6 ± 1	16 ± 7*†	18 ± 5*†	18 ± 5*†	18 ± 5*†	15 ± 4*†	13 ± 3*†	12 ± 2*†	12 ± 3†
Left ventricular +dP/dt (mm Hg/s)											
	0	3,808 ± 1,094	3,805 ± 1,383	3,988 ± 1,310	3,479 ± 1,304	3,022 ± 1,096	3,430 ± 1,086	3,258 ± 856	3,606 ± 661	3,114 ± 778	3,526 ± 349
	400	3,408 ± 1,528	3,425 ± 1,369	2,657 ± 597	2,535 ± 368	3,008 ± 536	2,924 ± 621	2,441 ± 382	2,208 ± 372*†	2,271 ± 437	1,968 ± 353*
	2,000	2,544 ± 420	2,805 ± 371	2,116 ± 430	2,021 ± 358	2,131 ± 373	2,136 ± 443	1,998 ± 403	2,085 ± 360*	1,860 ± 192*	1,897 ± 455*
Rate pressure product ([beats × mm Hg]/min)											
	0	27,013 ± 12,284	25,689 ± 14,353	24,730 ± 1,2412	21,099 ± 11,842	18,531 ± 10,006	19,799 ± 8,974	19,702 ± 9,652	21,288 ± 7,209	18,544 ± 5,760†	20,699 ± 5,148†
	400	17,714 ± 10,604	17,780 ± 9,453	21,199 ± 5,835	19,123 ± 3,553	19,042 ± 2,627	18,672 ± 2,586	17,463 ± 2,688	16,530 ± 2,635	16,714 ± 2,994	15,640 ± 2,754
	2,000	18,807 ± 5,672	19,972 ± 6,068	18,117 ± 7,229	18,620 ± 2,837	18,368 ± 3,012	17,488 ± 3,157	14,862 ± 6,539	15,854 ± 2,298	14,477 ± 5,237	14,489 ± 1,547
Blood temperature (C)											
	0	37.5 ± 0.6	37.3 ± 0.8	37.1 ± 0.9	37.1 ± 0.9	37.0 ± 1.0	37.0 ± 1.1	37.0 ± 1.1	37.2 ± 1.3	37.3 ± 1.2	37.5 ± 0.9
	400	37.2 ± 0.6	37.1 ± 0.7	37.3 ± 0.7	37.4 ± 0.7	37.5 ± 0.8	37.6 ± 0.8	37.7 ± 0.8	37.9 ± 0.8	38.0 ± 0.9	37.7 ± 0.9
	2,000	37.1 ± 0.7	37.0 ± 0.7	37.2 ± 0.7	37.3 ± 0.7	37.4 ± 0.8	37.5 ± 0.8	37.6 ± 0.9	37.9 ± 0.9	38.0 ± 0.9	37.7 ± 1.0
Venous pH											
	0	7.31 ± 0.02	7.30 ± 0.01	7.30 ± 0.02	7.29 ± 0.02	7.28 ± 0.02	7.28 ± 0.03	7.28 ± 0.01	7.29 ± 0.02	7.28 ± 0.02	7.30 ± 0.03
	400	7.28 ± 0.03	7.28 ± 0.04	7.26 ± 0.03	7.25 ± 0.03	7.24 ± 0.02†	7.23 ± 0.03*†	7.22 ± 0.03*†	7.22 ± 0.03*†	7.23 ± 0.04*†	7.22 ± 0.02*†
	2,000	7.27 ± 0.05	7.27 ± 0.04	7.25 ± 0.05	7.22 ± 0.05	7.21 ± 0.04†	7.20 ± 0.04*†	7.20 ± 0.04*†	7.19 ± 0.03*†	7.19 ± 0.03*†	7.21 ± 0.05*†
Pv_{O_2} (mm Hg)											
	0	65.5 ± 8.8	66.9 ± 5.4	60.3 ± 5.7	58.3 ± 9.5	59.5 ± 15.5	58.7 ± 9.9	57.0 ± 10.2	56.4 ± 1.7	48.6 ± 7.5	58.6 ± 15.5
	400	62.7 ± 9.0	58.9 ± 9.7	41.7 ± 7.7*†	41.2 ± 7.4*†	42.6 ± 6.5*†	39.8 ± 5.3*†	39.0 ± 5.2*†	38.8 ± 5.8*†	39.4 ± 7.1*†	48.9 ± 8.0†
	2,000	62.6 ± 10.9	64.4 ± 7.5	37.6 ± 5.5*†	38.5 ± 7.1*†	38.8 ± 5.8*†	38.9 ± 4.9*†	38.3 ± 5.4*†	36.8 ± 4.9*†	37.0 ± 5.7*†	43.4 ± 6.9†
$Pvco_2$ (mm Hg)											
	0	41.8 ± 4.6	40.5 ± 3.4	39.2 ± 2.3	41.5 ± 3.0	40.9 ± 3.5	43.2 ± 2.2	43.7 ± 2.9	42.5 ± 4.5	45.5 ± 4.4	46.0 ± 3.4
	400	43.4 ± 3.3	43.2 ± 4.3	45.2 ± 5.9	46.7 ± 4.4	47.9 ± 6.2	51.2 ± 4.9	51.9 ± 6.1	54.5 ± 4.0*†	55.6 ± 6.7*†	60.8 ± 3.9*†
	2,000	44.8 ± 4.9	42.9 ± 4.9	47.6 ± 4.9	48.7 ± 4.3	50.6 ± 5.4	53.0 ± 7.9†	53.9 ± 6.1†	55.6 ± 6.6*†	55.8 ± 7.0*†	57.8 ± 9.7*†
Arterial pH											
	0	7.33 ± 0.01	7.36 ± 0.01	7.34 ± 0.05	7.31 ± 0.02	7.30 ± 0.05	7.32 ± 0.02	7.33 ± 0.02	7.35 ± 0.01	7.33 ± 0.03	7.35 ± 0.04
	400	7.33 ± 0.05	7.36 ± 0.06	7.32 ± 0.03	7.29 ± 0.04	7.28 ± 0.05	7.27 ± 0.04	7.29 ± 0.03	7.31 ± 0.08	7.30 ± 0.07	7.30 ± 0.03
	2,000	7.33 ± 0.06	7.31 ± 0.05	7.29 ± 0.07	7.24 ± 0.07	7.25 ± 0.05	7.25 ± 0.06	7.27 ± 0.03	7.27 ± 0.03	7.27 ± 0.05	7.27 ± 0.05
Pa_{O_2} (mm Hg)											
	0	352.1 ± 135.4	445.3 ± 31.0	403.8 ± 49.4	349.4 ± 135.8	475.3 ± 32.0	473.2 ± 41.9	455.0 ± 55.8	471.2 ± 26.2	468.9 ± 25.3	438.2 ± 29.6
	400	480.0 ± 42.2	477.9 ± 61.3	488.6 ± 36.9	445.7 ± 73.1	440.6 ± 61.3	447.0 ± 52.5	439.5 ± 85.1	442.5 ± 67.8	452.1 ± 48.2	464.0 ± 52.1
	2,000	494.6 ± 39.2	476.7 ± 55.4	401.2 ± 145.4	434.0 ± 117.9	475.1 ± 60.0	470.4 ± 41.1	468.8 ± 36.2	468.4 ± 38.6	472.1 ± 57.0	443.5 ± 42.1
$Paco_2$ (mm Hg)											
	0	39.7 ± 2.1	31.9 ± 1.8	34.4 ± 5.5	36.1 ± 2.2	39.9 ± 5.0	37.7 ± 1.2	35.1 ± 0.8	34.9 ± 1.6	37.6 ± 2.9	38.4 ± 5.0
	400	35.7 ± 4.7	34.5 ± 7.8	35.8 ± 4.1	38.2 ± 6.1	38.3 ± 6.4	39.1 ± 7.7	37.7 ± 5.1	38.1 ± 8.7	39.2 ± 8.0	43.6 ± 3.7
	2,000	37.4 ± 5.2	38.3 ± 5.2	38.1 ± 6.9	40.5 ± 7.9	39.5 ± 6.6	39.8 ± 7.5	38.3 ± 4.2	37.9 ± 5.0	39.7 ± 5.9	45.6 ± 8.2

*Within a time period, value differs significantly ($P < 0.05$) from value for 0 µg/kg. †Within a treatment group, value differs significantly ($P < 0.05$) from values obtained at –15 and –5 minutes (baseline).

Time 0 = Time of romifidine administration. +dP/dt = Rate of change of pressure.

(**Table 1**). The LVSP remained increased for approximately 45 minutes and then gradually returned toward baseline values. The LVEDP increased from baseline values in cats administered romifidine and reached peak values between 5 and 15 minutes after administration of romifidine. The LVEDP returned to baseline values between 90 and 120 minutes after administration of romifidine at a dose of 400 µg/kg, but it remained above baseline values until 240 minutes after IM administration of 2,000 µg/kg. The mPAP increased from baseline values in cats administered romifidine; it remained increased for approximately 30 minutes and then gradually returned to baseline values. The change in mPAP was similar after administration of 400 and 2,000 µg/kg. Mean RAP increased from baseline values in cats administered romifidine. Changes in RAP were greater after administration of 2,000 µg/kg, but these values did not differ significantly from values obtained after administration of 400 µg/kg.

Cardiac output decreased from baseline values in cats administered romifidine; it reached a nadir value 5 minutes after romifidine administration (Fig 1). The decrease in cardiac output paralleled the decrease in heart rate. Cardiac output remained decreased for the duration of the study period but began to return toward baseline values at 90 minutes in cats administered 400 µg/kg. Left ventricular +dP/dt did not change in any cat immediately following IM administration of romifidine, but it began to decrease at approximately 60 minutes after administration of 400 and 2,000 µg/kg (Table 1). Changes in left ventricular +dP/dt were similar after administration of 400 and 2,000 µg/kg. The SVR increased from baseline values in all cats administered romifidine. The SVR remained increased for approximately 90 minutes after IM administration of romifidine and then gradually decreased but did not reach baseline values by the end of the 240-minute recording period. The RPP decreased but at later times after the administration of 400 or 2,000 µg/kg.

Arterial pH, Pa_{O_2}, and Pa_{CO_2} did not change in any cat in any of the 3 groups at any time point following administration of romifidine (Table 1). Venous P_{CO_2} gradually increased from baseline values after the administration of 400 and 2,000 µg/kg, reaching peak values at 240 minutes. Changes in venous P_{CO_2} were similar after administration of 400 and 2,000 µg/kg. Venous P_{O_2} decreased from baseline values 5 minutes after administration of 400 and 2,000 µg/kg and remained decreased for the duration of the experiments. The changes in venous P_{O_2} were similar after administration of 400 and 2,000 µg/kg. Blood temperature was unchanged from baseline values after IM administration of romifidine.

Discussion

To our knowledge, the results reported here are the first to document that romifidine produces hemodynamic effects in cats that are qualitatively similar to those reported after administration of xylazine, medetomidine, and detomidine in cats, dogs, and horses.[9,24,25] Furthermore, analysis of our results suggests that there may be a maximal or ceiling effect on cardiovascular changes similar to that reported in dogs following IV administration of romifidine.[10] It was not our intention to determine the minimum dose of romifidine required to produce a maximum cardiovascular response, although this would have provided clinically relevant information.

The α_2-agonists (xylazine, medetomidine, detomidine) produce profound sedative, analgesic, muscle relaxant, and cardiovascular effects by activating central and peripheral α_2-agonist receptor subtypes (α-2A, α-2B, α-2D).[16,26] Extensive research efforts are underway to identify the pharmacologic importance of the various subtypes of α_2-agonists receptors in mammals, and investigators have only just begun to segregate the sedative, analgesic, and cardiovascular (bradycardia, vasoconstriction) effects. Until this task is accomplished, analysis of results of in vitro and in vivo experiments suggests that current α_2-agonists produce relatively nonselective stimulation of central and peripheral α_2-agonist receptors, resulting in an array of cardiovascular and endocrine effects.[16,26]

Cardiovascular effects produced by romifidine in the cats used in the study reported here are qualitatively similar to those observed after IM or IV administration of xylazine, medetomidine, dexmedetomidine, or detomidine to dogs, cats, and horses and can be attributed to the dose selected, route of administration, and each drug's affinity for, and ability to, activate α_2-agonist receptors in the CNS and peripheral nervous system.[7-13,25] This pharmacologic pattern would be expected to produce the qualitative and temporal cardiovascular effects that we observed and that have been reported elsewhere. The fact that we chose to administer the drug IM instead of IV did not delay the onset of qualitative or temporal cardiovascular effects attributable to romifidine, compared with similar values following IV or IM administration of medetomidine to cats and dogs and IV administration of romifidine to dogs.[7,8,10] Interestingly and despite differences in the onset and duration of the effects of α_2-agonists, the percentage decrease in heart rate and cardiac output reported in other studies[7-10] varies from 40 to 60% and from 50 to 70%, regardless of the dosage or whether the α_2-agonist is administered IV or IM. This finding suggests that the onset of drug effect is relatively rapid and dependent on prevailing autonomic tone. It also suggests that the decrease in heart rate contributes to the decrease in cardiac output and that the factors responsible for the observed cardiovascular changes reach a maximal effect. The rapid onset of effects after IV or IM administration of α_2-agonists is not surprising because of their relatively high lipophilicity.[16]

Bradycardia may account for most but not all of the decrease in cardiac output, because cardiac output continues to decrease after change in heart rate reaches a plateau.[7,8,25] Dramatic decreases in cardiac output following the administration of α_2-agonists in general and romifidine in particular in the study reported here are responsible for the associated decrease in venous P_{O_2} and increase in venous P_{CO_2}, because blood would be expected to spend more time in the capillary exchange vessels. The decrease in cardiac output is probably not related to a direct effect on cardiac

inotropy, because we did not detect a change in left ventricular +dP/dt, a load-dependent index of cardiac contractility. Furthermore, the cardiovascular effects of xylazine in denervated dogs and medetomidine in nerve-intact dogs were investigated by use of load-dependent and -independent indices of cardiac contractility, and researchers were unable to document a significant direct negative inotropic effect.[11-13] Additionally, increases in cardiac preload caused by bradycardia or α_2-agonist-induced venoconstriction, as suggested by an increase in central venous pressure, would be expected to increase cardiac inotropy via the Starling mechanism. Analysis of results of the study reported here combined with results of another study[11] suggests that the decrease in cardiac output beyond that produced by the decrease in heart rate is most likely attributable to an increase in cardiac afterload caused by arterial vasoconstriction and the gradual withdrawal of CNS sympathetic tone. Similar conclusions have been reached by other investigators who have conducted research on dose-response characteristics of medetomidine in dogs and cats.[7-9,13]

Similarity of the cardiovascular effects produced by IM administration of romifidine at 400 and 2,000 µg/kg is an interesting finding and is consistent with effects reported following the administration of medetomidine and dexmedetomidine to dogs and cats and romifidine to dogs.[7-10] Analysis of results of 2 studies[9,10] suggests that maximal cardiovascular effects are produced in dogs at lower dosages after IV administration of medetomidine than after IV administration of romifidine. Those dosages may reflect differences in potency, because medetomidine is reportedly 5 times more potent than romifidine.[10] Analysis of results of the study reported here and results of other studies[6,9,10,23-25] in dogs, cats, and horses suggests that maximum cardiovascular effects of currently available α_2-agonists can be reached at clinically relevant dosages and before maximum sedative effects are observed. The pharmacologic mechanism or mechanisms responsible for eliciting maximal cardiovascular effects mediated by α_2-agonists remain undetermined, but this phenomenon may be explainable by the spare-receptor concept whereby activation of a relatively small number of receptors produces a maximal apparent effect.[26] The contribution of the spare-receptor concept in the production of α_2-agonist-induced maximal cardiovascular effects remains to be investigated.

Analysis of the results of the study reported here suggests that IV administration of propofol at a rate of 10 mg/kg/h can be used in mechanically ventilated cats without producing substantial cardiovascular depression, because data for cats that received 0 µg of romifidine as well as baseline data obtained from cats in groups 2 and 3 before administration of romifidine were comparable to data reported for healthy conscious cats.[7,8] Propofol can produce remarkably stable hemodynamics in humans, dogs, and cats, although arterial blood pressure may decrease as a result of dose-dependent inhibition of medullary pressor mechanisms and direct actions on vascular smooth muscle.[20,21,26-30] Propofol produces minimal changes in baroreflex activity in humans and cats and should not interfere with pressor effects of romifidine, but it may contribute to the long-term decreases in arterial blood pressure.[21,30] Additional studies are required in spontaneously breathing cats to determine whether a combination of propofol-romifidine negatively impacts cardiovascular stability.

Additional studies are indicated in cats to investigate the dose-response characteristics of lower dosages of romifidine than those used in the study reported here, as well as those of other commonly used α_2-agonists, to determine the dose at which maximal cardiovascular effects are produced. It also is necessary to determine whether such doses would produce clinically relevant sedative, analgesic, and anesthetic-sparing effects.

[a]Swan-Ganz thermodilution catheter, Baxter Healthcare Corp, Santa Ana, Calif.
[b]Cardiac Output Computer, American Edwards Laboratories, Irvine, Calif.
[c]Mikro-tip catheter, Millar Instruments, Houston, Tex.
[d]PE 90, Becton Dickinson and Co, Persippany, NJ.
[e]PE 160, Becton Dickinson and Co, Persippany, NJ.
[f]PO-NE-MAH data acquisition computer, Gould Instruments Systems Inc, Valley View, Ohio.
[g]ABL 500, Radiometer Medical, Copenhagen, Denmark.

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