Effects of a dexmedetomidine constant rate infusion and atropine on changes in global perfusion variables induced by hemorrhage followed by volume replacement in isoflurane-anesthetized dogs

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Objective—To evaluate the effects of a dexmedetomidine constant rate infusion (CRI) and atropine on changes in global perfusion variables induced by hemorrhage and volume replacement (VR) in isoflurane-anesthetized dogs.

Animals—8 adult dogs.

Procedures—Each dog was anesthetized twice, with a 2-week interval between anesthetic sessions. Anesthesia was maintained with 1.3 times the minimum alveolar concentration of isoflurane with and without dexmedetomidine (1.6 µg/kg, IV bolus, followed by 2 µg/kg/h, CRI). Dogs were mechanically ventilated and received an atracurium neuromuscular blockade during both sessions. During anesthesia with isoflurane and dexmedetomidine, atropine was administered 30 minutes before baseline measurements were obtained. After baseline data were recorded, 30% of the total blood volume was progressively withdrawn and VR was achieved with an equal proportion of autologous blood.

Results—Following hemorrhage, cardiac index, oxygen delivery index, and mixed-venous oxygen saturation were significantly decreased and the oxygen extraction ratio was significantly increased from baseline. The anaerobic threshold was not achieved during either anesthetic session. When dogs were anesthetized with isoflurane and dexmedetomidine, they had a significantly lower heart rate, cardiac index, and mixed-venous oxygen saturation during VR than they did when anesthetized with isoflurane alone. Plasma lactate concentration, mixed venous-to-arterial carbon dioxide difference, base excess, and anion gap were unaltered by hemorrhage and VR and did not differ between anesthetic sessions.

Conclusions and Clinical Relevance—Results indicated that the use of a dexmedetomidine CRI combined with atropine in isoflurane-anesthetized dogs that underwent volume-controlled hemorrhage followed by VR did not compromise global perfusion sufficiently to result in anaerobic metabolism. (*Am J Vet Res* 2014;75:964–973)

Dexmedetomidine is a potent hypnotic-sedative drug with analgesic properties, and those properties have garnered interest in the use of dexmedetomidine in CRIs for balanced anesthesia regimens and for veterinary patients that require prolonged sedation.[1,2] Although a CRI of dexmedetomidine may induce substantial decreases in HR and CI owing to its vasopres-

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Abbreviations

BE_{ecf}	Extracellular fluid base excess
Cao_2	Arterial oxygen content
$Ca\text{-}\bar{v}o_2$	Arterial-to–mixed-venous oxygen difference
CI	Cardiac index
CRI	Constant rate infusion
$C\bar{v}o_2$	Mixed-venous oxygen concentration
CVP	Central venous pressure
Do_2I	Oxygen delivery index
$ETco_2$	End-tidal concentration of carbon dioxide
ET_{ISO}	End-tidal concentration of isoflurane
HR	Heart rate
MAC	Minimum alveolar concentration
MAP	Mean arterial pressure
MPAP	Mean pulmonary arterial pressure
O_2ER	Oxygen extraction ratio
PAOP	Pulmonary artery occlusion pressure
$P\bar{v}\text{-}aco_2$	Mixed-venous–to-arterial carbon dioxide difference
$P\bar{v}co_2$	Mixed-venous partial pressure of carbon dioxide
$P\bar{v}o_2$	Mixed-venous partial pressure of oxygen
PVRI	Pulmonary vascular resistance index
$S\bar{v}o_2$	Mixed-venous oxygen saturation
SVRI	Systemic vascular resistance index
TPP	Total plasma protein
$\dot{V}o_2I$	Oxygen consumption index
VR	Volume replacement

sor activity, those effects appear to be well tolerated by healthy dogs because the $D\bar{o}_2I$ does not generally decrease below the anaerobic threshold (ie, the $\dot{V}o_2I$ is unaffected by the decrease in $D\bar{o}_2I$) and the plasma lactate concentration remains within reference limits.[1,2] Despite the growing popularity of the use of a CRI of dexmedetomidine in anesthetic protocols for veterinary patients, the effect of dexmedetomidine on the cardiovascular function of patients with acute hypovolemia has not been elucidated.

Acute loss of circulating blood volume can be detected by changes in global perfusion variables. Tissues compensate for the decrease in $D\bar{o}_2I$ by increasing the O_2ER from arterial blood, which results in a decrease in $P\bar{v}o_2$ and $S\bar{v}o_2$.[3,4] For patients with hypovolemic shock, the decrease in $D\bar{o}_2I$ becomes critical when the dependency relationship between $D\bar{o}_2I$ and $\dot{V}o_2I$ becomes evident (ie, when additional reductions in $D\bar{o}_2I$ cause a further decrease in $\dot{V}o_2I$ and vice versa).[3,4]

Consensus is lacking regarding which perfusion variables should be monitored for early indication that tissue perfusion is approaching critical compromise in patients with progressive intraoperative hemorrhage. Arterial blood pressure is poorly correlated with tissue perfusion.[5] Hemodynamic monitoring via a pulmonary artery (Swan-Ganz) catheter can provide precise evaluation of variables associated with global perfusion ($D\bar{o}_2I$, $\dot{V}o_2I$, $P\bar{v}o_2$, and $S\bar{v}o_2$).[6] However, these catheters are not routinely placed in the pulmonary artery of veterinary patients, and use of such catheters is associated with rare but serious complications.[7] Variables associated with global tissue perfusion that can be assessed without catheterization of the pulmonary artery include plasma lactate concentration, BE_{ecf}, and venous-to-arterial carbon dioxide difference.[4,8,9]

The use of pressor doses of α-adrenergic agonists, such as norepinephrine, may compromise intestinal and renal perfusion in normovolemic individuals.[10,11] Dexmedetomidine causes a decrease in blood flow primarily to the skin, spleen, and arteriovenous anastomoses (eg, pulmonary circulation), whereas blood flow to the liver and intestines is preserved despite a substantial reduction in cardiac output.[12] Although dexmedetomidine may preserve blood perfusion to the brain, heart, liver, and intestines,[12] results of a study[a] that involved a model of septic shock in pigs indicate that dexmedetomidine can compromise global tissue metabolism (ie, cause a critical decrease in $D\bar{o}_2I$, which results in a measureable decrease in $\dot{V}o_2I$). Thus, the vasopressor effects of dexmedetomidine might contribute to the initiation of anaerobic metabolism and worsen global indicators of tissue perfusion in dogs with acute hemorrhage. Because the decrease in regional blood flow associated with the administration of dexmedetomidine is secondary to the decrease in HR and CI and to the vasoconstrictive action of this drug,[1,12] administration of an anticholinergic (eg, atropine) during a CRI of dexmedetomidine could reverse bradycardia and return CI to near reference limits and allow evaluation of the isolated effects of dexmedetomidine-induced vasoconstriction on global perfusion variables. The purpose of the study reported here was to evaluate the effects of a dexmedetomidine CRI in the presence of an atropine-induced vagal blockade on changes in global perfusion variables induced by hemorrhage and VR in isoflurane-anesthetized dogs.

Materials and Methods

Animals—All study protocols were approved by the Institutional Animal Care Committee of São Paulo State University. Eight English Pointers (5 males and 3 females) between 12 and 14 months old that weighed between 19.2 and 29.4 kg were used in the study. Each dog was deemed healthy on the basis of results of a physical examination, CBC, serum biochemical analysis, and venous blood gas analysis that included measurement of electrolytes.

Experimental design—The experiment consisted of 2 phases. During phase 1, the MAC for isoflurane alone and during a CRI of dexmedetomidine was determined during a single anesthetic session for each dog. Phase 2 consisted of a randomized crossover study in which each dog was anesthetized twice with a 2-week interval between anesthetic sessions. Each dog was anesthetized once with isoflurane alone and once with isoflurane and a CRI of dexmedetomidine. During both anesthetic sessions of phase 2, each dog underwent volume-guided hemorrhage; 10%, 20%, and 30% of the dog's circulating blood volume was progressively withdrawn and then replaced with an equal volume of autologous blood.

Instrumentation of dogs—For each dog during each anesthetic session, anesthesia was induced with 5% isoflurane[b] in oxygen administered via a face mask with a circle breathing circuit.[c] Once each dog was intubated with an appropriately sized endotracheal tube, it was positioned in lateral recumbency and anesthesia was maintained with isoflurane in oxygen (flow rate, 1 to 2 L/min) administered by the circle breathing circuit under intermittent mandatory ventilation (tidal volume, 12 mL/kg; inspiration-to-expiration ratio, 1:1.5), with the respiratory rate adjusted as necessary to prevent the $ETco_2$ from exceeding 45 mm Hg. A 20-gauge catheter was placed in a cephalic vein, and lactated Ringer's solution (3 mL/kg/h, IV) was administered by use of an infusion pump[d] throughout the remainder of the anesthetic session. Esophageal temperature was monitored and maintained between 37.5° and 38.5°C by means of a forced warm air blanket.[e] A gas sampling port was placed between the circle breathing circuit and the endotracheal tube, and an infrared gas analyzer[f] was used to record ET_{ISO} and $ETco_2$. The infrared gas analyzer was calibrated and its accuracy verified before each anesthetic session by the use of standard gas mixtures[g] that contained 0.7%, 1.4%, and 2.1% isoflurane.

During phase 2, each dog received further instrumentation. Adhesive electrodes were placed on each dog in a lead II configuration for ECG[h] monitoring of HR and rhythm. A 20-gauge catheter was placed in the cephalic vein contralateral to the one in which the lactated Ringer's solution was being administered for transfusion of autologous blood. Another 20-gauge catheter was placed in a dorsal pedal artery and connected to

a fluid-filled pressure transducer system[i] that was zeroed at the level of the heart for measurement of MAP; this catheter was also used to obtain blood samples for measurement of temperature-corrected pH, Pa_{CO_2}, and Pa_{O_2}; BE_{ecf}; anion gap; plasma lactate concentration; Hct; and TPP. The pH, Pa_{CO_2}, Pa_{O_2}, BE_{ecf}, and anion gap were determined by means of a blood gas analyzer,[j] and the plasma lactate concentration was determined by means of a handheld point-of-care device.[k]

An 8.0F catheter introducer was placed in a jugular vein, and a 7F Swan-Ganz catheter[l] was advanced into the jugular vein through the catheter introducer until its tip was positioned in the pulmonary artery as determined by waveform guidance observed on the screen of a monitor.[m] Central venous pressure and MPAP were recorded from the proximal and distal ports of the Swan-Ganz catheter by means of 2 fluid-filled pressure transducer systems.[i] Pulmonary artery occlusion pressure was intermittently recorded by insufflation of the balloon located at the tip of the Swan-Ganz catheter with 0.8 mL of air. The Swan-Ganz catheter was also used to obtain blood samples for measurement of $S\bar{v}O_2$, $P\bar{v}O_2$, and $P\bar{v}CO_2$ with the blood gas analyzer.[j] Cardiac output was measured by a thermodilution technique in which 5-mL boluses of an ice-cold (3° to 5°C) 5% dextrose solution were injected into the central venous port of the Swan-Ganz catheter. At each sampling time, the cardiac output was calculated as the mean of 3 measurements that differed from each other by < 10%.

Determination of MAC (phase 1)—For each dog, the MAC for isoflurane was defined as the arithmetic mean of the highest ET_{ISO} that allowed gross purposeful movement in response to an electrical current (50 V, 50 Hz, and 10 milliseconds) applied by a pulse stimulator[n] to the medial aspect of the radius and the lowest ET_{ISO} that inhibited such a response.[13] One observer (TDC) classified the motor response to nociceptive stimulation as positive or negative (ie, the presence or absence of gross purposeful movement, respectively).

Once the MAC for isoflurane (MAC_{ISO}) was determined, dexmedetomidine hydrochloride[o] (1.6 µg/kg, IV bolus over a 1-minute period, followed by 2 µg/kg/h, CRI) was administered by a syringe pump.[p] Simultaneously with the initiation of the dexmedetomidine CRI, the ET_{ISO} was decreased by 50% from the minimum ET_{ISO} that yielded a negative response to noxious stimulation. The MAC for isoflurane when administered in combination with dexmedetomidine ($MAC_{ISO\text{-}DEX}$) was determined once at 2 ± 0.5 hours and again at 4 ± 0.5 hours after initiation of the dexmedetomidine CRI to verify the stability of the MAC over time. After the $MAC_{ISO\text{-}DEX}$ was determined for the last time, the CRI of dexmedetomidine was discontinued and the dogs were allowed to recover from anesthesia.

Determination of hemodynamic variables (phase 2)—Fifteen days after the MAC_{ISO} and $MAC_{ISO\text{-}DEX}$ were determined, phase 2 began. Each dog was randomly assigned to be anesthetized with isoflurane and dexmedetomidine[o] (1.6 µg/kg, IV bolus over a 1-minute period, followed by 2 µg/kg/h, CRI; ISO-DEX treatment) or isoflurane only (ISO treatment) with a CRI of physiologic saline (0.9% NaCl) solution administered by a syringe pump[p] in a volume equal to the volume of dexmedetomidine administered during the ISO-DEX treatment. Concomitantly with the start of the CRI, the ET_{ISO} was adjusted to be equivalent to 1.3 times the MAC_{ISO} during the ISO treatment and 1.3 times the $MAC_{ISO\text{-}DEX}$ during the ISO-DEX treatment.

A second syringe pump[p] was used to administer a CRI of atracurium[q] (0.3 mg/kg, IV bolus, followed by 0.3 mg/kg/h, CRI) to facilitate mechanical ventilation. The effectiveness of muscle paralysis was monitored by a train-of-four electrical stimulus[r] of an ulnar nerve. During the neuromuscular blockade, the ventilator was adjusted to deliver a tidal volume of 12 mL/kg with a positive end-expiratory pressure of 7 cm H_2O and an inspiration-to-expiration ratio of 1:1.3. The respiratory rate was adjusted to achieve moderate hypercapnia (Pa_{CO_2}, 45 to 55 mm Hg) without exceeding 20 breaths/min. During the ISO-DEX treatment, atropine sulfate (0.01 mg/kg, IV and 0.03 mg/kg, IM) was administered 30 minutes before baseline data collection (90 minutes after the CRI of dexmedetomidine was initiated) to stabilize the HR and rhythm.

For both treatments, after baseline data were recorded, blood was withdrawn in 3 stages. Each stage (HV10, HV20, and HV30) represented a withdrawal (ie, experimentally induced hemorrhage) of 10% (8 mL/kg) of the dog's estimated circulating blood volume (80 mL/kg), such that at the end of HV30, a total of 30% (24 mL/kg) of the dog's estimated circulating blood volume had been withdrawn. The volume corresponding to each stage was transferred to 1 of 3 blood collection bags[s] containing the amount of anticoagulant solution (citrate, phosphate, dextrose, and adenine) necessary for the volume of blood that was to be withdrawn during that stage. A graduated syringe was used to aspirate 20 mL of blood from the catheter placed in the dorsal pedal artery. The weight of the blood aspirated in the syringe (weight of the blood-filled syringe minus weight of the empty syringe) was calculated to determine the weight-to-volume ratio of the blood, and the weight of the volume of blood required for withdrawal during each stage was calculated. The same syringe was used to continue the withdrawal of blood from the catheter in the dorsal pedal artery until each stage was completed over a 10-minute period. Blood collection for each stage was complete when the appropriate weight of blood had been added to the bag.

After HV30 was complete, VR was initiated in 3 stages (VR10, VR20, and VR30) by transfusion of the autologous blood withdrawn during experimentally induced hemorrhage by means of a peristaltic infusion pump.[d] Each stage, completed over a 10-minute period, represented replacement of 10% of the dog's estimated circulating blood volume.

Recovery from anesthesia—After all data were collected, the CRIs of atracurium and dexmedetomidine and saline solution were discontinued and all catheters were removed. Dogs remained anesthetized with isoflurane and were mechanically ventilated until the train-of-four response spontaneously returned to its baseline level (all 4 contractions of the thoracic limb returned). Once the dogs began breathing spontaneously, isoflurane administration was discontinued and the dogs were allowed to recover from anesthesia. For each anesthetic session, the duration of anesthesia and the time

required for each dog to recover from anesthesia (time that elapsed from discontinuation of isoflurane administration until the dog was standing) were recorded.

Phase 2 data collection—During both the ISO and ISO-DEX treatments, cardiopulmonary data were recorded at baseline and at the end of each stage of experimentally induced hemorrhage and VR.

For each dog, body surface area was calculated as (body weight in grams)$^{2/3} \times 10.1 \times 10^{-4}$. Hemodynamic variables were calculated as described. Cardiac index was calculated as cardiac output divided by body surface area. The SVRI was calculated as ([MAP – CVP]/CI) × 79.9, and the PVRI was calculated as ([MPAP – CVP]/CI) × 79.9. The Ca_{O_2} was calculated as (hemoglobin concentration × Sa_{O_2} × 1.34) + (0.003 × Pa_{O_2}), and the $C\bar{v}_{O_2}$ was calculated as (hemoglobin concentration × $S\bar{v}_{O_2}$ × 1.34) + (0.003 × $P\bar{v}_{O_2}$). The $D_{O_2}I$ was calculated as (CI × Ca_{O_2}). The $Ca\text{-}\bar{v}_{O_2}$ was calculated as (Ca_{O_2} – $C\bar{v}_{O_2}$). The $\dot{V}_{O_2}I$ was calculated as (CI × $Ca\text{-}\bar{v}_{O_2}$). The O_2ER was calculated at ($\dot{V}_{O_2}I/D_{O_2}I$ × 100), and the $P\bar{v}\text{-}a_{CO_2}$ was calculated as ($P\bar{v}_{CO_2}$ – Pa_{CO_2}).

Statistical analysis—The distributions of all data were assessed for normality by means of the Shapiro-Wilk test. The duration of anesthesia and the time required to recover from anesthesia were compared between treatments with a paired *t* test. For variables that were normally distributed, a 2-way ANOVA for repeated measures was used with treatment (ISO or ISO-DEX) and data collection time included in the model as the main factors. A Tukey-Kramer multiple comparison test was used to assess the interaction between treatment and data collection time (ie, nested effect). The respective effects of the progressive stages of hemorrhage and VR on each variable were evaluated with a 1-way ANOVA for repeated measures, and a Dunnett test was used to compare the difference between variables at baseline and after each stage of hemorrhage or VR. For each variable that was asymmetrically distributed, an inverse Gaussian distribution was assumed, and a generalized linear model was used to assess the effect of treatment and data collection time on that variable, followed by a Wald multiple comparison test to assess the interaction between treatment and data collection time. All analyses were performed with a computer software program,[t] and values of $P < 0.05$ were considered significant. Results were reported as the mean ± SD.

Results

Phase 1—The mean ± SD MAC_{ISO} was 1.36 ± 0.32%. The mean ± SD $MAC_{ISO\text{-}DEX}$ was 0.71 ± 0.14% at both 2 hours (actual time acquired, 118 ± 9 minutes) and 4 hours (actual time acquired, 237 ± 14 minutes) after initiation of a CRI of dexmedetomidine, which represented a significant 47 ± 7% decrease from the MAC_{ISO}. All dogs recovered from anesthesia uneventfully, and the mean ± SD time to recovery (time that elapsed from discontinuation of isoflurane administration until the dog was standing) was 33 ± 5 minutes.

Phase 2—The mean ± SD values for hemodynamic variables, Hct, and TPP concentrations were summarized (**Table 1**). During the ISO-DEX treatment, HR was decreased significantly from baseline (immediately before initiation of hemorrhage) after VR of 10% and 20% of the circulating blood volume. Although the mean HR for the ISO and ISO-DEX treatments did not differ significantly after the 3 stages of progressive hemorrhage (HV10, HV20, and HV30), the HR for the ISO-DEX treatment was significantly lower than that for the ISO treatment after each of the 3 stages of VR (VR10, VR20, and VR30).

During the ISO treatment, the CI was significantly decreased from baseline after the withdrawal of 20% and 30% of the circulating blood volume and significantly increased from baseline after VR of 30% of the circulating blood volume. During the ISO-DEX treatment, the CI was significantly decreased from baseline after the withdrawal of 20% and 30% of the circulating blood volume and after VR of 10% of the circulating blood volume. The CI for the ISO-DEX treatment was significantly lower than that for the ISO treatment after each stage of VR.

Central venous pressure and PAOP did not differ significantly between the ISO and ISO-DEX treatments at any data collection time. The CVP was significantly decreased from baseline after the withdrawal of 20% and 30% of the circulating blood volume during both treatments. The PAOP was significantly decreased from baseline after the withdrawal of 20% and 30% of the circulating blood volume during the ISO-DEX treatment.

The MAP was significantly decreased from baseline after the withdrawal of 30% of the circulating blood volume during the ISO treatment and after the withdrawal of 20% and 30% of the circulating blood volume and VR of 10% of the circulating blood volume during the ISO-DEX treatment. During the ISO treatment, the SVRI was significantly increased from baseline after all 3 stages of hemorrhage and significantly decreased from baseline after all 3 stages of VR. During the ISO-DEX treatment, the SVRI was significantly increased from baseline after the withdrawal of 20% and 30% of the circulating blood volume. For all data collection times, the mean MAP and SVRI for the ISO-DEX treatment were significantly higher than those values for the ISO treatment.

For both the ISO and ISO-DEX treatments, the MPAP was significantly decreased from baseline after the withdrawal of 30% of the circulating blood volume; however, the MPAP did not differ significantly between the 2 treatments at any data collection time. The PVRI was increased from baseline after the withdrawal of 30% of the circulating blood volume during the ISO treatment and after the withdrawal of 20% and 30% of the circulating blood volume during the ISO-DEX treatment. The PVRI during the ISO-DEX treatment was significantly higher than that during the ISO treatment after the withdrawal and VR of 10% of the circulating blood volume.

The mean Hct at baseline was significantly higher for the ISO-DEX treatment, compared with that for the ISO treatment. However, the Hct did not differ significantly between the 2 treatments or from baseline at

any other data collection time. The TPP concentration did not differ significantly between the 2 treatments but was significantly decreased from baseline after the withdrawal of 30% of the circulating blood volume and all 3 stages of VR during the ISO treatment.

The mean ± SD values for global perfusion and arterial blood gas variables were summarized (**Table 2**). The Do_2I was significantly decreased from baseline after the withdrawal of 20% and 30% of the circulating blood volume during the ISO treatment and after the withdrawal of 20% and 30% of the circulating blood volume and VR of 10% of the circulating blood volume during the ISO-DEX treatment. However, the Do_2I did not differ significantly between the 2 treatments. The O_2ER was significantly in-

Table 1—Mean ± SD values for hemodynamic variables, Hct, and TPP concentration for 8 healthy adult English Pointers that were anesthetized with isoflurane alone (ISO treatment) and isoflurane and dexmedetomidine (1.6 µg/kg, IV bolus; followed by 2 µg/kg/h, CRI; ISO-DEX treatment); values were obtained immediately before (baseline) and after progressive hemorrhage of 10% (HV10), 20% (HV20), and 30% (HV30) of the circulating blood volume and VR of 10% (VR10), 20% (VR20), and 30% (VR30) of the circulating blood volume with autologous blood.

		Sample collection time						
Variable	**Treatment**	**Baseline**	**HV10**	**HV20**	**HV30**	**VR10**	**VR20**	**VR30**
HR (beats/min)	ISO	113 ± 8	110 ± 7	107 ± 7	107 ± 6	111 ± 7	115 ± 8	118 ± 9
	ISO-DEX	108 ± 10	101 ± 7	100 ± 5	102 ± 3	95 ± 5*†	94 ± 6*†	102 ± 16†
CI (L/min/m^2)	ISO	4.07 ± 0.55	3.45 ± 0.57	2.84 ± 0.67*	2.6 ± 0.76*	3.68 ± 0.79	4.45 ± 0.86	4.93 ± 1.05*
	ISO-DEX	3.44 ± 0.48	2.91 ± 0.40	2.38 ± 0.43*	2.04 ± 0.46*	2.68 ± 0.42*†	3.18 ± 0.5†	3.56 ± 0.67†
CVP (mm Hg)	ISO	6 ± 2	5 ± 1	4 ± 1*	4 ± 1*	5 ± 1	6 ± 1	8 ± 2*
	ISO-DEX	6 ± 1	4 ± 1	3 ± 1*	3 ± 1*	4 ± 1	6 ± 1	7 ± 2
PAOP (mm Hg)	ISO	10 ± 3	10 ± 2	9 ± 2	7 ± 3	10 ± 2	11 ± 3	12 ± 3
	ISO-DEX	11 ± 2	9 ± 3	7 ± 2*	7 ± 2*	8 ± 2	10 ± 3	12 ± 4
MAP (mm Hg)	ISO	72 ± 10	66 ± 10	60 ± 14	52 ± 17*	57 ± 12	60 ± 11	63 ± 11
	ISO-DEX	116 ± 15†	103 ± 16†	92 ± 16*†	80 ± 17*†	85 ± 13*†	96 ± 14†	102 ± 17†
SVRI (dynes•s/cm^5/m^2)	ISO	1,314 ± 271	1,441 ± 287*	1,607 ± 452*	1,517 ± 443*	1,161 ± 341*	983 ± 220*	903 ± 187*
	ISO-DEX	2,630 ± 565†	2,764 ± 630†	3,084 ± 788*†	3,141 ± 820*†	2,510 ± 791†	2,346 ± 688†	2,252 ± 794†
MPAP (mm Hg)	ISO	16 ± 3	15 ± 2	13 ± 2	12 ± 3*	15 ± 3	16 ± 3	18 ± 3
	ISO-DEX	16 ± 3	15 ± 2	13 ± 2	12 ± 2*	14 ± 2	16 ± 2	18 ± 3
PVRI (dynes•s/cm^5/m^2)	ISO	124 ± 37	111 ± 37	111 ± 72	155 ± 78*	94 ± 41	99 ± 54	96 ± 56
	ISO-DEX	129 ± 68	174 ± 77†	222 ± 73*	231 ± 127*	175 ± 66†	150 ± 45	138 ± 57
Hct (%)	ISO	44.3 ± 3.9	44.1 ± 3.9	44.6 ± 4.2	44.4 ± 4.5	43.1 ± 4.2	43.3 ± 5.3	44.6 ± 5.7
	ISO-DEX	51.5 ± 2.7†	50.4 ± 3.2	49.9 ± 3.6	49.3 ± 3.6	48.9 ± 2.1	49.0 ± 1.5	49.6 ± 2.7
TPP (g/dL)	ISO	5.1 ± 0.3	5.0 ± 0.3	4.7 ± 0.3	4.6 ± 0.4*	4.4 ± 0.3*	4.4 ± 0.4*	4.6 ± 0.4*
	ISO-DEX	5.3 ± 1.0	5.5 ± 0.5	5.3 ± 0.3	5.0 ± 0.3	5.0 ± 0.3	5.0 ± 0.2	5.1 ± 0.3

*Within a row, value differs significantly ($P < 0.05$) from the baseline value. †Within a variable, value differs significantly ($P < 0.05$) from the corresponding value for ISO treatment.

All dogs were anesthetized 3 times. During the first anesthetic session (phase 1; data not shown), the MACs for isoflurane alone (MAC_{ISO}) and for isoflurane with dexmedetomidine (1.6 µg/kg, IV bolus; followed by 2 µg/kg/h, CRI; $MAC_{ISO\text{-}DEX}$) were determined. All dogs were anesthetized with both the ISO and ISO-DEX treatments in a random order with a 14-day interval between treatments. During the ISO treatment, anesthesia was maintained with isoflurane at 1.3 MAC_{ISO}, and a CRI of saline (0.9% NaCl) solution was administered in a volume equal to the volume of the CRI of dexmedetomidine that was administered during the ISO-DEX treatment. During the ISO-DEX treatment, anesthesia was maintained with isoflurane at 1.3 $MAC_{ISO\text{-}DEX}$.

Table 2—Mean ± SD values for global perfusion and arterial blood gas variables for the dogs of Table 1.

		Sample collection time						
Variable	**Treatment**	**Baseline**	**HV10**	**HV20**	**HV30**	**VR10**	**VR20**	**VR30**
Do_2I (mL/min/m^2)	ISO	846 ± 145	738 ± 126	575 ± 177*	526 ± 190*	737 ± 208	877 ± 208	1,007 ± 249
	ISO-DEX	785 ± 146	654 ± 125	527 ± 126*	448 ± 119*	589 ± 117*	687 ± 124	787 ± 152
O_2ER (%)	ISO	13.6 ± 2.5	16.1 ± 3.8*	20.8 ± 6.5*	26.5 ± 11.6*	17.1 ± 4.2*	14.6 ± 3.3*	13.8 ± 3.9
	ISO-DEX	13.4 ± 1.6	15.4 ± 3.1*	19.7 ± 4.3*	24.2 ± 10.4*	19.7 ± 4.2*†	16.2 ± 2.4*	14.9 ± 2.5*
$P\bar{v}o_2$ (mm Hg)	ISO	79.0 ± 9.0	72.3 ± 9.5	65.0 ± 9.6	55.8 ± 10.5*	74.0 ± 9.6	81.3 ± 12.5	85.9 ± 14.8
	ISO-DEX	78.3 ± 6.2	72.1 ± 8.6	64.6 ± 8.4	64.0 ± 24.0	62.5 ± 9.2*	72.6 ± 5.8	75.9 ± 6.6
$S\bar{v}o_2$ (%)	ISO	92.1 ± 2.4	89.3 ± 4.0	85.0 ± 6.8	79.1 ± 12.1*	88.7 ± 4.5	91.1 ± 3.6	91.9 ± 4.1
	ISO-DEX	92.0 ± 1.1	89.8 ± 2.8	85.4 ± 4.2*	80.5 ± 10.5*	85.6 ± 4.2†	89.3 ± 2.4†	90.3 ± 2.4
$\dot{V}o_2I$ (mL/min/m^2)	ISO	113 ± 17	116 ± 21	113 ± 25	125 ± 31	121 ± 28	124 ± 25	134 ± 31
	ISO-DEX	103 ± 9	98 ± 9	100 ± 13	99 ± 26	112 ± 9	109 ± 10	114 ± 13
Lactate (mmol/L)	ISO	2.8 ± 0.5	2.5 ± 0.7	3.1 ± 0.5	3.1 ± 0.5	3.0 ± 0.6	2.9 ± 0.8	2.6 ± 0.7
	ISO-DEX	2.8 ± 0.4	2.8 ± 0.5	3.0 ± 0.6	3.3 ± 0.7	3.0 ± 0.3	2.7 ± 0.5	3.1 ± 0.7
BE_{ecf} (mmol/L)	ISO	–3.8 ± 0.9	–4.0 ± 0.7	–3.5 ± 1.3	–4.0 ± 1.7	–4.7 ± 2.1	–5.3 ± 0.6	–4.54 ± 1.44
	ISO-DEX	–4.7 ± 1.8	–4.4 ± 1.3	–4.6 ± 1.3	–5.1 ± 0.7	–4.8 ± 1.0	–4.1 ± 0.7	–3.81 ± 1.09
Anion gap (mmol/L)	ISO	12.6 ± 2.7	12.0 ± 2.9	11.3 ± 2.2	10.3 ± 2.8	12.7 ± 2.9	14.6 ± 2.0	13.8 ± 2.6
	ISO-DEX	14.8 ± 4.0	15.2 ± 3.2	13.6 ± 2.2	12.8 ± 3.6	13.6 ± 4.7	12.5 ± 2.2	13.1 ± 2.3
$P\bar{v}$-aco_2 (mm Hg)	ISO	6.3 ± 2.2	6.8 ± 2.8	7.1 ± 3.5	8.8 ± 4.6	8.2 ± 5.5	6.5 ± 2.5	6.2 ± 2.7
	ISO-DEX	7.2 ± 2.3	6.2 ± 2.6	8.8 ± 2.3	9.1 ± 2.2	7.7 ± 1.4	5.4 ± 4.4	5.4 ± 1.7
pH (arterial blood)	ISO	7.28 ± 0.03	7.27 ± 0.03	7.26 ± 0.03	7.25 ± 0.03	7.22 ± 0.04*	7.21 ± 0.04*	7.21 ± 0.05*
	ISO-DEX	7.27 ± 0.03	7.26 ± 0.03	7.26 ± 0.04	7.25 ± 0.04	7.23 ± 0.04	7.23 ± 0.04	7.23 ± 0.03
$Paco_2$ (mm Hg)	ISO	50.6 ± 3.8	51.9 ± 4.6	53.9 ± 4.3	55.4 ± 5.1	58.7 ± 5.1*	58.7 ± 6.5*	59.86 ± 6.26*
	ISO-DEX	50.1 ± 6.5	51.0 ± 5.8	51.5 ± 7.7	52.0 ± 7.5	55.9 ± 6.0	58.7 ± 7.9	58.88 ± 6.68

Anion gap = (plasma sodium concentration + plasma potassium concentration) – (plasma chloride concentration + plasma bicarbonate concentration).

See Table 1 for remainder of key.

creased from baseline after each stage of hemorrhage and VR of 10% and 20% of the circulating blood volume during the ISO treatment and after all stages of hemorrhage and VR during the ISO-DEX treatment. The O_2ER was significantly increased in the ISO-DEX treatment compared to the ISO treatment after VR of 10% of the circulating volume.

The $P\bar{v}O_2$ was significantly decreased from baseline after withdrawal of 30% of the circulating blood volume during the ISO treatment and after VR of 10% of the circulating blood volume during the ISO-DEX treatment. However, the $P\bar{v}O_2$ did not differ significantly between the 2 treatments at any data collection time. The $S\bar{v}O_2$ was significantly decreased from baseline after withdrawal of 30% of the circulating blood volume during the ISO treatment and after withdrawal of 20% and 30% of the circulating blood volume during the ISO-DEX treatment. The $S\bar{v}O_2$ during the ISO-DEX treatment was significantly lower than that during the ISO-DEX treatment after VR of 10% and 20% of the circulating blood volume.

The $\dot{V}O_2I$, lactate concentration, BE_{ecf}, anion gap, and $P\bar{v}\text{-}aCO_2$ did not differ significantly from baseline within either the ISO or ISO-DEX treatment or between the 2 treatments at any data collection time. The plasma lactate concentration was increased from the reference range[14] (2.5 to 3.5 mmol/L) after withdrawal of 30% of the circulating blood volume for 1 dog (3.8 mmol/L) during the ISO treatment and 1 dog (4.7 mmol/L) during the ISO-DEX treatment and after VR of 30% of the circulating blood volume for 1 dog (3.8 mmol/L) during the ISO treatment and 1 dog (3.8 mmol/L) during the ISO-DEX treatment.

During the ISO treatment, the arterial pH was significantly decreased, whereas the $PaCO_2$ was significantly increased, compared with those baseline values after each stage of VR. However, the arterial pH and $PaCO_2$ did not differ significantly between the ISO and ISO-DEX treatments at any data collection time. The mean respiratory rate and PaO_2 did not differ significantly from baseline within either the ISO or ISO-DEX treatment or between the 2 treatments at any data collection time (data not shown). For both treatments combined, the mean ± SD respiratory rate was 20 ± 1 breaths/min and PaO_2 was 511 ± 32 mm Hg.

All dogs had uneventful recoveries from all anesthetic sessions. The mean ± SD duration of anesthesia (379 ± 35 minutes) and time for recovery (time that elapsed from discontinuation of isoflurane administration until the dog was standing; 37 ± 13 minutes) during the ISO-DEX treatment were shorter, albeit not significantly so, than the duration of anesthesia (424 ± 18 minutes) and time for recovery (90 ± 42 minutes) during the ISO treatment.

Discussion

Results of the present study indicated that the model of acute hemorrhage implemented resulted in the expected hemodynamic changes (ie, decrease in CI and MAP with a compensatory increase in SVRI, compared with baseline values obtained immediately before initiation of hemorrhage). Compared with baseline values, progressive blood loss resulted in significant decreases in DO_2I, $P\bar{v}O_2$, and $S\bar{v}O_2$ and an increase in O_2ER, which suggested that global tissue perfusion of isoflurane-anesthetized dogs was decreased during acute hemorrhage. However, during both the ISO and ISO-DEX treatments, the resultant decrease in DO_2I after the withdrawal of 30% of the circulating blood volume was insufficient to decrease the $\dot{V}O_2I$ and cause anaerobic metabolism. Although administration of a dexmedetomidine CRI to isoflurane-anesthetized dogs had a substantial vasoconstrictive effect, as evidenced by a sustained increase in SVRI, it did not cause a significant reduction in any of the global perfusion variables evaluated when its negative chronotropic effects and associated decrease in CI were antagonized by atropine during the 3 stages of experimentally induced hemorrhage. Those findings, as well as the absence of significant changes in plasma lactate concentration, BE_{ecf}, anion gap, and $P\bar{v}\text{-}aCO_2$, suggested that administration of dexmedetomidine combined with atropine did not substantially impair tissue perfusion in this model of acute hemorrhage followed by VR with autologous blood.

During isoflurane anesthesia, the CVP (ie, cardiac preload) and CI were significantly decreased from baseline after withdrawal of 20% and 30% of the circulating blood volume; however, the significant increase in SVRI from baseline throughout the 3 stages of experimentally induced hemorrhage minimized the decrease in MAP, which was decreased significantly from baseline only after the withdrawal of 30% of the circulating blood volume. The vasoconstrictive response to acute hemorrhage is preserved better in isoflurane-anesthetized patients, compared with that in patients anesthetized with equipotent concentrations of halothane or sevoflurane.[15] For the isoflurane-anesthetized dogs of the present study, the significant reduction in SVRI from baseline observed during VR might have been caused by the release of proinflammatory mediators or cytokines into the systemic circulation subsequent to reperfusion of hypoxic tissue or a response to the autologous blood transfusion.[16]

The mean MAP throughout the ISO-DEX treatment was significantly greater than that throughout the ISO treatment. This may have been caused by dexmedetomidine stimulation of postjunctional α_2-adrenergic receptors located in the smooth muscle of arterial vessels, which caused vasoconstriction and a subsequent increase in SVRI,[17] and by the anticholinergic effects of atropine, which prevented or minimized the negative chronotropic effects of dexmedetomidine that cause a decrease in CI.[18] In isoflurane-anesthetized patients, hypotension is caused by the vasodilatory properties of the inhalant and is directly proportional to the ET_{ISO}.[19] Therefore, the mean MAP during the ISO-DEX treatment might have been higher than that during the ISO treatment because the mean ET_{ISO} concentration during the ISO-DEX treatment was 47 ± 7% less than that during the ISO treatment.

Although the CRI of dexmedetomidine had significant systemic vasopressor effects, it did not cause a substantial effect on the pulmonary circulation, as evidenced by the nonsignificant difference in mean MPAP between the ISO and ISO-DEX treatments. In some instances (eg, after the withdrawal and VR of 10% of the circulating blood volume), the mean PVRI was significantly greater during the ISO-DEX treatment than

that during the ISO treatment, which suggested that the CRI of dexmedetomidine affected the vascular tone of pulmonary vessels. However, that effect was highly variable because the SD values for PVRI were relatively large throughout the ISO-DEX treatment. Interestingly, results of another study[1] indicate the PVRI and MPAP of dogs anesthetized with propofol or isoflurane were not altered significantly from preinfusion values during a CRI of dexmedetomidine.

During the ISO-DEX treatment, atropine was administered to dogs 30 minutes before baseline data collection (90 minutes after commencing the α_2 adrenergic agonist CRI) to counteract dexmedetomidine-induced decreases in HR and CI so that they would not interfere with the evaluation of the vasoconstrictive effects of dexmedetomidine on global perfusion variables. Although the mean CI for the ISO-DEX treatment was 16% to 21% lower than that for the ISO treatment during the 3 stages of progressive hemorrhage, the mean HR and CI did not differ significantly between the ISO and ISO-DEX treatments, which suggested that atropine administration to dogs during the ISO-DEX treatment successfully minimized the dexmedetomidine-induced bradycardia and stabilized the CI. The present study involved healthy dogs, and the mean CI and $D\bar{o}_2I$ did not differ between the ISO and ISO-DEX treatments during the 3 stages of controlled hemorrhage; however, these findings may not apply to critically ill dogs that hemorrhage during anesthesia because CI and $D\bar{o}_2I$ can be further decreased by comorbidities such as severe shock, hypoxemia, and anemia, which might exacerbate inadequate tissue perfusion and poor oxygen carrying capacity.

The mean HR and CI for the ISO-DEX treatment were significantly lower than those for the ISO treatment during VR, most likely because the vagal blockade induced by the atropine became less effective over time. For dogs during the ISO-DEX treatment, VR began approximately 60 minutes after atropine was administered, and the reported duration of the positive chronotropic effects of atropine is 50 to 60 minutes.[20]

The cardiovascular effects sof atropine administered during a CRI of dexmedetomidine (2 µg/kg/h) differed substantially from those recorded after administration of dexmedetomidine (≥ 5 µg/kg) as an IM or IV bolus.[18,21] Atropine did not cause excessive hypertension (MAP, > 140 mm Hg), tachycardia (HR, > 140 beats/min), or ventricular arrhythmias in any of the dogs of the present study; however, when atropine was administered to conscious dogs prior to an IM or IV bolus of dexmedetomidine, severe hypertension and tachyarrhythmias were frequently observed.[18,21] These findings are similar to those observed in horses following administration of anticholinergics and other α_2-adrenergic agonists. Administration of atropine to horses to reverse bradycardia induced by an IV bolus of detomidine caused severe hypertension and tachycardia.[22] However, administration of anticholinergics concurrently during a CRI of xylazine in horses anesthetized with halothane resulted in reversal of bradycardia and improved cardiac output without an excessive increase in MAP or HR.[23,24]

In the present study, dexmedetomidine had substantial vasopressor activity that was not associated with significant decreases in global perfusion variables when its negative chronotropic effects were antagonized by atropine administration. When dogs are administered a large dose of dexmedetomidine (10 µg/kg, IV), the subsequent decrease in cardiac output causes a decrease in blood flow to the skin and spleen, whereas blood flow to the heart, brain, kidneys, liver, and intestines is preserved or only moderately affected.[12] In another study[1] in which normovolemic dogs that were anesthetized with isoflurane or propofol were administered a CRI of dexmedetomidine (1 to 3 µg/kg/h), $\dot{V}\bar{o}_2I$ and plasma lactate concentration were unaltered despite a significant decrease in $D\bar{o}_2I$ subsequent to decreases in HR and CI. In a septic shock model that involved pigs,[a] administration of dexmedetomidine exacerbated anaerobic metabolism (the decrease in $D\bar{o}_2I$ caused a decrease in $\dot{V}\bar{o}_2I$). For the model of controlled, acute hemorrhage used in the present study, administration of atropine prevented substantial dexmedetomidine-induced decreases in CI and $D\bar{o}_2I$ during blood withdrawal. Had atropine administration not prevented dexmedetomidine-induced bradycardia, it is likely that the mean CI during the ISO-DEX treatment would have been decreased even more, which could have caused further deterioration of global perfusion variables. Although use of atropine in the present study represented a confounder, it allowed us to isolate and assess the vasopressor activity of dexmedetomidine without associated decreases in HR, CI, and $D\bar{o}_2I$. Whether global tissue perfusion would have been maintained during the ISO-DEX treatment without atropine administration remains to be determined.

Although global perfusion variables evaluated in the present study did not differ significantly between the ISO and ISO-DEX treatments during the 3 stages of progressive hemorrhage, some of those variables ($S\bar{v}o_2$ and O_2ER) deteriorated to a greater extent during VR in the ISO-DEX treatment than they did during the ISO treatment. This might have been the result of the negative chronotropic effects of dexmedetomidine during VR or the effects of reperfusion of ischemic tissues. Reperfusion might be a less plausible explanation because a decrease in $S\bar{v}o_2$ and an increase in O_2ER would be expected to be associated with an increase in plasma lactate concentration and other changes suggestive of metabolic acidosis (ie, increase in anion gap and decrease in BE_{ecf}).

During both the ISO and ISO-DEX treatments, the mean $\dot{V}\bar{o}_2I$ did not differ significantly from baseline despite a progressive decrease in $D\bar{o}_2I$ induced by blood withdrawal, which indicated that the accompanying increase in O_2ER was sufficient to compensate for the decrease in $D\bar{o}_2I$ and sustain aerobic metabolism. Those findings in combination with the absence of significant differences in plasma lactate concentration, BE_{ecf}, anion gap, and $P\bar{v}$-a$C\bar{o}_2$ within or between the ISO and ISO-DEX treatments suggested that the anaerobic threshold was not achieved at any point during this study.

In human trauma patients, $S\bar{v}o_2$ is considered a sensitive variable for evaluating the extent of blood loss.[25] In the dogs of the present study, $S\bar{v}o_2$ was significantly decreased from baseline after 20% and 30% of the circulating blood volume was withdrawn, which suggested that mild hemorrhage (≤ 10% of the total

blood volume) might not produce a detectable change in $S\bar{v}O_2$. After 30% of the circulating blood volume was withdrawn during the ISO treatment, only 2 of 8 dogs had an $S\bar{v}O_2 < 70\%$, the threshold indicative of tissue hypoxia in human patients.[25] Both of those dogs had O_2ER values suggestive of anaerobic metabolism (> 30%), despite the fact that only 1 dog had a plasma lactate concentration (3.8 mmol/L) above the upper reference limit (3.6 mmol/L). Following VR, the plasma lactate concentration, $S\bar{v}O_2$, and O_2ER returned to baseline values for that dog. After 30% of the circulating blood volume was withdrawn during the ISO-DEX treatment, only 1 dog had an $S\bar{v}O_2 < 70\%$ and $O_2ER > 30\%$; however, its plasma lactate concentration was within reference limits and the $S\bar{v}O_2$ and O_2ER returned to baseline values following VR.

After 20% and 30% of the circulating blood volume was withdrawn from the dogs of the present study, the mean DO_2I for both the ISO and ISO-DEX treatments was decreased to below the minimum target DO_2I (600 mL/min/m^2)[26] for conscious patients with systemic inflammatory response syndrome. The DO_2I findings of the present study must be interpreted cautiously because inhalation anesthetics decrease global oxygen consumption and alter the relationship between DO_2I and $\dot{V}O_2I$[27] and variable thresholds for conscious patients might not be directly extrapolated to anesthetized patients. On the basis of the results of the present study, it is likely that the critical DO_2I for conscious dogs will be higher than the mean DO_2I observed during the ISO and ISO-DEX treatments.

In the present study, the mean ± SD DO_2I values indexed to body weight after withdrawal of 30% of the circulating blood volume (ISO treatment, 22.7 ± 7 mL/min/kg; ISO-DEX treatment, 19 ± 5 mL/min/kg) were substantially higher than the critical DO_2I associated with anaerobic metabolism in anesthetized dogs (10 mL/kg/min),[3,4] which suggested that the anaerobic threshold was not achieved in any of the dogs during either treatment. On the basis of these results, it appears that withdrawal of larger volumes of blood would be necessary to achieve the anaerobic threshold and increases in plasma lactate concentrations and $P\bar{v}\text{-}aCO_2$ values similar to those achieved in other acute models of hypovolemia in dogs.[3,4] Because of the nonterminal nature of the present study, we chose to not withdraw > 30% of the circulating blood volume from any of the dogs so as to preserve their physical integrity.

The mean Hct at baseline was significantly higher during the ISO-DEX treatment, compared with that during the ISO treatment, and this might have been caused by dexmedetomidine-induced contraction of the spleen. Results of another study[28] indicate that administration of dexmedetomidine to dogs induced a reduction in splenic volume as determined by CT. In dogs, the spleen is a reservoir for RBCs; thus, splenic contraction might increase Hct.

During the ISO treatment, the mean TPP concentration was decreased from baseline after withdrawal of 30% of the circulating blood volume and after each of the 3 stages of VR. This temporal reduction in TPP concentration might have been the result of a decrease in capillary hydrostatic pressure, which caused fluid to shift from the extravascular to the intravascular compartment. A similar reduction in TPP concentration was not observed during the ISO-DEX treatment, most likely because the mean MAP (and consequently the capillary hydrostatic pressure) was significantly higher throughout the observation period, compared with that during the ISO treatment.

Throughout both the ISO and ISO-DEX treatments, the mean $P\bar{v}\text{-}aCO_2$ values did not differ significantly from that at baseline and were substantially higher than the $P\bar{v}\text{-}aCO_2$ reference limits (2 to 5 mm Hg) established for human patients.[29] Although anesthesia decreases the metabolic activity and consequently the production of CO_2, it also causes cardiovascular depression, which reduces blood flow to tissues and causes CO_2 retention in stagnant venous blood that drains those tissues.[29] The $P\bar{v}\text{-}aCO_2$ is inversely proportional to cardiac output; therefore, the large $P\bar{v}\text{-}aCO_2$ values recorded during the present study were likely the result of a decrease in blood flow induced by anesthesia.

The increase in $PaCO_2$ from baseline after each of the 3 stages of VR during the ISO treatment was likely caused by the accumulation of CO_2 in the tissues subsequent to stagnation of tissue blood flow during experimentally induced hemorrhage.[29] Reperfusion of the tissues during VR allowed the accumulated CO_2 to reenter the systemic circulation, resulting in an increase in $PaCO_2$. This same mechanism was also evident in the ISO-DEX treatment, as the $PaCO_2$ was increased (although not significantly) from baseline after each of the 3 stages of VR.

The present study was originally designed to allow a state of permissive hypercapnia ($PaCO_2$, 45 to 55 mm Hg); however, the mean $PaCO_2$ was > 55 mm Hg during VR in both the ISO and ISO-DEX treatments. Although the tidal volume was held constant (12 mL/kg), the limitation of the respiratory rate to 20 breaths/min resulted in suboptimal minute volume ventilation, which resulted in mean $PaCO_2$ values higher than the targeted maximum $PaCO_2$ (55 mm Hg). Additionally, the use of a positive end–expiratory pressure of 7 cm H_2O and the associated increase in functional residual capacity of the lungs during mechanical ventilation could have also contributed to suboptimal ventilation and CO_2 retention.[30] Respiratory acidosis with a pH < 7.2 may alter cell homeostasis, and hypercapnia causes the release of endogenous catecholamines, which might stimulate the cardiovascular system.[31] However, during the present study, respiratory changes did not affect the comparison between the ISO and ISO-DEX treatments because the mean pH and $PaCO_2$ did not differ significantly between the 2 treatments at any data collection time.

Comparison of the time to recovery between the ISO and ISO-DEX treatments was not a primary objective of the present study; however, the mean time to recovery was shorter for the ISO-DEX treatment, compared with that for the ISO treatment, although that difference was not significant ($P = 0.07$). This finding coincided with a shorter mean duration of anesthesia during the ISO-DEX treatment, compared with that for the ISO treatment, which suggested that

the train-of-four responses returned to baseline conditions quicker when isoflurane-anesthetized dogs were administered a CRI of dexmedetomidine than when they were not administered the α_2-adrenergic agonist. Unfortunately, we could not determine why these differences between the 2 treatments were observed.

The present study had some limitations. The artificial nature of the hemorrhage model used may not mimic clinical scenarios in which the global perfusion variables of affected animals might be more substantially challenged. Administration of atropine to anesthetized patients to prevent the negative chronotropic effects of a CRI of dexmedetomidine is not commonly performed in clinical situations. The decrease in CI secondary to vagally mediated decreases in HR may also affect tissue perfusion after dexmedetomidine administration[1,2]; therefore, studies to evaluate the consequences of dexmedetomidine administration without concurrent administration of anticholinergics in hypovolemic patients are warranted. Also, critically ill patients with clinically normal global perfusion variables can have compromised regional perfusion,[32] and additional studies are necessary to determine whether dexmedetomidine administration exacerbates the impairment of regional perfusion in such patients.

In the present study, experimentally induced hemorrhage and VR of up to 30% of the circulating blood volume in isoflurane-anesthetized dogs that received a CRI of dexmedetomidine caused significant decreases in CI and Do_2I from prehemorrhage (baseline) values; however, $\dot{V}o_2I$, plasma lactate concentration, BE_{ecf}, anion gap, and $P\bar{v}\text{-}aCO_2$ remained relatively constant, which suggested that the threshold for initiation of anaerobic metabolism was not achieved. This indicated that administration of a CRI of dexmedetomidine during conditions of vagal blockade induced by atropine did not deteriorate global perfusion variables beyond their respective thresholds for anaerobic metabolism in this particular model of acute hemorrhage and VR in isoflurane-anesthetized dogs.

a. Carnicelli P, Fantoni D, Otsuki D, et al. Hemodynamic, metabolic and inflammatory effects of dexmedetomidine in a pig model of septic shock (abstr). *Crit Care* 2011;15:354.
b. Isoforine, Cristália Ltda, São Paulo, Brazil.
c. Dräger Primus, Drägerwerk AG & CO, Lübeck, Germany.
d. Infusion pump LP8x, Digicare Biomedical Technology, Boynton Beach, Fla.
e. Warmtouch, Mallinkrodt Medical, Pleasanton, Calif.
f. Vamos, Drägerwerk AG & CO, Lübeck, Germany.
g. White Martins Gases Especiais, São Paulo, Brazil.
h. Monitor DX-2020, Dixtal, São Paulo, Brazil.
i. TruWave PX 260, Edwards Lifesciences, Irvine, Calif.
j. pH/blood-gas analyzer model 348, Siemens Diagnostics, Halstead, Essex, England.
k. Accutrend Plus, Roche, São Paulo, Brazil.
l. Swan-Ganz catheter model 131HF7, Edwards Lifesciences, Irvine, Calif.
m. AS/3 anesthesia monitor, Datex-Ëngstrom, Helsinki, Finland.
n. S48 Stimulator, Astro-Med Inc, West Warwick, RI.
o. Precedex, Hospira, São Paulo, Brazil.
p. Digipump SR7x, Digicare Biomedical Technology, Boynton Beach, Fla.
q. Tracrium, Cristália Ltda, São Paulo, Brazil.
r. Neuroestimulador E2107, BGE Médica Ltda, São Paulo, Brazil.
s. CPDA blood collection bag, JP Indústria Famacêutica SA, Ribeirão Preto, Brazil.
t. SAS for Windows, version 9.2, SAS Institute Inc, Cary, NC.

References

1. Lin GY, Robben JH, Murrell JC, et al. Dexmedetomidine constant rate infusion for 24 hours during and after propofol or isoflurane anaesthesia in dogs. *Vet Anaesth Analg* 2008;35:141–153.
2. Uilenreef JJ, Murrell JC, McKusick BC, et al. Dexmedetomidine continuous rate infusion during isoflurane anaesthesia in canine surgical patients. *Vet Anaesth Analg* 2008;35:1–12.
3. Van der Linden P, Gilbart E, Engeman E, et al. Effects of anesthetic agents on systemic critical O_2 delivery. *J Appl Physiol* 199l;71:83–93.
4. Van der Linden P, Rausin I, Deltell A, et al. Detection of tissue hypoxia by arteriovenous gradient for Pco_2, and pH in anesthetized dogs during progressive hemorrhage. *Anesth Analg* 1995;80:269–275.
5. Johnson, JO, Grecu L, Lawson NW. Autonomic nervous system. In: Barash PG, Cullen BF, Stoelting RK, et al, eds. *Clinical anesthesia.* 6th ed. Philadelphia: Lippincott Williams and Wilkins, 2009;326–368.
6. Pestel GJ, Fukui K, Kimberger O, et al. Hemodynamic parameters change earlier than tissue oxygen tension in hemorrhage. *J Surg Res* 2010;160:288–293.
7. Lopes MC, de Cleva R, Zilberstein B, et al. Pulmonary artery catheter complications: report on a case of a knot accident and literature review. *Rev Hosp Clin Fac Med Sao Paulo* 2004;59:77–85.
8. Wilson M, Davis AP, Coimbra R. Diagnosis and monitoring of hemorrhagic shock during the initial resuscitation of multiple trauma patients: a review. *J Emerg Med* 2003;24:413–422.
9. Allen M. Lactate and acid base as a hemodynamic monitor and markers of cellular perfusion. *Pediatr Crit Care Med* 2011;12(suppl 4):43–49.
10. Pawlik W, Shepherd AP, Jacobson ED. Effect of vasoactive agents on intestinal oxygen consumption and blood flow in dogs. *J Clin Invest* 1975;56:484–490.
11. Richer M, Robert S, Lebel M. Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. *Crit Care Med* 1996;24:1150–1156.
12. Lawrence CJ, Prinzen FW, Lange S. The effect of dexmedetomidine on nutrient organ blood flow. *Anesth Analg* 1996;83:1160–1165.
13. Valverde A, Morey TE, Hernández J, et al. Validation of several types of noxious stimuli for use in determining the minimum alveolar concentration for inhalation anesthetics in dogs and rabbits. *Am J Vet Res* 2003;64:957–962.
14. Pang DS, Boysen S. Lactate in veterinary critical care: pathophysiology and management. *J Am Anim Hosp Assoc* 2007;43:270–279.
15. Teixeira Neto FJ, Luna SPL, Cruz ML, et al. A study of the effect of hemorrhage on the cardiorespiratory actions of halothane, isoflurane and sevoflurane in the dog. *Vet Anaesth Analg* 2007;34:107–116.
16. Fink MP. Reactive oxygen species as mediators of organ dysfunction caused by sepsis, acute respiratory distress syndrome, or hemorrhagic shock: potential benefits of resuscitation with Ringer's ethyl pyruvate solution. *Curr Opin Clin Nutr Metab Care* 2002;5:167–174.
17. Bloor BC, Frankland M, Alper G, et al. Hemodynamic and sedative effects of dexmedetomidine in dog. *J Pharmacol Exp Ther* 1992;263:690–697.
18. Congdon JM, Marquez M, Niyom S, et al. Evaluation of the sedative and cardiovascular effects of intramuscular administration of dexmedetomidine with and without concurrent atropine administration in dogs. *J Am Vet Med Assoc* 2011;239:81–89.
19. Bernard JM, Doursout MF, Wouters P, et al. Effects of sevoflurane and isoflurane on hepatic circulation in the chronically instrumented dog. *Anesthesiology* 1992;77:541–545.
20. Hendrix PK, Robinson EP. Effects of a selective and a nonselective muscarinic cholinergic antagonist on heart rate and intestinal motility in dogs. *J Vet Pharmacol Ther* 1997;20:387–395.
21. Alvaides RK, Teixeira Neto FJ, Aguiar AJA, et al. Sedative and cardiorespiratory effects of acepromazine or atropine given before dexmedetomidine in dogs. *Vet Rec* 2008;162:852–856.

22. Pimenta EL, Teixeira Neto FJ, Sá PA, et al. Comparative study between atropine and hyoscine-N-butylbromide for reversal of detomidine induced bradycardia in horses. *Equine Vet J* 2011;43:332–340.
23. Teixeira Neto FJ, McDonell WN, Black WD, et al. Effects of glycopyrrolate on cardiorespiratory function in horses anesthetized with halothane and xylazine. *Am J Vet Res* 2004;65:456–463.
24. Teixeira Neto FJ, McDonell WN, Black WD, et al. Effects of a muscarinic type-2 antagonist on cardiorespiratory function and intestinal transit in horses anesthetized with halothane and xylazine. *Am J Vet Res* 2004;65:464–472.
25. Scalea TM, Hartnett RW, Duncan AO, et al. Central venous oxygen saturation: a useful clinical tool in trauma patients. *J Trauma* 1990;30:1539–1543.
26. Hardie EM. Life-threatening bacterial infection. *Compend Contin Educ Pract Vet* 1995;17:763–777.
27. Rock P, Beattie C, Kimball AW, et al. Halothane alters the oxygen consumption-oxygen delivery relationship compared with conscious state. *Anesthesiology* 1990;73:1186–1197.
28. Baldo CF, Garcia-Pereira FL, Nelson NC, et al. Effects of anesthetic drugs on canine splenic volume determined via computed tomography. *Am J Vet Res* 2012;73:1715–1719.
29. Lamia B, Monnet X, Teboul JL. Meaning of arteriovenous P_{CO_2} difference in circulatory shock. *Minerva Anestesiol* 2006;72: 597–604.
30. Michard F, Chemla D, Richard C, et al. Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. *Am J Respir Crit Care Med* 1999;159:935–939.
31. Rose CE, Althaus JA, Kaiser DL, et al. Acute hypoxemia and hypercapnia: increase in plasma catecholamines in conscious dogs. *Am J Physiol* 1983;245:924–929.
32. Ekbal NJ, Dyson A, Black C, et al. Monitoring tissue perfusion, oxygenation, and metabolism in critically ill patients. *Chest* 2013;143:1799–1808.