Cardiovascular and respiratory effects of ketamine infusions in isoflurane-anesthetized dogs before and during noxious stimulation

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Objective—To characterize the effects of ketamine administration on the cardiovascular and respiratory systems and on acid-base balance and to record adverse effects of ketamine in isoflurane-anesthetized dogs.

Animals—6 healthy adult mongrel dogs.

Procedure—Dogs were anesthetized with isoflurane (1.25 times the individual minimum alveolar concentration) in oxygen, and ketamine was administered IV to target pseudo–steady-state plasma concentrations of 0, 0.5, 1, 2, 5, 8, and 11 μg/mL. Isoflurane concentration was reduced to an equipotent concentration. Cardiovascular, respiratory, and acid-base variables; body temperature; urine production; and adverse effects were recorded before and during noxious stimulation. Cardiac index, stroke index, rate-pressure product, systemic vascular resistance index, pulmonary vascular resistance index, left ventricular stroke work index, right ventricular stroke work index, arterial oxygen concentration, mixed-venous oxygen concentration, oxygen delivery, oxygen consumption, oxygen extraction ratio, alveolar-arterial oxygen partial pressure gradient, and venous admixture were calculated. Plasma ketamine and norketamine concentrations were measured.

Results—Overall, ketamine administration improved ventilation, oxygenation, hemodynamics, and oxygen delivery in isoflurane-anesthetized dogs in a dose-dependent manner. With the addition of ketamine, core body temperature was maintained or increased and urine production was maintained at an acceptable amount. However, at the higher plasma ketamine concentrations, adverse effects such as spontaneous movement and profuse salivation were observed. Myoclonus and dysphoria were observed during recovery in most dogs.

Conclusions and Clinical Relevance—Infusion of ketamine appears to be a suitable technique for balanced anesthesia with isoflurane in dogs. Plasma ketamine concentrations between 2 to 3 μg/mL elicited the most benefits with minimal adverse effects. (*Am J Vet Res* 2005;66:2122–2129)

Inhalant anesthetics cause cardiovascular depression in dogs. For example, isoflurane causes a dose-dependent decrease in arterial blood pressure, stroke volume, total peripheral resistance, and left ventricular work.[1-3] For this reason, the use of balanced anesthesia has been advocated in hemodynamically compromised patients. During balanced anesthesia, each drug contributes its own pharmacologic effects while potentially undesirable adverse effects may be limited by decreasing the dose of each drug used. Although opioids have been traditionally administered for balanced anesthesia, ketamine may represent an alternative. Ketamine preserves or increases **cardiac output** (CO), arterial blood pressure, oxygen transport, and core body temperature in healthy dogs.[4-6] Furthermore, ketamine confers good postoperative analgesia to surgical patients including dogs.[7-13] However, ketamine may cause a decrease in myocardial contractility, skeletal muscle myoclonus, and excessive salivation.[4,14,15]

Results of previous work indicate that ketamine reduces the enflurane and isoflurane requirements in dogs.[16,17] However, the hemodynamic effects of ketamine in combination with inhalant anesthetics have not been reported. The purpose of the study reported here was to assess the hemodynamic effects of ketamine at various plasma concentrations in isoflurane-anesthetized dogs, compared with those of isoflurane alone, when administered at an equipotent dose. We hypothesized that ketamine would improve hemodynamics in a dose-dependent manner.

Materials and Methods

Animals—Six healthy adult mongrel dogs that weighed (mean ± SD) 27.8 ± 2.6 kg were used in the study. The pharmacokinetics of ketamine and the **minimum alveolar concentration** (**MAC**; tail-clamp technique) of isoflurane and isoflurane combined with ketamine at target plasma concentrations of 0.5, 1, 2, 5, 8, and 11 μg/mL had been determined in each dog in a study[18] reported elsewhere. Food was withheld from dogs for 12 hours before the experiments. An institutional animal care and use committee approved the study.

Instrumentation—Anesthesia was induced with isoflurane in oxygen administered through a face mask. The trachea was intubated with a cuffed endotracheal tube, and anesthesia was maintained with isoflurane in oxygen via a circle system. Ventilation was spontaneous throughout the study. Instrumentation was performed within 60 minutes after induction. A catheter was passed through the endotracheal tube with the catheter tip positioned at the end of the endotracheal tube for end-tidal gas sample collection. A 20-gauge, 48-mm-long catheter was inserted in a cephalic vein for lactated Ringer's solution (3 mL/kg/h) and ketamine administration. A 20-gauge, 48-mm-long catheter was inserted in a dorsal pedal artery for continuous arterial blood pressure measurement and arterial blood sample collection. An

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8-F, 10-cm-long introducer[a] was placed in the right jugular vein, and a 7-F, 110-cm-long thermodilution balloon catheter[b] was inserted via the introducer. The distal port and thermistor of the thermodilution catheter were positioned in the pulmonary artery under fluoroscopic observation. This catheter was used to measure CO, **central venous pressure (CVP)**, **mean pulmonary arterial pressure (PAP)**, **pulmonary artery occlusion pressure (PAOP)**, and core body temperature and to collect mixed-venous blood samples (ie, samples from the pulmonary artery). A 6-F Foley urinary catheter[c] was inserted in the urinary bladder and connected to a syringe for collection of urine.

Measurements—Dogs were placed in left lateral recumbency. The ECG (lead II), **systolic arterial pressure (SAP)**, **mean arterial pressure (MAP)**, **diastolic arterial pressure (DAP)**, PAP, and CVP were continuously recorded by use of a physiograph[d] and acquisition software.[e] All pressure transducers were calibrated against a mercury manometer before each experiment, and the 0 value was designated at the level of the sternum. End-tidal samples were collected by hand, and isoflurane concentrations were determined by use of an infrared analyzer[f] calibrated prior to each experiment with standard gases[g] of known concentrations (0.5%, 1.5%, and 2.5% isoflurane). The measurement was performed in triplicate, and the mean value for the 3 measurements was calculated. Arterial and mixed-venous pH, P_{CO_2}, and P_{O_2} were measured, and bicarbonate concentration and **standard base excess (SBE)** were calculated by use of a blood gas analyzer[h] that corrected measurements for body temperature. Oxygen saturation and **hemoglobin concentration (Hb)** were measured in arterial and mixed-venous blood by use of a 6-wavelength hemoximeter.[i] The PCV and **total plasma protein concentration (TP)** were measured in arterial blood by use of microcentrifugation and refractometry, respectively. Ketamine and norketamine concentrations were measured in arterial blood samples. The CO was determined in triplicate by use of the thermodilution technique with a CO computer.[j] Five milliliters of iced 5% dextrose solution was injected though the proximal port of the thermodilution catheter for each measurement. The mean of the 3 measurements was then calculated. Core body temperature was maintained between 37° and 39°C throughout the study by use of warm water circulating blankets, forced-air blankets, or ice packs as needed.

The urinary bladder was emptied after induction of anesthesia and at the end of each ketamine infusion period. The volume of urine was measured, and its specific gravity was determined by refractometry. Effects of ketamine infusion, such as defecation, regurgitation, and salivation, were also recorded.

Calculations—The **cardiac index (CI)**, **stroke index (SI)**, **rate-pressure product (RPP)**, **systemic vascular resistance index (SVRI)**, pulmonary vascular resistance index, **left ventricular stroke work index (LVSWI)**, right ventricular stroke work index, **arterial oxygen concentration** (Ca_{O_2}), **mixed-venous oxygen concentration** (Cv_{O_2}), **oxygen delivery** (D_{O_2}), **oxygen consumption** (V_{O_2}), oxygen extraction ratio, **alveolar-arterial oxygen partial pressure difference** (PA_{O_2}-Pa_{O_2}), and venous admixture were calculated by use of standard equations.[19-21] Barometric pressure was obtained for each experiment day from the Davis Climate Station, University of California, Davis.

Protocol—Sixty minutes after induction of anesthesia and subsequent instrumentation, end-tidal isoflurane concentration was set at 1.25 times the individual MAC that had been determined in a previous study.[18] After 20 minutes of stable conditions, end-tidal gas was sampled by hand and the isoflurane concentration was measured. Heart rate, SAP, MAP, DAP, CVP, PAP, and PAOP were recorded. Arterial and mixed-venous blood samples (1 mL) were collected anaerobically and immediately analyzed. A second arterial blood sample (2 mL) was collected, transferred in a tube containing ethylenediaminetetraacetic acid, and immediately centrifuged for 10 minutes, and the plasma was separated and frozen for later determination of plasma ketamine and norketamine concentrations. The CO was measured. A supramaximal noxious stimulus was then applied to the tail for 5 minutes. The stimulus involved closure of a 20-cm-long Martin forceps to the first ratchet. The actual location of the forceps differed at each stimulation. With the stimulation ongoing, measurements were repeated, with the exception of the collection of blood for determination ketamine and norketamine concentrations.

Ketamine was administered to target pseudo–steady-state plasma concentrations of 0, 0.5, 1, 2, 5, 8, and 11 µg/mL by use of a target-controlled infusion system consisting of a syringe pump[k] and computer program.[l] With this system, the central compartment was rapidly loaded to the desired concentration. The infusion rate was then updated every 10 seconds as needed to maintain pseudo–steady-state plasma concentrations, according to the following equation:

$$R = C_T \times V_1 (k_{10} + k_{12}e^{-k_{21}t} + k_{13}e^{-k_{31}t})$$

where R is the infusion rate; C_T is the target plasma concentration; V_1 is the volume of the central compartment; t is the time; and k_{10}, k_{12}, k_{21}, k_{13}, and k_{31} are the microrate constants. Individual pharmacokinetic data that had been determined for each dog in a previous study[18] were used. A 3-compartment model was used for 2 dogs and a 2-compartment model for the remaining 4 dogs, according to the model that best described the disposition of ketamine in each dog by use of visual observation and Akaike information criterion. When a 2-compartment model was used, k_{13} and k_{31} were equal to 0. The isoflurane concentration was changed at each plasma ketamine concentration to maintain equipotent concentrations, as determined in the previous study.[18] Twenty minutes was allowed after each change of isoflurane and ketamine target plasma concentrations for conditions to equilibrate. Ketamine target plasma concentrations were arranged in an ascending order to minimize experimental time and potential accumulation of ketamine or its metabolites. Measurements were obtained at each ketamine concentration as already described. Total anesthesia time (from induction to discontinuation of isoflurane and ketamine administration) was < 5 hours in all dogs. At the end of the experiment, instruments were removed and dogs were allowed to recover under observation. Recovery time was recorded.

Ketamine and norketamine plasma concentrations—Standard solutions of ketamine[m] and norketamine[n] were prepared in **acetonitrile (ACN)**[o] at a concentration of 1 mg/mL. Working standard solutions were prepared by diluting the standard solution with ACN:acetic acid[p] (9:1, vol/vol) to concentrations ranging from 0.2 to 40 µg/mL. All standard solutions were stored in the dark at –15°C when not in use.

Ketamine and norketamine concentrations in canine plasma were measured by use of liquid chromatography–mass spectrometry after a simple protein precipitation cleanup procedure. Calibrators were prepared by adding appropriate volumes of the working standard solutions to drug-free control canine plasma. The range of concentrations used for serum calibrators was 0.04 to 14.0 µg/mL. Plasma samples and calibrators were processed for analysis by mixing 250-µL aliquots with 300 µL of ACN:acetic acid (9:1, vol/vol), chilling the solution at 4°C for 30 minutes, and then centrifuging and harvesting the deproteinated supernatant.

For quantitative measurements, high-performance liquid chromatography[q] and a triple quadruple mass spectrometer[r] with an electrospray interface were used. Chromatography used a 2.1-mm, 50-mm-long column[s] with 3-µm particles and a linear gradient of ACN in water with a constant flow 0.05% trifluoroacetic acid[t] at a flow rate of 0.4 mL/min. The ACN concentration was held at 2% for 0.2 minutes and ramped from 2% to 45% for 2.3 minutes and 45% to 75% for 1.2 minutes. Prior to analysis, the deproteinated supernatant of all samples, controls, and calibrators was diluted up to 5-fold in the initial mobile phase. Injection volumes were 10 µL.

Multiple selected reaction-monitoring transitions of initial product ions for ketamine (**mass-to-charge ratio [m/z]**, 238 to 125, 220, 179, and 163) and norketamine (m/z, 224 to 125, 207, 179, and 163) were used for detection and quantification. The total response for the major product ions of ketamine (m/z, 125 and 179) and norketamine (m/z, 207 and 179) was plotted, and peaks at the proper retention time were integrated by use of a software program.[u] The software was used to generate calibration curves and quantitate these analytes in all samples.

Statistical analysis—All data are reported as mean ± SD values. Normality of raw and log-transformed data was evaluated by use of the Shapiro-Wilk test. The effect of plasma ketamine concentrations and noxious stimulation on all variables was analyzed by use of repeated-measures (mixed-model) ANOVA methods. Raw or log-transformed data were used in accordance with results of the Shapiro-Wilk test. The form of the ketamine response was examined by looking at the linear and quadratic terms of an orthogonal polynomial decomposition on the basis of overall ANOVA. Significance was set at a value of $P < 0.05$. The relationship between ketamine and norketamine concentrations was examined by use of the Pearson product-moment correlation. Linear regression was used to examine the change in plasma ketamine concentration according to the target plasma concentrations.

Results

End-tidal isoflurane and plasma ketamine and norketamine concentrations—Infusions of ketamine

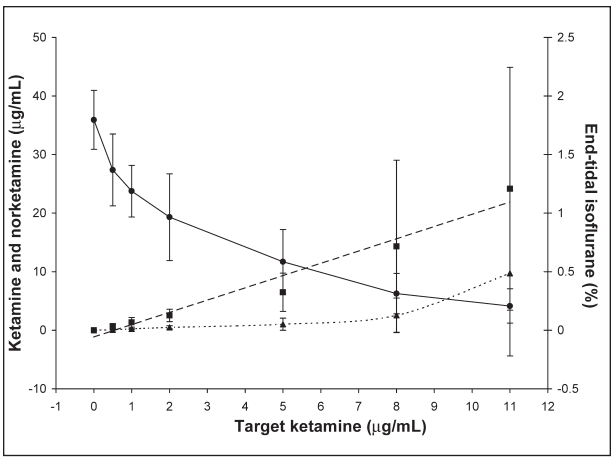

Figure 1—Mean ± SD plasma ketamine (squares) and norketamine (triangles) concentrations and end-tidal isoflurane (circles) concentration for various plasma ketamine target concentrations in 6 dogs. The line for ketamine was obtained by linear regression, illustrating the linear ($R^2 = 0.97$) increase in the actual plasma concentration.

Table 1—Effects of various plasma ketamine concentrations on blood gas, pH, and derived variables before and during noxious stimulation in 6 dogs.

	Plasma ketamine concentrations (µg/mL)															
	0		0.66		1.36		2.52		6.49		14.34		24.16			
Variables	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	*P* (1)	*P* (2)
$Paco_2$ (mm Hg)	54 ± 6.2	51 ± 5.5	53 ± 8.2	46 ± 11	49 ± 9.6	43 ± 11	43 ± 8.2	44 ± 7.5	40 ± 5.8	34 ± 5.8	33 ± 4.6	28 ± 5.5	36 ± 8.4	32 ± 5.2	< 0.01	< 0.01
$Pvco_2$ (mm Hg)	61 ± 5.2	60 ± 6.9	60 ± 9.5	57 ± 9.6	56 ± 11	51 ± 11	50 ± 7.7	49 ± 6.6	46 ± 6.6	41 ± 5.7	41 ± 5.3	37 ± 7.7	44 ± 8.4	40 ± 8.2	0.02	0.01
Pao_2 (mm Hg)	505 ± 139	485 ± 135	497 ± 139	467 ± 115	512 ± 128	483 ± 115	525 ± 123	514 ± 103	555 ± 89	561 ± 84	589 ± 45	576 ± 51	563 ± 53	559 ± 44	0.06	0.02
Pvo_2 (mm Hg)	71 ± 10	74 ± 11	80 ± 12	74 ± 10	80 ± 19	79 ± 15	76 ± 11	75 ± 8	72 ± 9	74 ± 14	62 ± 12	61 ± 12	63 ± 8	64 ± 6	0.07	0.06
PAo_2 (mm Hg)	657 ± 6	660 ± 5	657 ± 8	664 ± 11	660 ± 9	666 ± 11	665 ± 6	664 ± 7	667 ± 5	673 ± 5	673 ± 4	678 ± 6	670 ± 9	674 ± 5	0.03	0.02
PAo_2-Pao_2 (mm Hg)	152 ± 135	174 ± 132	159 ± 133	197 ± 110	148 ± 121	183 ± 112	139 ± 121	150 ± 102	112 ± 90	112 ± 81	84 ± 44	102 ± 52	106 ± 50	115 ± 44	0.02	< 0.01
Qs/Qt	0.12 ± 0.08	0.17 ± 0.09	0.14 ± 0.08	0.17 ± 0.07	0.12 ± 0.08	0.16 ± 0.08	0.16 ± 0.11	0.17 ± 0.11	0.09 ± 0.07	0.11 ± 0.05	0.05 ± 0.02	0.07 ± 0.02	0.07 ± 0.03	0.15 ± 0.05	0.02	0.07
Art pH	7.28 ± 0.03	7.28 ± 0.03	7.27 ± 0.04	7.32 ± 0.07	7.31 ± 0.05	7.34 ± 0.06	7.33 ± 0.03	7.33 ± 0.04	7.36 ± 0.03	7.4 ± 0.04	7.39 ± 0.03	7.43 ± 0.07	7.37 ± 0.06	7.39 ± 0.05	0.06	0.02
Ven pH	7.25 ± 0.02	7.25 ± 0.03	7.24 ± 0.04	7.27 ± 0.04	7.27 ± 0.05	7.31 ± 0.05	7.3 ± 0.02	7.31 ± 0.03	7.33 ± 0.02	7.36 ± 0.03	7.35 ± 0.03	7.38 ± 0.07	7.33 ± 0.05	7.35 ± 0.05	0.13	0.02
Art SBE (mmol/L)	–1.3 ± 1.2	–2 ± 1	–1.8 ± 1.1	–2.3 ± 1.9	–2 ± 1.4	–2.3 ± 1.5	–2.3 ± 2.5	–2.5 ± 2.4	–2.3 ± 2	–2.8 ± 2.3	–3.6 ± 1.6	–4.6 ± 1.3	–3.8 ± 1.1	–4.6 ± 1.2	0.04	0.03
Art HCO_3 (mmol/L)	24.3 ± 1.3	23.6 ± 1.5	23.6 ± 1.5	22.6 ± 2.8	23.3 ± 2	22.3 ± 2.7	22.3 ± 3	22.5 ± 2.7	22 ± 2.3	20.8 ± 2.7	19.6 ± 1.8	18.5 ± 1.3	19.8 ± 1.7	18.6 ± 1.2	< 0.01	< 0.01

Art = Arterial. Ven = Mixed-venous. PAo_2-Pao_2 = Alveolar-arterial oxygen partial pressure difference. Qs/Qt = Physiologic shunt fraction. SBE = Standard base excess (mmol/L). HCO_3 = Bicarbonate concentration (mmol/L). *P* (1) = *P* value for the effect of ketamine plasma concentrations (mixed model ANOVA). *P* (2) = *P* value for the effect of noxious stimulation (mixed model ANOVA).

to maintain plasma concentrations of 0, 0.5, 1, 2, 5, 8, and 11 µg/mL produced a linear increase in plasma concentration (R^2 = 0.97; **Figure 1**). The actual plasma ketamine concentrations ranged from 0.5- to 1.5-fold higher than the targeted concentrations, with the exception of 1 dog in which the plasma concentrations for the 2 highest doses were 4.5 times the targeted concentrations.

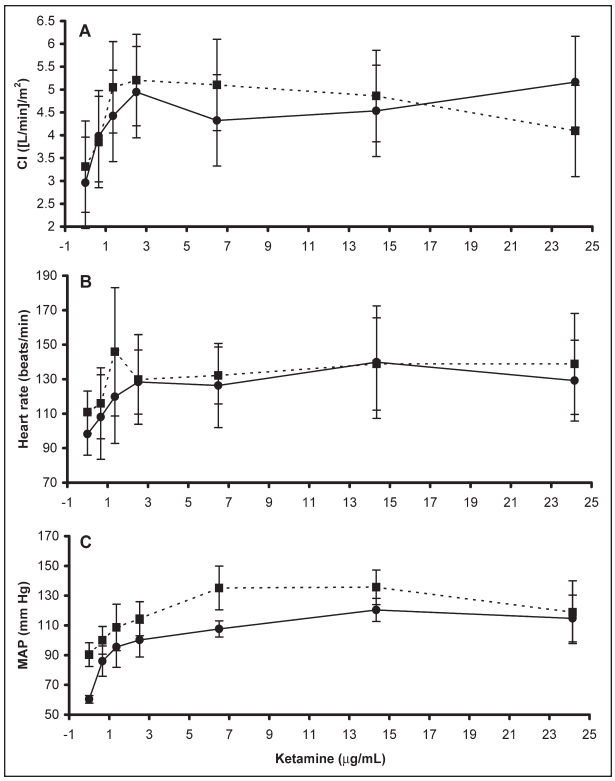

Figure 2—Mean ± SD cardiac index (CI; panel A), heart rate (HR; panel B), and mean arterial pressure (MAP; panel C) values observed at various plasma ketamine concentrations before (circles) and during (squares) noxious stimulation with a tail clamp in 6 dogs. All 3 variables increased significantly ($P < 0.05$) with increasing ketamine concentrations.

End-tidal isoflurane concentration was reduced from 1.79 ± 0.25% to 0.20 ± 0.14% to maintain an equipotent amount with increasing ketamine concentrations, according to the results of a previous study[18] (Figure 1). At these isoflurane concentrations, no movement in response to tail clamping was observed in any dog.

Norketamine concentrations significantly increased with increasing ketamine concentrations (Figure 1). Norketamine and ketamine concentrations were highly correlated (R^2 = 0.81). The plasma norketamine concentration remained 12% to 16% of the total plasma drug concentration (ketamine and norketamine), with the exception of the highest administered dose in which norketamine was 29% of the total concentration.

Ventilation, oxygenation, and acid-base status—Hypoventilation was observed in all dogs when isoflurane was administered alone at 1.25 MAC ($PaCO_2$, 54 ± 6.2 mm Hg). The $PaCO_2$ and $PvCO_2$ decreased significantly and proportionally to the ketamine concentration, with an apparent ceiling reached at a target plasma concentration of 8 µg/mL (**Table 1**). Tachypnea was observed in most dogs at the 2 highest plasma ketamine concentrations.

Noxious stimulation resulted in a further significant decrease of $PaCO_2$ and $PvCO_2$. Hyperventilation, with a $PaCO_2$ below 30 mm Hg, was observed only at the 2 highest plasma ketamine concentrations during stimulation in 4 of 6 dogs.

Alveolar but not arterial PO_2 significantly increased in a linear form with increasing ketamine concentra-

Table 2—Effects of various plasma ketamine concentrations on selected cardiovascular variables, before and during noxious stimulation in 6 dogs.

	Plasma ketamine concentrations (µg/mL)															
	0		0.66		1.36		2.52		6.49		14.34		24.16			
Variables	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	*P* (1)	*P* (2)
SI	30.4 ± 6.1	30 ± 4.9	36.9 ± 4.9	32.9 ± 3.7	37 ± 6.2	35 ± 7.6	38.5 ± 4.3	40.4 ± 6.5	34.5 ± 4.7	38.3 ± 9	32.7 ± 3.9	35.4 ± 7.5	43.3 ± 34.8	29.2 ± 5.2	0.76	0.02
SAP (mm Hg)	93 ± 13	124 ± 7	129 ± 23	144 ± 12	140 ± 18	155 ± 24	151 ± 24	170 ± 25	160 ± 14	192 ± 25	179 ± 16	192 ± 20	163 ± 22	172 ± 29	< 0.01	< 0.01
DAP (mm Hg)	48 ± 4	77 ± 8	71 ± 6	82 ± 10	77 ± 14	88 ± 11	81 ± 8	94 ± 9	87 ± 7	112 ± 12	100 ± 8	112 ± 8	96 ± 13	97 ± 16	< 0.01	< 0.01
RPP	9,133±1,440	13,810±1,966	14,208±5,165	16,810±3,871	16,696±3,924	23,215±8,882	19,574±5,179	22,500±7,867	20,348±4,676	25,538±5,443	25,382±688	26,763±6,158	21,227±5,168	24,376±8,115	< 0.01	< 0.01
SVRI	1,583 ± 300	2,126 ± 336	1,745 ± 248	2,149± 542	1,824± 619	1,819± 599	1,654± 388	1,809± 433	2,032± 329	2, 217± 485	2,180 ± 460	2,307 ± 481	2,088± 789	2,399± 587	0.04	0.08
LVSWI	22 ± 4.7	33 ± 5.9	40 ± 9.1	42 ± 5.2	44 ± 5.9	47 ± 9.9	50 ± 6.1	59 ± 6.8	48 ± 6	68 ± 21.5	50 ± 5.1	62 ± 16.5	65 ± 55.9	46 ± 15.7	< 0.01	0.03
PVRI	152 ± 63	134 ± 28	118 ± 31	151 ± 43	113 ± 45	130 ± 41	150 ± 45	122 ± 30	121 ± 67	104 ± 51	140 ± 62	141 ± 54	135 ± 82	159 ± 55	0.40	0.20
RVSWI	3 ± 1.1	4.2 ± 0.7	4.9 ± 1.1	4.9 ± 0.9	5.2 ± 1.1	6.1 ± 1.9	6.1 ± 1.3	6.6 ± 3.1	5.1 ± 1.2	6.1 ± 2	5.2 ± 1.5	6.6 ± 2.2	6.3 ± 5.4	5 ± 2.5	0.19	0.20

SI = Stroke index ([mL/beat]/m²). SAP = Systolic arterial pressure. DAP = Diastolic arterial pressure. RPP = Rate-pressure product (beats per minute × mm Hg).

SVRI = Systemic vascular resistance index ([{dynes × s}/cm⁵]/m²). LVSWI = Left ventricular stroke work index ([g × m]/m²). PVRI = Pulmonary vascular resistance index ([{dynes × s}/cm⁵]/m²). RVSWI = Right ventricular stroke work index ([g × m]/m²).

See Table 1 for remainder of key.

Table 3—Effects of various ketamine plasma concentrations on selected variables, before and during noxious stimulation in 6 dogs.

	Plasma ketamine concentrations (μg/mL)															
	0		0.66		1.36		2.52		6.49		14.34		24.16			
Variables	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During	*P* (1)	*P*(2)
PCV (%)	38 ± 1.9	37 ± 1.9	38 ± 3.6	38 ± 1.2	38 ± 2.8	39 ± 2.9	40 ± 4	40 ± 3.8	40 ± 3.7	42 ± 3.8	44 ± 4.8	43 ± 4.2	42 ± 1.7	41 ± 3.8	0.01	0.02
Hb (g/dL)	13.7 ± 0.5	13.4 ± 0.4	14.1 ± 0.9	14 ± 0.7	14 ± 0.8	14.4 ± 1.2	14.4 ± 1.7	14.7 ± 1.7	14.8 ± 1.2	15.3 ± 1.4	15.9 ± 1.4	15.9 ± 1.2	15.2 ± 0.9	14.3 ± 1.6	< 0.01	0.04
TP (g/L)	5.1 ± 0.3	5 ± 0.3	5.2 ± 0.3	5.1 ± 0.2	5.1 ± 0.3	5.2 ± 0.2	5.1 ± 0.2	5.3 ± 0.5	5.5 ± 0.2	5.3 ± 0.3	5.5 ± 0.3	5.4 ± 0.4	5.5 ± 0.4	5.1 ± 0.7	0.02	0.30

Hb = Arterial hemoglobin concentration. TP = Total plasma protein concentration.
See Table 1 for remainder of key

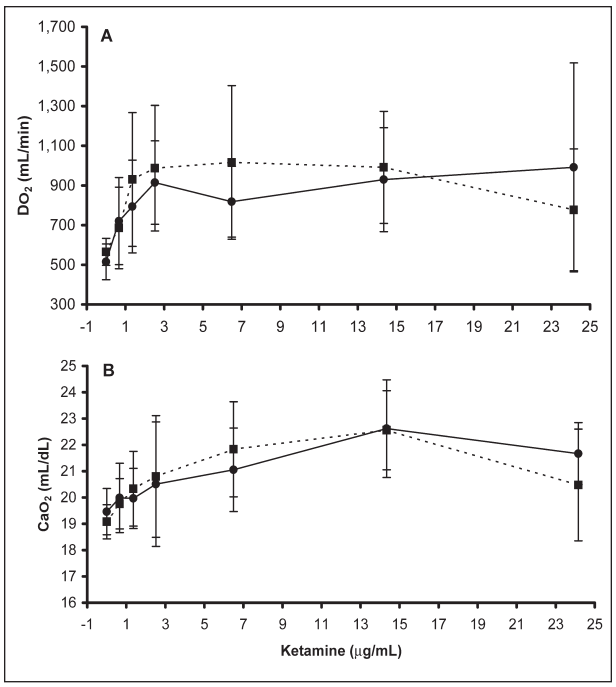

Figure 3—Mean ± SD oxygen delivery (Do_2; panel A) and arterial oxygen content (Cao_2; panel B) values observed at different plasma ketamine concentrations before (circles) and during (squares) noxious stimulation with a tail clamp in 6 dogs. Both Do_2 and Cao_2 increased significantly ($P < 0.05$) with increasing ketamine concentrations.

tions. A plateau was observed at a targeted concentration of 8 μg/mL. Moreover, the PAo_2-Pao_2 gradient decreased significantly also with a plateau at 8 μg/mL (Table 1). The PAo_2-Pao_2 gradient decrease was associated with a decrease in the shunt fraction (venous admixture, from 0.12 ± 0.09 to 0.06 ± 0.03). During noxious stimulation, PAo_2 increased further.

Respiratory acidosis (arterial and mixed-venous pH, 7.28 ± 0.03 and 7.25 ± 0.02, respectively; arterial and mixed-venous SBE, –1.3 ± 1.2 mmol/L and –0.7 ± 1.2 mmol/L, respectively; and arterial and mixed-venous bicarbonate concentration, 24.3 ± 1.4 mmol/L and 26 ± 1.4 mmol/L, respectively; Table 1) was observed during administration of isoflurane alone. Ketamine administration resulted in decreases in arterial SBE and bicarbonate concentration in a linear fashion; however, pH, venous SBE, and bicarbonate concentration remained constant. The decrease in $Paco_2$ with ketamine compensated for the mild metabolic acidosis observed. Noxious stimulation resulted in a further decrease in arterial SBE and bicarbonate concentration.

Body temperature—Core body temperature increased in a dose-dependent manner with the administration of ketamine. Core body temperature started at 37.2 ± 0.58°C without ketamine and increased linearly, reaching 38.9 ± 0.52°C at the highest ketamine concentration, with the use of cooling techniques to prevent further increases in core body temperature.

Cardiovascular variables—In dogs receiving 1.25 MAC isoflurane, heart rate, SAP, MAP, DAP, SI, CI, and RPP were 98 ± 12 beats/min, 93 ± 13 mm Hg, 60 ± 3 mm Hg, 49 ± 4 mm Hg, 30.4 ± 6.2 (mL/beats)/m^2, 2.95 ± 0.54 (L/min)/m^2, and 9,133 ± 1,440 beats × mm Hg, respectively. With the exception of SI, ketamine administration resulted in significant increases in these variables, reaching a plateau at the targeted concentration of 2 μg/mL (**Figure 2**; **Table 2**). Overall, noxious stimulation resulted in significant increases in these variables, even though the effect may not be present at all ketamine concentrations. A significant interaction between ketamine administration and stimulation was detected for heart rate, SAP, MAP, DAP, and RPP, illustrating a dose-dependent blunting effect of ketamine on the cardiovascular response to noxious stimulation.

The PAP, PAOP, and CVP were 10 ± 2 mm Hg, 5 ± 2 mm Hg, and 3 ± 3 mm Hg, respectively, with 1.25 MAC of isoflurane alone. Ketamine infusions and noxious stimulation did not alter these variables.

The SVRI increased with administration of ketamine (from 1,583 ± 300 [{dynes × s}/cm^5] × m^2 to a maximum of 2,180 ± 460 [{dynes × s}/cm^5] × m^2); however, no clear relationship with the plasma concentration was observed. The LVSWI increased and reached a plateau at the targeted concentration of 2 μg/mL (from 22.7 ± 4.7 [{g × m}/m^2] to 50.3 ± 6.1 [{g × m}/m^2]). In contrast, pulmonary vascular resistance index and right ventricular stroke work index were not affected by the ketamine infusions (Table 2).

Hematologic values—Arterial PCV, Hb, and TP during isoflurane anesthesia were 37.8 ± 1.9%, 13.7 ± 0.5 g/dL, and 5.1 ± 0.3 g/dL, respectively. Ketamine infusions had a mild but significant effect on these hematologic values. High plasma concentrations of ketamine elicited a PCV of 43.6 ± 4.8%, Hb of 15.9 ± 1.4 g/dL, and TP of 5.5 ± 0.4 g/dL. The PCV and Hb further increased during noxious stimulation (**Table 3**).

Do_2 and Vo_2—The Cao_2 and Do_2 increased during ketamine administration from 19.4 ± 0.8 mL/dL to 22.6 ± 1.8 mL/dL and from 515 ± 90 mL/min to 929 ± 262 mL/min, respectively, when targeting plasma concentrations of 8 µg/mL. The Cvo_2, Vo_2, and O_2 utilization ratios were 14 ± 6.8 mL/dL, 153 ± 206 mL/min, and 0.28 ± 0.34, respectively, before ketamine administration. These values remained unchanged during all ketamine infusions (**Figure 3**). Noxious stimulation further increased Cao_2 and Do_2. A significant interaction between the ketamine administration and stimulation was detected for Cao_2, indicating that ketamine blunted the increase in Cao_2 in response to noxious stimulation in a dose-dependent manner.

Urine production and specific gravity—After the bladder was emptied at induction of anesthesia, mean urine production was constant (0.75 to 1.2 mL/kg/h) and independent of the ketamine concentration. The urine specific gravity remained within the normal reference range for dogs (1.036 to 1.049).

Adverse effects—All dogs defecated on the morning prior to induction of anesthesia. During the study, 5 dogs defecated, but no relationship with the plasma ketamine concentration was observed. None of the dogs regurgitated or vomited during the study. However, 1 dog vomited about 1.5 hours after anesthesia. Spontaneous movement, tachypnea, and profuse salivation were observed in all dogs given high ketamine concentrations. At these high concentrations, dogs had open eyes and dilated pupils and appeared to be in a dissociated state similar to that seen following ketamine administration alone. They did not move in response to noxious stimulation, but heart rate, blood pressure, and respiratory rate increased. Recovery was prolonged, and myoclonus was observed in several dogs. Depending on the total ketamine dose administered, 2 to 8 hours was needed for dogs to recover their ability to walk without assistance.

Discussion

In our study, we have shown that combining ketamine with isoflurane, compared with isoflurane alone at equipotent doses, results in improved ventilation, oxygenation, hemodynamics, and Do_2. Moreover, with the addition of ketamine, core body temperature was maintained or increased, resulting in the need to use cooling techniques. Urine production was maintained at an acceptable amount. For these reasons, continuous infusion of ketamine appears to be a suitable technique for balanced anesthesia with isoflurane in dogs.

Results of our study should be interpreted in view of several limitations. Firstly, to decrease experimental time, increasing plasma target concentrations were used. Because of the lack of randomization of doses, it is impossible to differentiate between drug and time effects. It is therefore possible that some of the effects observed in our study could be the result of temporal changes in the effects of isoflurane, ketamine, or both rather than those of ketamine and decreasing isoflurane concentrations. In dogs, temporal changes have been reported for methoxyflurane and halothane but not for isoflurane.[22,23] Experimental time was kept relatively short (< 5 hours) in an attempt to minimize time-dependent effects. Moreover, the lower isoflurane concentrations used at the later times in this study may have minimized these potential temporal changes. Also, effects of the lower plasma ketamine concentrations that had the most beneficial effect and that were studied early in the experiments were unlikely to have been affected by temporal changes. Secondly, actual plasma ketamine concentrations in our study were not as close to our targets as predicted by the pharmacokinetic modeling. Because of this high variability, individual concentrations cannot be compared and only the overall response can be statistically analyzed. The same considerations apply to the effects of noxious stimulation. Thirdly, ketamine infusions were administered in healthy dogs; compromised dogs may have different ketamine pharmacokinetics and a lower threshold for adverse effects. They might also have a different cardiorespiratory response to ketamine. Lastly, because multiple concentrations were administered in the same study, no observation could be made on duration or quality of recovery after infusion at a given plasma concentration.

Independent of whether a 2- or 3-compartment model was used, the variability in plasma concentrations was higher than desired. A possible explanation for the ketamine concentration variability is that hepatic function was impaired directly by ketamine.[24] Other factors include high interindividual variability in the disposition of ketamine, nonlinear kinetics within the concentration range studied, and poor performance of the pharmacokinetic models. Because the variability was highest for the high plasma concentrations and the agreement between target and actual plasma concentrations was acceptable at the lower plasma concentrations, the models used may have been less able to predict the disposition of high plasma ketamine concentrations, possibly because they were derived from data obtained after administration of a moderate dose (3 mg/kg). We cannot exclude the possibility that ketamine accumulation did occur during the prolonged infusions. In fact, norketamine concentration was proportionally higher during the last and highest dose used. Whether this norketamine concentration reflects accumulation or whether the pharmacokinetics of ketamine and norketamine are nonlinear remains to be elucidated. Regardless of the origin of variability observed in our study, large differences in plasma ketamine concentrations are to be expected in clinical patients if constant rate infusions are used.

Norketamine is an active metabolite of ketamine and has been reported to cause effects similar to those of ketamine.[25,26] It is likely that the effects observed in our study are the results of the combined action of ketamine and norketamine. Because of the high correlation between plasma ketamine and norketamine concentrations, it was not possible to determine whether norketamine had a specific effect (different from ketamine) on the cardiovascular and respiratory variables studied.

As demonstrated in previous studies,[1-3,27] isoflurane anesthesia directly depresses the respiratory and cardiovascular systems in a dose-dependent manner. In addi-

tion to the direct cardiovascular depression, isoflurane decreases myocardial perfusion, renal blood flow, intestinal blood flow, and skeletal muscle blood flow in dogs.[28]

Ketamine may improve the respiratory and cardiovascular performances during isoflurane anesthesia. Similar to our study, previous studies[4-6] have shown the hemodynamic benefits of ketamine alone. However, to our knowledge, no other study has examined the dose dependence of the hemodynamic effects of ketamine infusions in isoflurane-anesthetized dogs.

In our study, it appeared that plasma ketamine concentrations between 2 to 3 μg/mL elicited the most benefits with minimal adverse effects. These concentrations decreased the isoflurane requirements by close to 50%. At these concentrations, compared with isoflurane alone, alveolar ventilation increased by approximately 20%, as illustrated by the changes in Pa_{CO_2}, correcting the respiratory acidosis seen with isoflurane alone. The D_{O_2} increased by approximately 77%, mostly from a combination of increased CI (approx 67%), with a minor contribution of Ca_{O_2} (approx 6%). Temperature, urine output, and gastrointestinal integrity appeared to be preserved, similar to that reported by others in dogs with ketamine alone.[6,29,30] Whether the benefits observed in our study are the result of a direct effect of ketamine, the decreased isoflurane concentration, or a combination of both remains to be elucidated. The increased CI during ketamine infusions appeared to be related to the increase in heart rate. Thus, heart rate monitoring could be a useful tool to predict CI performance during ketamine infusions. The only adverse effect observed at ketamine concentrations of 2 to 3 μg/mL was an increase in LVSWI by approximately 110%, which is related to a combination of increased SI and MAP.

Higher concentrations (> 5 μg/mL) increased LVSWI further, increased SVRI, and did not appear to result in further improvement of CI or D_{O_2}. These high concentrations also caused additional adverse effects such as tachypnea, hyperthermia, profuse salivation, uncoordinated movements, and myoclonus. This apparent increase in metabolism may account for the mild changes observed in SBE and bicarbonate concentration. It is likely that the prolonged recovery seen in most dogs was related to the administration of high ketamine concentrations. Recovery time appeared to correlate to the total dose of ketamine administered, suggesting that accumulation may occur. The adverse effects from high ketamine concentrations could be attributed to decreased myocardial contractility[14,15]; negative psychomimetic effects[8]; excessive catecholamine release; and interaction with multiple receptors, transmitters, and ion channels occurring with high concentrations of the drug.[31]

The positive effects observed with the lower plasma ketamine concentrations (2 to 3 μg/mL) may be related to similar pharmacodynamic properties. These effects could indeed be attributed to direct sympathetic nerve system stimulation at the CNS level[32]; direct catecholamine release from nerve endings[33-35]; inhibition of catecholamine reuptake[36,37]; inhibition of baroreceptor reflex,[38] inhibition of nitric oxide, and endothelium-hyperpolarizing factor release from the vascular system[39]; and preservation of hypoxic pulmonary vasoconstriction.[40]

In addition to respiratory and hemodynamic stability, ketamine may provide additional benefits. Analgesia has been reported for dogs and people.[7-13] Furthermore, a decrease in postoperative opioid requirements and pain scores has been described with ketamine infusions in humans.[41,42] Ketamine also reduces the production of proinflammatory cytokines, which may be an indication for its use in septic patients.[43,44] During septic shock, cardiovascular stability and D_{O_2} were better preserved with continuous infusions of ketamine than with other anesthetic agents in dogs and pigs and a reduced mortality was shown in rats.[45-47]

In conclusion, ketamine, at plasma concentrations of 2 to 3 μg/mL, appears suitable for balanced anesthesia in dogs because it improves cardiovascular and respiratory function, compared with isoflurane alone. Further studies are warranted to characterize additional features of ketamine infusions targeting these plasma concentrations, such as recovery quality and duration. At higher plasma concentrations, adverse effects are prominent and cardiovascular stability is not maintained. Caution is therefore recommended in clinical patients in whom high plasma concentrations may be inadvertently reached.

a. Percutaneous sheath introducer set, Arrow International, Reading, Pa.
b. Thermodilution balloon catheter, Arrow International, Reading, Pa.
c. Cook Veterinary Products, Global Veterinary Products, New Buffalo, Mich.
d. Physiograph, Gould Instrument Systems, Valley View, Ohio.
e. Ponehma, version 3.0, Gould Instrument Systems, Valley View, Ohio.
f. Medical gas analyzer LB1, Beckman Instruments, Schiller Park, Ill.
g. Soflurane primary standard, Matheson Gas Products, Newark, Calif.
h. ABL 5, Radiometer Medical, Copenhagen, Denmark.
i. Hemoximeter OSM 3, Radiometer Medical, Copenhagen, Denmark.
j. COM-1, American Edwards Laboratories, Irvine, Calif.
k. PHD 2000 Programmable, Harvard Apparatus, Holliston, Mass.
l. Rugloop I, Demed, Temse, Belgium.
m. Sigma Chemical Co, St Louis, Mo.
n. Cerilliant, Round Rock, Tex.
o. Burdick & Jackson, Muskegon, Mich.
p. Fisher Scientific, Pittsburgh, Pa.
q. 1100 Series, Agilent Technologies, Palo Alto, Calif.
r. Finnigan TSQ Quantum, Thermo Electron, San Jose, Calif.
s. Discovery HS C_{18}, Supelco, Bellefonte, Pa.
t. Sigma-Aldrich, St Louis, Mo.
u. LCQuan, Thermo Electron, San Jose, Calif.

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