Effects of intravenous administration of tiletamine-zolazepam, alfaxalone, ketamine-diazepam, and propofol for induction of anesthesia on cardiorespiratory and metabolic variables in healthy dogs before and during anesthesia maintained with isoflurane

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OBJECTIVE
To compare effects of tiletamine-zolazepam, alfaxalone, ketamine-diazepam, and propofol for anesthetic induction on cardiorespiratory and acid-base variables before and during isoflurane-maintained anesthesia in healthy dogs.

ANIMALS
6 dogs.

PROCEDURES
Dogs were anesthetized with sevoflurane and instrumented. After dogs recovered from anesthesia, baseline values for cardiorespiratory variables and cardiac output were determined, and arterial and mixed-venous blood samples were obtained. Tiletamine-zolazepam (5 mg/kg), alfaxalone (4 mg/kg), propofol (6 mg/kg), or ketamine-diazepam (7 and 0.3 mg/kg) was administered IV in 25% increments to enable intubation. After induction (M_0) and at 10, 20, 40, and 60 minutes of a light anesthetic plane maintained with isoflurane, measurements and sample collections were repeated. Cardiorespiratory and acid-base variables were compared with a repeated-measures ANOVA and post hoc *t* test and between time points with a pairwise Tukey test.

RESULTS
Mean ± SD intubation doses were 3.8 ± 0.8 mg/kg for tiletamine-zolazepam, 2.8 ± 0.3 mg/kg for alfaxalone, 6.1 ± 0.9 mg/kg and 0.26 ± 0.04 mg/kg for ketamine-diazepam, and 5.4 ± 1.1 mg/kg for propofol. Anesthetic depth was similar among regimens. At M_0, heart rate increased by 94.9%, 74.7%, and 54.3% for tiletamine-zolazepam, ketamine-diazepam, and alfaxalone, respectively. Tiletamine-zolazepam caused higher oxygen delivery than propofol. Postinduction apnea occurred in 3 dogs when receiving alfaxalone. Acid-base variables remained within reference limits.

CONCLUSIONS AND CLINICAL RELEVANCE
In healthy dogs in which a light plane of anesthesia was maintained with isoflurane, cardiovascular and metabolic effects after induction with tiletamine-zolazepam were comparable to those after induction with alfaxalone and ketamine-diazepam. (*Am J Vet Res* 2019;80:33–44)

ABBREVIATIONS

CaO_2	Arterial oxygen content
CO	Cardiac output
DAP	Diastolic arterial blood pressure
DO_2	Oxygen delivery
MAP	Mean arterial blood pressure
O_2ER	Oxygen extraction ratio
PAP	Mean pulmonary arterial pressure
PAWP	Mean pulmonary arterial wedge pressure
$PETCO_2$	End-tidal partial pressure of carbon dioxide
PET_{Iso}	End-tidal partial pressure of isoflurane
PVRI	Pulmonary vascular resistance index
RAP	Mean right atrial pressure
SAP	Systolic arterial blood pressure
SVRI	Systemic vascular resistance index
$\dot{V}O_2$	Oxygen consumption

In clinical settings, a veterinary practitioner's preference for an induction regimen is dictated by familiarity with the protocol, preanesthetic examination findings, expense, and expected duration of the anesthetic episode.[1] Common injectable agents used in veterinary medicine for induction of anesthesia include propofol, ketamine, tiletamine-zolazepam, and alfaxalone. Some of these injectable anesthetic agents are often used in an extralabel manner owing to a lack of labeling that covers various species and routes of administration, often because of expense associated with the approval process of the US FDA. This is the case for the combination of tiletamine

and zolazepam, which is marketed and registered in the United States for use in dogs and cats by only IM administration.

Tiletamine and ketamine are referred to as dissociative agents; they cause functional disorganization of the limbic and thalamocortical systems, which results in a state defined as dissociative anesthesia. Benzodiazepines such as diazepam, midazolam, and zolazepam have historically been used in conjunction with dissociative agents to decrease the degree of muscle rigidity that results when a dissociative agent is used as the sole induction drug.[2] Alfaxalone is a synthetic neurosteroid that has entered the North American veterinary market in a new carrier; thus, the product does not have the adverse effects linked to older formulations. This agent rapidly and smoothly induces unconsciousness and muscle relaxation and has a short duration of action.[3,4] Propofol is an extremely popular induction agent in both human and veterinary anesthesia[2] because of rapid induction[5] and rapid recovery from anesthesia with minimal residual effects.[6]

Anesthetic death in small animals is usually caused by cardiovascular complications, such as cardiac arrest resulting from cardiac arrhythmias, myocardial hypoxia, effects of specific anesthetic agents, preexisting pathological conditions, myocardial depression from anesthetic overdose, and complications during endotracheal intubation and respiratory failure.[7] The product of CO and Ca_{O_2} is D_{O_2}. Many anesthetic and sedative compounds can depress CO via various mechanisms.[2] Furthermore, factors such as anesthetic-induced hypoventilation can decrease Ca_{O_2} and further impair D_{O_2}. Cardiorespiratory effects of induction agents evaluated in the study reported here have been investigated in the past. However, a study has not been performed to compare the cardiorespiratory and acid-base status of these induction agents administered IV to dogs.

The objective of the study reported here was to compare the effects of tiletamine-zolazepam, alfaxalone, ketamine-diazepam, and propofol administered IV for anesthetic induction on the cardiorespiratory system and acid-base status before and during anesthesia maintained with isoflurane for 60 minutes in healthy dogs. The null hypothesis was that there would be no difference in the measured variables for dogs receiving tiletamine-zolazepam or the other induction agents.

Materials and Methods

Animals

Six healthy purpose-bred adult hound-type dogs were enrolled in the study. Dogs comprised 3 sexually intact females and 3 sexually intact males. Mean ± SD age was 14.6 ± 3 months, and mean body weight was 22.1 ± 2.6 kg. Dogs were deemed healthy on the basis of results of a physical examination and complete hematologic and serum biochemical analyses. Approval for the study was obtained from the Oregon State University Institutional Animal Care and Use Committee.

Study design

A prospective, blinded, randomized, crossover study was designed, with each dog serving as its own control animal. Randomization of dogs and drug sequence was performed by use of randomization software.[a] Each dog was anesthetized 4 times (anesthetic induction once each with tiletamine-zolazepam,[b] alfaxalone,[c] a combination of ketamine[d] and diazepam,[e] and propofol[f]) in separate anesthetic episodes. There was a washout period of at least 7 days between subsequent anesthetic episodes. Sedative or analgesic drugs were not administered as premedications prior to induction with the studied agents.

Instrumentation

Dogs were allowed an acclimation period of 7 days before the start of the study. Food was withheld for 12 hours and water was withheld for 2 hours before each anesthetic episode. Preanesthetic physical examinations were performed within 1 hour before the instrumentation process. Dogs were excluded if the preanesthetic physical status (American Society of Anesthesiologists grade) was > I. Induction of anesthesia was performed via an induction mask by delivering 7% sevoflurane[g] in oxygen (4 L/min) via an anesthesia machine[h] connected to a breathing system.[i] When muscle relaxation, lack of jaw tone, and lack of a palpebral reflex were detected, the trachea was intubated with a cuffed endotracheal tube. A leak test was performed to verify sealing of the endotracheal tube cuff within the trachea (pressure, 20 cm H_2O), and the amount of air necessary to seal the cuff was recorded for each dog. Mechanical ventilation (P_{ETCO_2} between 35 and 45 mm Hg) was initiated. Cardiovascular and respiratory monitoring was performed with a multiparametric monitor[j] that provided data for pulse oximetry,[k] ECG, oscillometric blood pressure, side-stream capnography, and gas analysis. Before each anesthetic episode, the respiratory gas analyzer[l] was calibrated in accordance with the manufacturer's recommendation by use of a mixture of oxygen, desflurane, and carbon dioxide.[m] Body temperature was monitored continuously via an esophageal probe and maintained with a warm-air blowing device.[n] An 18-gauge, 50-mm catheter[o] was placed in the right saphenous vein. Two 20-gauge, 38-mm catheters[o] were placed (one in the coccygeal artery and the other in the right dorsal pedal artery). Patency of the catheters was maintained by flushing with 1 mL of heparinized saline (0.9% NaCl) solution (1 U/mL) every 15 minutes until the beginning of data collection. Lactated Ringer solution was administered IV at a rate of 5 mL/kg/h, in accordance with published guidelines.[8] An 8F, 13-cm introducer[p] was aseptically placed in the right jugular vein by use of the modified Seldinger technique. Cefazolin[q] (22 mg/kg, IV) was administered prophylactically. After instrumentation

was completed, sevoflurane administration was discontinued and oxygen flow was maintained at 2 L/min for approximately 5 minutes. Dogs were then allowed to recover from anesthesia, with a minimal degree of physical restraint. Dogs were allowed to stand only when there was a substantial coordinated effort. Ambulation was restricted if dogs were ataxic. Baseline measurements were then obtained, providing the following criteria were met: at least 30 minutes had passed since extubation, the dog was no longer ataxic, and the dog actively interacted with research personnel.

An ice bath was prepared and used to cool a sterile bowl filled with 200 mL of sterile saline solution[r] to a temperature of 1°C. Temperature of the saline solution was allowed to stabilize in the ice bath for 30 minutes and was measured continuously to ensure proper temperature of the saline solution at the time of injection. Total calculated dose for each induction regimen was 5 mg/kg for tiletamine-zolazepam; 4 mg/kg for alfaxalone; 7 and 0.3 mg/kg for ketamine and diazepam, respectively; and 6 mg/kg for propofol. Total volume of each regimen was divided into 4 masked syringes, each of which contained 25% of the calculated dose. Total volumes of ketamine and diazepam were mixed in 1 syringe before being divided into the 4 masked syringes.

Measurement of cardiorespiratory and metabolic variables

Dogs were placed in left lateral recumbency on a radiolucent table and gently restrained. A 3-port, 7F, Swan-Ganz catheter[s] was inserted via the introducer catheter into the right jugular vein and advanced into the main pulmonary artery by use of fluoroscopic guidance. The proximal and distal ports of the Swan-Ganz catheter were connected via noncompliant tubing to a pressure transducer[t] calibrated with a mercury column manometer at 2-point scale. The catheter placed in the dorsal pedal artery was connected to a pressure transducer[u] via noncompliant tubing to measure peripheral arterial blood pressures. Both transducers were zeroed to atmospheric pressure at the level of the manubrium. Correct location of the Swan-Ganz catheter was confirmed by direct observation of pressure waveform changes.

Prior to collection of a 1-mL blood sample, approximately 1- and 8-mL of waste blood were withdrawn from the coccygeal arterial catheter and from the pulmonary artery port of the Swan-Ganz catheter, respectively. Samples were collected into heparinized polypropylene syringes prepared as described elsewhere[9] and stored on ice until analyzed. Within 10 minutes after samples were collected, a blood gas analyzer[v] was used to assess arterial and mixed-venous blood samples to determine pH, P_{CO_2}, P_{O_2}, and hemoglobin oxygen saturation; mixed-venous blood samples to determine lactate, bicarbonate, glucose, sodium, chloride, potassium, and calcium concentrations, base excess, and Hct; and arterial blood samples to determine total arterial hemoglobin concentration. Blood gas variables were corrected on the basis of temperature, inspired fraction of oxygen, and barometric pressure. Mixed-venous total plasma protein concentration was determined with a refractometer.[w]

Lactated Ringer solution was infused (5 mL/kg/h) throughout the experimental procedures. An ECG (lead II) was used to monitor cardiac rate and rhythm, and pulse oximetry was used to measure hemoglobin oxygen saturation. Heart rate was derived from the arterial waveform. Baseline measurements were obtained in triplicate at the time when heart rates returned to values similar to those detected during the preanesthetic physical examination and dogs appeared to be relaxed. Data were collected in the order of RAP, PAP, PAWP, CO, heart rate, SAP, MAP, DAP, and respiratory rate. At the end of expiration, 5 mL of cooled saline solution was injected into the proximal port of the Swan-Ganz catheter to measure CO via thermodilution[x]; 3 values (within ± 10%) were collected and used to calculate a mean CO value. Temperature was measured with a rectal thermometer at baseline and with the thermistor in the Swan-Ganz catheter after induction and throughout the remainder of each experiment.

After baseline data were collected, successive 25% increments of each induction agent were administered over a period of 10 seconds, with a 15-second pause between increments. Successful endotracheal intubation was the end point at which administration for an induction regimen was discontinued. When the total calculated dose of the induction regimen was insufficient to enable endotracheal intubation, an additional 25% of the induction regimen was available for injection. Personnel performing tracheal intubation, assessing jaw tone, and administering induction agents were unaware of the agents administered. Intubation quality was scored as follows: 0 = good, no swallowing and no coughing; 1 = fair, some tongue movement with slight and transient coughing; 2 = poor, marked jaw tone with tongue movements and swallowing; and 3 = very poor, similar to poor but requiring an additional 25% induction dose to complete the intubation. The cuff of the endotracheal tube was inflated with the amount of air recorded for each dog during the instrumentation phase. A leak test was not performed at that time to avoid iatrogenic depletion of carbon dioxide and consequent alteration of the respiratory pattern after induction. A universal F-circuit[i] with an attached sidestream adaptor for collection of respiratory and anesthetic gas samples and a reservoir bag were used to deliver oxygen (2 L/min) and isoflurane[y] via a precision vaporizer.[z] Oxygen flow rate was kept constant during the anesthetic period, and a light plane of anesthesia (absence of palpebral reflex, slight jaw tone, and the eyes rotated in a ventromedial position) was maintained by adjustment of the vaporizer dial. The same gas analyzer used in the instrumentation phase was used to measured $P_{ET_{Iso}}$.

Hypoxemia was defined as Pa_{O_2} < 70 mm Hg, apnea was the absence of inspiration for > 30 seconds,[10] and hypotension was MAP < 60 mm Hg. If apnea lasted > 30 seconds, 1 breath was manually administered every 30 seconds until spontaneous ventilation resumed. For purposes of data collection during apnea, P_{ETCO_2} was recorded as 0 mm Hg. If hypotension was detected for > 2 time points in the same dog, a bolus of lactated Ringer solution (10 mL/kg) was administered over a 15-minute period. Measurement of cardiorespiratory variables and collection of blood samples were repeated immediately after induction (M_0) and at 10 (M_{10}), 20 (M_{20}), 40 (M_{40}), and 60 (M_{60}) minutes after induction. Throughout the procedures, body temperature was maintained between 37.8° and 39°C with a warm-air blowing device.[n] Cefazolin was administered after the last data collection point, and fluid administration was discontinued. The Swan-Ganz catheter, introducer, and arterial catheters were removed; isoflurane and oxygen administration was discontinued; and dogs were moved to a kennel for recovery from anesthesia. Dogs were positioned in left lateral recumbency throughout data collection and recovery from anesthesia. The venous catheter was removed before dogs were returned to their boarding facility.

Veterinary digital anesthetic software[aa] was used to record anesthetic data. Post hoc calculation of cardiac index, stroke volume, stroke volume index, PVRI, SVRI, arterial and mixed-venous oxygen contents, D_{O_2}, $\dot{V}_{O_2}$, and O_2ER was performed with standard equations.[11]

Statistical analysis

Statistical analysis was performed with commercially available statistical software.[bb] Parametric data were reported as mean ± SD. Hemodynamic, respiratory, and metabolic variables were analyzed with a mixed repeated-measures ANOVA for differences among induction regimens and across and within time points. Residuals of the mixed ANOVA were normally distributed. The repeated-measures ANOVA was adjusted for dog (random factor), sequence of induction regimen (fixed factor), and time point (fixed factor). A second mixed ANOVA that included the time points M_0 to M_{60} was used to test effects of the induction regimens on the overall anesthetic period. A third mixed ANOVA was used to test the linearity of mixed-venous Hct, arterial hemoglobin concentration, mixed-venous total protein concentration, and body temperature. Slope for the interaction was calculated and tested to detect differences among induction regimens. For all tests, significance was set at values of $P < 0.05$. If significance was detected among induction regimens for each time point, a post hoc Student *t* test was used to compare tiletamine-zolazepam with the other induction regimens. A Bonferroni correction was then applied ($P < 0.017$). For calculation of coefficients, tiletamine-zolazepam was set as the reference to which differences for the other induction regimens were compared. These differences were reported as a positive or negative coefficient representing variation from the reference induction regimen. A post hoc pairwise Tukey test was used to test the difference among time points (baseline vs M_0, M_0 vs M_{10}, M_{10} vs M_{20}, M_{20} vs M_{40}, M_{40} vs M_{60}, M_0 vs M_{60}, and baseline vs M_{60}) within the same induction regimen.

Results

Dogs were classified as American Society of Anesthesiologists grade I; no other procedures were performed while the animals were enrolled in the present study. Mean ± SD dose necessary to perform tracheal intubation was 3.8 ± 0.8 mg/kg for tiletamine-zolazepam, 2.8 ± 0.3 mg/kg for alfaxalone, 6.1 ± 0.9 mg/kg and 0.26 ± 0.04 mg/kg for ketamine-diazepam, and 5.4 ± 1.1 mg/kg for propofol. At these doses, depth of anesthesia was judged to be adequate to allow tracheal intubation. Intubation quality was smooth and uneventful for most dogs. All intubations after administration of alfaxalone were scored as 0, whereas 2 intubations with tiletamine-zolazepam were scored as 1 (1 dog had profuse salivation). Two intubations with ketamine-diazepam were scored as 2, and 1 intubation was scored as 1. One induction with propofol was scored as 3, and the additional dose was administered to allow intubation. The $P_{ET_{Iso}}$ used for maintenance of anesthesia did not differ among induction regimens at any time point **(Tables 1 and 2)**. For alfaxalone, $P_{ET_{Iso}}$ was significantly lower at M_0 than at M_{10}, M_{20}, and M_{60}. Mean ± SD volume of lactated Ringer solution was 130.5 ± 17.5 mL, 137.9 ± 11.8 mL, 143.6 ± 17.5 mL, and 137.7 ± 23.2 mL for tiletamine-zolazepam, alfaxalone, ketamine-diazepam, and propofol, respectively. Infused volumes did not differ among induction regimens. Body temperature decreased from baseline to M_0 in dogs after induction with tiletamine-zolazepam and propofol. For all induction regimens, body temperature decreased linearly (slope, 0.27°C/h; $P < 0.001$) and independently of the induction regimen used. All dogs recovered from anesthesia without complications.

Cardiovascular variables

Cardiovascular variables were summarized. Heart rate increased significantly from baseline to M_0 by 94.9%, 74.7%, and 54.3% in dogs when anesthesia was induced with tiletamine-zolazepam, ketamine-diazepam, and alfaxalone, respectively **(Table 3)**. At M_0, heart rate was significantly higher in dogs when anesthesia was induced with tiletamine-zolazepam than when anesthesia was induced with propofol (lower by 57 beats/min; $P < 0.001$), ketamine-diazepam (lower by 44 beats/min; $P = 0.005$), and alfaxalone (lower by 33 beats/min; $P = 0.012$). Induction with tiletamine-zolazepam also resulted in a significantly higher heart rate than for induction with propofol at M_{10} ($P = 0.002$) and M_{20} ($P = 0.002$). For all induction regimens, except for ketamine-diazepam, heart rate returned to baseline values by M_{60} and did not differ among induction regimens at M_{60}. When mean heart rate for the entire trial period was considered,

Table 1—Mean ± SD values for respiratory variables measured at baseline; after induction of anesthesia (M_0) by IV administration of tiletamine-zolazepam (TZ), alfaxalone (A), ketamine-diazepam (KD), and propofol (P); and at 10 (M_{10}), 20 (M_{20}), 40 (M_{40}), and 60 (M_{60}) minutes after induction in 6 dogs that did not receive sedatives before induction of anesthesia.

Variable	Induction regimen	Baseline	M_0	M_{10}	M_{20}	M_{40}	M_{60}
Respiratory rate (breaths/min)	TZ	30 ± 17	11 ± 8	27 ± 17	14 ± 13.7	12 ± 8	14 ± 9.3
	A	18 ± 3	4 ± 8*	7 ± 4[DTZ]	8 ± 5	12 ± 7	13 ± 6†
	KD	14 ± 3	9 ± 7	20 ± 13	17 ± 13	13 ± 6	17 ± 11
	P	18 ± 5	11 ± 7	14 ± 6	11 ± 5	12 ± 5	13 ± 5
$P_{ET_{ISO}}$ (%)	TZ	ND	1.0 ± 0.6	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
	A	ND	0.3 ± 0.5	1.1 ± 0.1†	1.2 ± 0.1†	1.3 ± 0.1	1.3 ± 0.1†
	KD	ND	1.1 ± 0.6	1.2 ± 0.2	1.2 ± 0.1	1.3 ± 0.1	1.3 ± 0.1
	P	ND	0.9 ± 0.5	1.2 ± 0.1	1.2 ± 0.1	1.3 ± 0.1	1.2 ± 0.1
P_{ETCO_2} (mm Hg)	TZ	ND	31 ± 18	37 ± 6	42 ± 5	43 ± 3	42 ± 5
	A	ND	14 ± 22	46 ± 2†	46 ± 2†	45 ± 4†	41 ± 10†
	KD	ND	32 ± 18	40 ± 5	38 ± 8	40 ± 6	41 ± 4
	P	ND	36 ± 18	44 ± 4	43 ± 4	44 ± 2	43 ± 3
Pa_{O_2} (mm Hg)	TZ	101.7 ± 7.6	385.8 ± 137.3*	579.5 ± 26.6†	580.3 ± 31.8	574.5 ± 33.1	574 ± 36.5*†
	A	96.3 ± 5.4	219.1 ± 156.4*	568.9 ± 18.3†	576 ± 18.3	573.7 ± 29.9	568.4 ± 18.6*†
	KD	98.1 ± 5.9	351.8 ± 183.4*	577.0 ± 21.7†	585.8 ± 19.4	556.1 ± 18.8	570.0 ± 14.8*†
	P	103.0 ± 5.1	382.4 ± 190.0*	541.7 ± 45.0†	567.9 ± 36.6	571.3 ± 25.3	569.4 ± 13.2*†
$P\bar{v}_{O_2}$ (mm Hg)	TZ	61.4 ± 27.6	70.7 ± 14.2	87.2 ± 13.7	84.3 ± 11.9	78.8 ± 5.1	78.7 ± 8.3
	A	50.2 ± 3.8	58.6 ± 11.5	93.1 ± 9.7†	88.6 ± 7.7	84.4 ± 7.8	80.7 ± 9.5*†
	KD	51 ± 7.1	54.6 ± 7.9	84.0 ± 9.8†	85.0 ± 13.7	80.0 ± 11.9	76.6 ± 7.2*†
	P	51.7 ± 7.2	81.9 ± 45.6	93.3 ± 20.1	83.2 ± 11.1	78.2 ± 9.2	78.5 ± 11.1
Pa_{CO_2} (mm Hg)	TZ	32.9 ± 1.2	38.2 ± 6.9	39.9 ± 5.2	39.2 ± 7.6	44.2 ± 6.8	45.9 ± 8.6
	A	32.8 ± 1.3	39.1 ± 3.4	44.1 ± 2.7	47.6 ± 9.7	42.8 ± 3.5	40.2 ± 3.9
	KD	34.3 ± 0.8	36.0 ± 6.0	39.2 ± 7.4	37.9 ± 6.5	40.8 ± 5.0	39.2 ± 5.2
	P	33.4 ± 3	39.6 ± 1.7*	42.8 ± 3.9	42.7 ± 5.3	42.2 ± 8.7	41.3 ± 8.2
$P\bar{v}_{CO_2}$ (mm Hg)	TZ	35.9 ± 4.2	39.9 ± 4.7	42.4 ± 5.7	45.4 ± 6.6	49.6 ± 6.3	50.5 ± 7.4†
	A	37.3 ± 1.7	39.4 ± 1.6	48.3 ± 3.3†	51.3 ± 6.2	49.0 ± 4.6	48.3 ± 3.9†
	KD	39.3 ± 1.5	35.7 ± 7.8	43.9 ± 5.2	43.9 ± 6.4	46.5 ± 4.9	46.7 ± 4.7†
	P	38.1 ± 2.3	40.4 ± 1.0*	46.4 ± 4.1	46.4 ± 4.5	47.1 ± 4.0	48.3 ± 4.0†
Sa_{O_2} (%)	TZ	98.7 ± 0.45	99.7 ± 0*	99.7 ± 0	99.7 ± 0	99.7 ± 0	99.7 ± 0*
	A	98 ± 0.3[DTZ]	96.7 ± 5.0	99.7 ± 0	99.7 ± 0.1	99.7 ± 0	99.7 ± 0
	KD	97.9 ± 0.4[DTZ]	97.4 ± 5.8	99.7 ± 0	99.7 ± 0	99.7 ± 0	99.7 ± 0
	P	98.6 ± 0.7	98.4 ± 3.2	99.7 ± 0	99.7 ± 0	99.7 ± 0	99.7 ± 0
$S\bar{v}_{O_2}$ (%)	TZ	85.1 ± 8.5	92.7 ± 3.2*	96.0 ± 1.8	95.5 ± 2.0	94.2 ± 1.6	93.7 ± 2.2*
	A	80.9 ± 4.2	85.7 ± 6.7	96.4 ± 1.7†	95.2 ± 3.0	94.6 ± 2.9	93.8 ± 3.0*†
	KD	81.7 ± 4.6	85.2 ± 6.2	95.7 ± 1.0†	95.2 ± 2.0	94.2 ± 2.0	93.9 ± 1.7*†
	P	81.5 ± 4.9	90.4 ± 6.9*	95.8 ± 2.7	94.6 ± 2.4	93.4 ± 2.5	93.1 ± 2.5*

A light plane of anesthesia was maintained with isoflurane in oxygen.

*Within a row, value differs significantly ($P < 0.05$) from the value for baseline. †Within a row, value differs significantly ($P < 0.05$) from the value for M_0.

[DTZ]Within a time point, value differs significantly ($P < 0.05$) from the value for tiletamine-zolazepam.

$P\bar{v}_{CO_2}$ = Mixed-venous partial pressure of carbon dioxide. $P\bar{v}_{O_2}$ = Mixed-venous partial pressure of oxygen. Sa_{O_2} = Arterial hemoglobin oxygen saturation. $S\bar{v}_{O_2}$ = Mixed-venous hemoglobin oxygen saturation.

induction with tiletamine-zolazepam resulted in the highest heart rate, with a significant difference from the heart rate after induction with propofol (lower by 27 beats/min), and ketamine-diazepam (lower by 18 beats/min).

Mean values for RAP, PAP, and PAWP from M_0 to M_{60} were significantly lower after tiletamine-zolazepam than after ketamine-diazepam and propofol administration. During the study, a malfunction of the pressure transducer used to measure RAP, PAP, and PAWP forced the investigators to change to another brand of transducer. Analysis of these variables with a mixed ANOVA revealed that RAP values were significantly ($P = 0.019$) higher after switching brands of the transducer, but that PAP and PAWP values were not significantly affected.

At M_0, the SAP decreased for all induction regimens (Table 3). The MAP decreased significantly after induction with tiletamine-zolazepam and propofol but not after induction with alfaxalone and ketamine-diazepam. The DAP decreased significantly after induction with tiletamine-zolazepam but not after induction with the other induction regimens. For tiletamine-zolazepam, stroke volume was sig-

nificantly lower than for propofol at M_{20} ($P = 0.011$), M_{40} ($P = 0.004$), and M_{60} ($P = 0.006$; **Table 4**). There was a corresponding change in stroke volume index, but only at M_{40} and M_{60}. Overall, induction with tiletamine-zolazepam resulted in a significantly lower stroke volume than induction with the other induction regimens.

The Do_2 after induction with tiletamine-zolazepam was significantly ($P = 0.006$) higher than that after induction with propofol. Mean of the cardiac index and Do_2 from M_0 to M_{60} was significantly higher after induction with tiletamine-zolazepam than after induction with propofol. The $\dot{V}o_2$ and O_2ER decreased over time during the trial period. The O_2ER decreased after induction with alfaxalone, ketamine-diazepam, and propofol but not after induction with tiletamine-zolazepam. No difference was found among induction regimens for CO, SAP, MAP, DAP, PVRI, SVRI, $\dot{V}o_2$, and O_2ER when mean values for M_0 to M_{60} were compared.

Respiratory variables

Results for the respiratory and metabolic variables were summarized (Tables 2 and 4), and coefficients were determined **(Table 5)**. Mean respiratory rate was significantly ($P = 0.003$) higher (by 7 breaths/min) after induction with tiletamine-zolazepam than after induction with alfaxalone. Postinduction apnea occurred in 5 of 24 inductions (3 for alfaxalone, 1 for tiletamine-zolazepam, and 1 for pro-

Table 2—Mean ± SD values for metabolic variables measured at baseline and at various times after induction of anesthesia by IV administration of various induction regimens in 6 dogs that did not receive sedatives before induction of anesthesia.

Variable	Induction regimen	Baseline	M_0	M_{10}	M_{20}	M_{40}	M_{60}
Mixed-venous pH	TZ	7.42 ± 0.05	7.38 ± 0.04*	7.35 ± 0.05	7.34 ± 0.05	7.31 ± 0.05	7.31 ± 0.04*†
	A	7.40 ± 0.01	7.38 ± 0.02	7.3 ± 0.03†	7.29 ± 0.04	7.31 ± 0.03	7.31 ± 0.04*†
	KD	7.40 ± 0.02	7.41 ± 0.06	7.35 ± 0.05	7.36 ± 0.06	7.34 ± 0.04	7.34 ± 0.04
	P	7.39 ± 0.02	7.36 ± 0.03*	7.32 ± 0.04†	7.32 ± 0.04	7.31 ± 0.04	7.31 ± 0.05*†
Mixed-venous HCO_3^- (mmol/L)	TZ	22.6 ± 1.0	22.9 ± 1.0	22.8 ± 1.5	23.7 ± 1.5	24.3 ± 0.9	24.8 ± 1.3†
	A	22.5 ± 0.7	22.5 ± 0.9	23.7 ± 1.1	24.2 ± 0.9	24 ± 1.5	23.7 ± 0.5†
	KD	23.8 ± 1.1	21.9 ± 2.8	23.6 ± 0.8	23.8 ± 1.4	24.6 ± 1.3	24.3 ± 0.9
	P	22.6 ± 1.7	22.3 ± 1.6	23.2 ± 1.3	23.1 ± 1.6	23.3 ± 2.1	23.7 ± 1.2†
Mixed-venous base excess (mmol/L)	TZ	–0.9 ± 1.1	–1.8 ± 1.1	–2.7 ± 1.6	–2.2 ± 1.3	–2.3 ± 1.0	–1.8 ± 0.9
	A	–1.5 ± 0.7	–2.1 ± 1.0	–2.8 ± 1.3	–2.8 ± 0.8	–2.6 ± 1.4	–2.6 ± 1.0
	KD	–0.5 ± 1.1	–2.0 ± 1.8	–1.9 ± 1.6	–1.7 ± 1.7	–1.4 ± 1.4	–1.7 ± 1.3
	P	–1.6 ± 1.6	–3.0 ± 1.8*DTZ	–3.0 ± 1.6	–3.1 ± 1.7	–3.0 ± 2.3	–2.6 ± 1.8
Mixed-venous lactate (mmol/L)	TZ	0.7 ± 0.3	0.8 ± 0.3	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.3
	A	1.0 ± 0.4	0.9 ± 0.2	0.8 ± 0.2	0.8 ± 0.3	0.8 ± 0.5	0.9 ± 0.6
	KD	0.9 ± 0.4	1.0 ± 0.3	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.3
	P	0.7 ± 0.3	0.8 ± 0.3	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
Mixed-venous Hct (%)	TZ	44.8 ± 5.7	43.7 ± 3.3	39.7 ± 2.1	38.8 ± 1.2	36.8 ± 1.0	36.3 ± 0.8*†
	A	45.7 ± 5.3	43.3 ± 3.8	41.7 ± 3.1	40.0 ± 2.5	38.8 ± 3.2	38.2 ± 3.0*†
	KD	44.8 ± 4.8	43.2 ± 3.3	40.7 ± 3.3	40.2 ± 3.4	38.3 ± 1.9	38.2 ± 2.3*†
	P	43.8 ± 3.8	42.2 ± 3.7	39.8 ± 1.5	38.0 ± 1.7	37.0 ± 2.0	36.2 ± 1.3*†
Arterial hemoglobin (g/dL)	TZ	15.2 ± 2.0	15.1 ± 1.6	13.8 ± 0.9	13.3 ± 0.5	12.6 ± 0.3	12.3 ± 0.5*†
	A	15.4 ± 1.5	14.5 ± 1.2	14.2 ± 1.0	13.6 ± 0.8	13.1 ± 0.8	13.1 ± 0.8*†
	KD	14.6 ± 1.4	15.3 ± 1.3	14.3 ± 0.9	13.7 ± 0.7	13.0 ± 0.9	12.8 ± 0.8*†
	P	15.0 ± 1.0	14.5 ± 1.9	13.7 ± 0.7	13.2 ± 0.8	12.7 ± 0.8	12.6 ± 0.4*†
Mixed-venous total protein (g/dL)	TZ	5.5 ± 0.3	5.5 ± 0.5	5.3 ± 0.4	5.1 ± 0.5	5.0 ± 0.4	4.9 ± 0.6*†
	A	5.2 ± 0.3	5.2 ± 0.3	5.0 ± 0.2	4.9 ± 0.2	4.8 ± 0.2	4.7 ± 0.2*†
	KD	5.4 ± 0.4	5.2 ± 0.3	5.1 ± 0.1	5.0 ± 0.3	4.6 ± 0.1‡	4.8 ± 0.2*†
	P	5.2 ± 0.3	5.1 ± 0.5	5.0 ± 0.3	4.8 ± 0.3	4.6 ± 0.3	4.7 ± 0.4*†
Mixed-venous potassium (mmol/L)	TZ	3.56 ± 0.19	3.54 ± 0.25*	3.42 ± 0.30	3.42 ± 0.27	3.45 ± 0.24	3.60 ± 0.25
	A	3.34 ± 0.27	3.18 ± 0.32DTZ	3.23 ± 0.23	3.34 ± 0.23	3.43 ± 0.23	3.52 ± 0.17†
	KD	3.63 ± 0.14	3.51 ± 0.10	3.40 ± 0.11	3.46 ± 0.07	3.53 ± 0.15	3.65 ± 0.22
	P	3.48 ± 0.20	3.34 ± 0.16	3.25 ± 0.12	3.24 ± 0.16	3.38 ± 0.21	3.54 ± 0.15†
Body temperature (°C)	TZ	37.3 ± 0.4	37.3 ± 0.5*	37 ± 0.5	36.8 ± 0.5	36.9 ± 0.4	36.9 ± 0.4*
	A	37.7 ± 0.3	37.5 ± 0.3	37.3 ± 0.4	37.2 ± 0.5	37.2 ± 0.6	37.2 ± 0.7*
	KD	37.3 ± 0.8	37.3 ± 0.5	37.2 ± 0.5	37.1 ± 0.4	37 ± 0.4	37.2 ± 0.4
	P	37.7 ± 0.4	37.2 ± 0.3*	37.2 ± 0.2	37.1 ± 0.2	37.1 ± 0.2	37.2 ± 0.2*

‡Within a row, value differs significantly ($P < 0.05$) from the value for M_{20}.
See Table 1 for remainder of key.

Table 3—Mean ± SD values for heart rate and blood pressures measured at baseline and at various times after induction of anesthesia by IV administration of various induction regimens in 6 dogs that did not receive sedatives before induction of anesthesia.

Variable	Induction regimen	Baseline	M_0	M_{10}	M_{20}	M_{40}	M_{60}
Heart rate (beats/min)	TZ	85 ± 27	167 ± 28*	128 ± 18†	116 ±17	102 ± 15	104 ± 12†
	A	84 ± 12	129 ± 23*	123 ± 24	115 ± 20	110 ± 14[DAI]	104 ± 13†
	KD	80 ± 2	141 ± 29*	118 ± 20	107 ± 19	103 ± 14[DAI]	104 ± 8*†
	P	90 ± 26	111 ± 20[DTZ]	98 ± 16[DTZ]	91 ± 15[DTZ]	92 ± 18[DAI]	93 ± 16†
RAP (mm Hg)	TZ	3.7 ± 4.2	1.8 ± 2.6	2.2 ± 3.4	1.5 ± 2.3	1.5 ± 1.8	1.2 ± 1.8
	A	2.8 ± 3.0	2.0 ± 2.5	1.8 ± 3.0	1.8 ± 2.8	2.2 ± 3.5	1.7 ± 2.6
	KD	6.2 ± 2.3	3.7 ± 2.0*	4.2 ± 2.6	4.3 ± 2.7	4.5 ± 2.4	4.2 ± 2.2*
	P	2.8 ± 2.8	3.3 ± 2.3	2.7 ± 1.5	2.7 ± 3.1	2.8 ± 2.9	2.7 ± 2.4
PAP (mm Hg)	TZ	17 ± 3	16 ± 2	13 ± 2	12 ± 2	11 ± 1	11 ± 1*†
	A	16 ± 2	15 ± 3	12 ± 1[DAI]	12 ± 2	11 ± 3†	13 ± 4
	KD	17 ± 4	17 ± 2	15 ± 2[DAI]	14 ± 1	13 ± 2	13 ± 1*†
	P	17 ± 3	19 ± 6	14 ± 3[DAI]	13 ± 3	12 ± 2	13 ± 3†
PAWP (mm Hg)	TZ	6.5 ± 2.2	2.7 ± 3.2*	2.8 ± 2.3	2.7 ± 3.4	2.3 ± 2.9	2.0 ± 3.1*
	A	4.7 ± 3.2	2.5 ± 2.8	1.7 ± 2.1	2.5 ± 3.0	2.5 ± 2.9	3.8 ± 4.6
	KD	9.0 ± 2.0	5.5 ± 1.6	6.2 ± 2.0	6.2 ± 1.3	6.0 ± 2.2	5.8 ± 1.7
	P	5.5 ± 3.2	5.3 ± 5.6	4.8 ± 4.9	4.7 ± 3.8	4.7 ±3.8	5.3 ± 4.6
SAP (mm Hg)	TZ	137 ± 7	100 ± 5*	89 ± 7	84 ± 8	81 ± 8	84 ± 4*†
	A	120 ± 23[DTZ]	96 ± 8*	81 ± 2†	80 ± 3	95 ± 18	96 ± 11*
	KD	128 ± 24	98 ± 25*	94 ± 9	88 ± 7	87 ± 9	101 ± 15*
	P	120 ± 15[DTZ]	92 ± 22*	88 ± 17	88 ± 17	89 ± 17	84 ± 9*§
MAP (mm Hg)	TZ	91 ± 9	76 ± 8*	67 ± 9†	62 ± 9	60 ± 8	62 ± 8*†
	A	86 ± 7	77 ± 7	64 ± 5†	63 ± 3	66 ± 17	69 ± 2*
	KD	87 ± 1	75 ± 19	69 ± 7	64 ± 6	63 ± 4	69 ± 6*
	P	87 ± 15	71 ± 17*	64 ± 13	64 ± 14	61 ± 18	72 ± 12*§
DAP (mmg Hg)	TZ	73 ± 13	60 ± 7*	55 ± 10	50 ± 8	48 ± 8	50 ± 8*†
	A	68 ± 7	62 ± 8	52 ± 6	52 ± 4	51 ± 12	56 ± 2*
	KD	69 ± 8	60 ± 17	54 ± 6	51 ± 5	51 ± 3	55 ± 5
	P	69 ± 13	59 ± 16	53 ± 12	52 ± 12	54 ± 12	58 ± 11*

§Within a row, value differs significantly ($P < 0.05$) from the value for M_{40}.

[DAI]Within a time point, value differs significantly ($P < 0.05$) among induction regimens but does not differ significantly from the value for tiletamine-zolazepam.

See Table 1 for remainder of key.

pofol). Induction with tiletamine-zolazepam resulted in a significantly ($P = 0.001$) higher respiratory rate at M_{10} than for induction with alfaxalone. A decrease in P_{ETCO_2}, compared with the baseline value, was observed after induction with alfaxalone, which was followed by a significant increase in P_{ETCO_2} at M_{10}. Hypoxemia was detected at M_0 after 3 inductions (1 for ketamine-diazepam [Pa_{O_2} = 54.3 mm Hg], 1 for alfaxalone [Pa_{O_2} = 59.1 mm Hg], and 1 for propofol [Pa_{O_2} = 64.9 mm Hg]). These hypoxemic dogs had a fraction of inspired oxygen of 98%, 92%, and 84%, respectively. The arterial and mixed-venous oxygen saturation increased after induction with tiletamine-zolazepam and reached values comparable to those for the other induction regimens. Arterial oxygen content did not differ significantly among induction regimens or time points.

Metabolic variables

All metabolic variables remained within reference limits, and baseline values for metabolic variables did not differ among induction regimens. No significant differences were found among induction regimens for mixed-venous pH, Hct, and concentrations of HCO_3^-, lactate, total protein, sodium, chloride, calcium, and glucose; arterial hemoglobin concentration; and body temperature at individual time points. Overall, induction with propofol resulted in a more negative mixed-venous base excess (coefficient, –0.85 mmol/L) and lower mixed-venous HCO_3^- concentration (0.65 mmol/L lower), compared with results for induction with tiletamine-zolazepam; however, results for propofol were within reference limits. Serum mixed-venous potassium concentration at M_0 for induction with tiletamine-zolazepam differed significantly ($P = 0.002$) from the concentration for induction with alfaxalone. Mean mixed-venous concentrations of sodium, calcium, and potassium were higher after induction with tiletamine-zolazepam than after induction with propofol. A progressive decrease in mixed-venous Hct (–6.6%/h), arterial hemoglobin concentration (–2.2 g/dL/h), and mixed-venous total protein concentration (–0.54 g/dL/h) was independent from the induction regimen used,

Table 4—Mean ± SD values for cardiorespiratory variables measured at baseline and at various times after induction of anesthesia by IV administration of various induction regimens in 6 dogs that did not receive sedatives before induction of anesthesia.

Variable	Induction regimen	Baseline	M_0	M_{10}	M_{20}	M_{40}	M_{60}
CO (mL/min)	TZ	4,400 ± 1,332	5,028 ± 1,289	4,050 ± 891	3,550 ± 790	3,128 ± 546	3,094 ± 484*†
	A	3,811 ± 728	4,917 ± 920*	4,011 ± 403†	3,817 ± 423	3,550 ± 612	3,472 ± 536†
	KD	4,161 ± 1,389	4,567 ± 636	3,933 ± 683	3,628 ± 605	3,317 ± 636	3,389 ± 536†
	P	4,505 ± 1,456	4,100 ± 1,116	3,789 ± 797	3,517 ± 815	3,444 ± 791	3,461 ± 761
Stroke volume (mL/beat)	TZ	52 ± 7	30 ± 6	32 ± 5	31 ± 4*	31 ± 2*	30 ± 3*
	A	45 ± 6	38 ± 6	33 ± 5	33 ± 5	32 ± 4	33 ± 5
	KD	51 ± 7	33 ± 4	34 ± 4	34 ± 4	32 ± 4	32 ± 3
	P	50 ± 3	36 ± 4	38 ± 5	38 ± 4*	37 ± 3*	37 ± 4*
PVRI (mm Hg/mL/kg/min)	TZ	0.052 ± 0.018	0.058 ± 0.017	0.053 ± 0.013	0.058 ± 0.017	0.060 ± 0.018	0.063 ± 0.020
	A	0.063 ± 0.010	0.058 ± 0.020	0.057 ± 0.008	0.053 ± 0.006	0.056 ± 0.009	0.058 ± 0.007
	KD	0.045 ± 0.016	0.060 ± 0.014	0.055 ± 0.020	0.050 ± 0.007	0.047 ± 0.009	0.049 ± 0.003
	P	0.057 ± 0.012	0.078 ± 0.034	0.053 ± 0.012	0.056 ± 0.012	0.050 ± 0.014	0.049 ± 0.013
SVRI (mm Hg/mL/kg/min)	TZ	0.450 ± 0.116	0.327 ± 0.072*	0.359 ± 0.113	0.381 ± 0.125	0.411 ± 0.133	0.431 ± 0.131
	A	0.498 ± 0.090	0.344 ± 0.022*	0.345 ± 0.048	0.360 ± 0.046	0.392 ± 0.069	0.434 ± 0.032
	KD	0.470 ± 0.168	0.344 ± 0.795	0.367 ± 0.042	0.370 ± 0.053	0.397 ± 0.043	0.426 ± 0.062
	P	0.436 ± 0.117	0.382 ± 0.119	0.370 ± 0.092	0.398 ± 0.100	0.386 ± 0.133	0.453 ± 0.106
Ca_{O_2} (mL/dL)	TZ	20.4 ± 2.8	20.5 ± 2.2	18.8 ± 1.3	18.1 ± 0.7	17.0 ± 0.4	16.6 ± 0.6*†
	A	20.6 ± 2.1	19.1 ± 1.9	19.2 ± 1.4	18.4 ± 1.1	17.8 ± 1.1	17.7 ± 1.1*
	KD	19.5 ± 1.9	20.2 ± 0.8	19.4 ± 1.3	18.6 ± 0.9	17.7 ± 1.2	17.4 ± 1.1*†
	P	20.2 ± 1.4	19.5 ± 1.8	18.6 ± 1.0	17.9 ± 1.1	17.2 ± 1.1	17.0 ± 0.6*†
D_{O_2} (mL/kg/min)	TZ	42.5 ± 15.6	47.7 ± 9.7	35.4 ± 6.4	30 ± 5.4	24.9 ± 3.4	24.1 ± 3*†
	A	35.8 ± 11.2	41.9 ± 6.3	34.9 ± 5	31.6 ± 3.4	28.5 ± 5.0	27.6 ± 3.9†
	KD	35.6 ± 15.8	42.2 ± 8.7	34.8 ± 7.9	30.8 ± 7.3	26.6 ± 5.6	26.7 ± 4.2†
	P	41.5 ± 14.5	35.4 ± 6.8[DTZ]	31.4 ± 4.4	27.9 ± 3.3	26.3 ± 3	26.3 ± 2.3*
$\dot{V}_{O_2}$ (mL/kg/min)	TZ	5.7 ± 3.1	3.7 ± 2.1	1.3 ± 0.5	1.2 ± 0.5	1.3 ± 0.3	1.4 ± 0.4*
	A	6.1 ± 0.7	4.7 ± 1.5*	1.1 ± 0.5†	1.4 ± 0.7	1.4 ± 0.5	1.6 ± 0.7*†
	KD	6.0 ± 1.3	5.0 ± 1.8	1.4 ± 0.5†	1.3 ± 0.5	1.4 ± 0.5	1.6 ± 0.4*†
	P	6.9 ± 1.8	2.7 ± 1.8*	1.1 ± 0.8	1.4 ± 0.6	1.6 ± 0.5	1.7 ± 0.6*
O_2ER (%)	TZ	14.0 ± 8.5	7.4 ± 3.3	3.8 ± 1.9	4.2 ± 2.1	5.6 ± 1.7	6.0 ± 2.3*
	A	18.0 ± 4.2	11.8 ± 5.2*	3.3 ± 1.7†	4.5 ± 3.0	5.1 ± 2.9	6.0 ± 3.0*†
	KD	18.2 ± 4.2	12.5 ± 4.7*	4.1 ± 1.0†	4.6 ± 2.1	5.6 ± 2.1	6.0 ± 1.8*†
	P	17.7 ± 4.9	8.2 ± 6.1*	3.8 ± 3.0	5.1 ± 2.6	6.4 ± 2.6	6.6 ± 2.7*

See Table 1 for key.

although values for these variables remained within physiologic limits. The mixed-venous concentration of total protein was higher for induction with tiletamine-zolazepam than for the other induction regimens. Mean mixed-venous concentration of lactate was lower for induction with propofol (−0.2 mmol/L) than for induction with tiletamine-zolazepam, although mixed-venous lactate concentrations for all induction regimens were within reference limits.

Discussion

In the study reported here, cardiorespiratory and metabolic effects after IV administration of tiletamine-zolazepam before and during anesthesia maintained with isoflurane were compared with those after IV administration of alfaxalone, ketamine-diazepam, and propofol in healthy dogs that did not receive sedative premedications. Each of the 4 induction regimens provided satisfactory induction of anesthesia and uncomplicated recovery from anesthesia. Acceptable D_{O_2} was maintained in the presence of a comparable $\dot{V}_{O_2}$, mixed-venous oxygen saturation, O_2ER, and lactate concentration, which indicated adequate global tissue perfusion for all induction regimens. Values of D_{O_2} and $\dot{V}_{O_2}$ were consistent with those reported for nonanesthetized dogs.[11] Titration of injectable induction drugs to achieve the desired effect is the standard used in veterinary medicine to perform endotracheal intubation while ensuring safety and minimizing adverse effects. Although equipotency would be desirable when comparing cardiorespiratory effects, this is only necessary for administration of a full dose of induction agent. In the present study, induction regimens were administered to enable endotracheal intubation. Doses of tiletamine-zolazepam,[12] alfaxalone,[13] ketamine-diazepam,[14] and propofol[13,15] used in this study were similar to those reported for nonsedated dogs.

Coughing during intubation can cause an increase in SAP, intracranial blood pressure, and intraocular pressure and potentially cause regurgitation owing to stimulation of the larynx.[16] For the present study, induction with propofol and alfaxalone seemed

Table 5—Coefficients and *P* values for cardiorespiratory and metabolic variables measured at baseline and at various times after induction of anesthesia by IV administration of various induction regimens in 6 dogs that did not receive sedatives before induction of anesthesia.

		Post hoc Bonferroni correction					
		Coefficient of comparison with TZ			*P* value for comparison with TZ		
Variable	ANOVA *P* value	A	KD	P	A	KD	P
Heart rate (beats/min)	< 0.001	–6	–18*	–27*	0.134	< 0.001	< 0.001
RAP (mm Hg)	< 0.001	0.9	2.2*	1.4*	0.027	< 0.001	0.001
PAP (mm Hg)	0.003	0.6	1.9*	1.7*	0.262	0.002	0.002
PAWP (mm Hg)	< 0.001	0.9	3.0*	2.7*	0.065	< 0.001	< 0.001
Cardiac index (mL/min/kg)	0.013	0.4	–9.3	–15.9*	0.941	0.141	0.006
Stroke volume (mL/beat)	< 0.001	2.9*	4.8*	6.7*	0.003	< 0.001	< 0.001
Stroke volume index (mL/beat/kg)	< 0.001	0.07	0.14*	0.25*	0.088	0.004	< 0.001
D_{O_2} (mL/kg/min)	0.007	0.3	–1.2	–3.5*	0.807	0.373	0.004
Respiratory rate (breaths/min)	0.029	–7*	–2	–3	0.003	0.489	0.139
Mixed-venous analysis							
pH	0.041	–0.013	0.004	–0.015	0.064	0.613	0.036
HCO_3^- (mmol/L)	0.011	0.02	–0.15	–0.65*	0.921	0.565	0.005
Base excess (mmol/L)	< 0.001	–0.22	–0.02	–0.85*	0.179	0.895	< 0.001
Lactate (mmol/L)	0.002	0	0	–0.2*	0.699	0.748	< 0.001
Total protein (g/dL)	< 0.001	–0.20*	–0.29*	–0.30*	0.005	< 0.001	< 0.001
Hct (%)	0.002	1.2	0.7	–0.8	0.031	0.224	0.125
Sodium (mmol/L)	0.013	–0.4	–0.2	–1.1*	0.292	0.648	0.002
Calcium (mg/dL)	0.010	–0.07	0.06	–0.15*	0.202	0.366	0.011
Potassium (mmol/L)	< 0.001	–0.13*	0.02	–0.14*	< 0.001	0.613	< 0.001

Coefficients were calculated as the mean of data collected from M_0 to the last data collection time point (M_{60}) and should be interpreted as the mean difference in unit of measure from the reference group.

*Value for the mean from M_0 to M_{60} differs significantly ($P < 0.05$ for ANOVA and $P < 0.017$ for post hoc Bonferroni correction) from the mean value for TZ.

See Table 1 for remainder of key.

to result in less coughing during intubation, compared with the amount of coughing after induction with ketamine-diazepam and tiletamine-zolazepam. Difficulty in assessing depth of anesthesia during induction with dissociative agents resides in the fact that ocular reflexes, jaw tone and movements, and pharyngeal and laryngeal reflexes are preserved. In some instances during the present study, intubation of dogs may have been attempted too soon, which resulted in occasional coughing and jaw movements. However, SAP decreased equally after induction with all induction regimens. During induction with propofol, 1 dog required administration of an additional dose of 1.5 mg/kg to perform intubation. This dog had an elevated heart rate and CO at baseline. Although these variables were not significantly different from the ones for other subjects, they may have influenced the dose of propofol required for intubation by altering its pharmacokinetic profile.

Expired concentrations of isoflurane did not differ among induction regimens at individual time points. Therefore, we believe that depth of anesthesia determined on the basis of clinical assessment of jaw tone, palpebral reflex, and $P_{ET_{ISO}}$ was consistent among induction regimens and appropriate for the purpose of this clinical trial. The amount of body temperature loss was similar among induction regimens (0.27°C/h), although a significant initial decrease was detected from baseline to induction for tiletamine-zolazepam and propofol.

All regimens caused an initial increase in heart rate after induction of anesthesia. The greatest and most significant change in heart rate was after administration of tiletamine-zolazepam (94.9%), ketamine-diazepam (74.7%), and alfaxalone (54.3%). The elevation in heart rate observed after induction with both combinations of dissociative agents was attributed to an increase in sympathetic nervous system outflow and inhibition of norepinephrine reuptake, which caused an increase in circulating catecholamine concentrations and stimulation of the sinus node.[12,17,18] Alfaxalone reportedly can increase heart rate after induction,[17] although the evidence of a consistent increase in heart rate attributable to alfaxalone is weak.[19] However, results of the present study indicated that alfaxalone caused an increase in heart rate after induction that lasted for the duration of the experiment, with an overall heart rate similar to that after tiletamine-zolazepam and higher than that after ketamine-diazepam and propofol induction. This finding is consistent with results of another study[20] of dogs premedicated with fentanyl in which alfaxalone was more likely to cause a higher heart rate than was propofol. The direct mechanism by which alfaxalone increases heart rate is unknown, although it has been speculated that this phenomenon may be attributable to a baroreceptor response.[18] The stimulatory effects of alfaxalone and the 2 combinations of dissociative agents on heart rate observed in the study reported here

may be beneficial in clinical practice for dogs that are bradycardic before induction.

Stroke volume was lowest after induction with tiletamine-zolazepam. We hypothesized that this was attributable to a physiologic decrease in diastolic filling time during sinus tachycardia, which has also been detected after IM administration of tiletamine-zolazepam to dogs.[21] Tachycardia can reduce coronary perfusion and consequently be proarrhythmic as a result of myocardial hypoperfusion. In the dogs of the study reported here, sinus tachycardia after induction with tiletamine-zolazepam, ketamine-diazepam, and alfaxalone did not cause cardiac arrhythmias, although extrapolation of this result to critically ill patients may result in different outcomes. Administration of sedatives before induction of anesthesia is commonly used in clinical settings to relieve anxiety and decrease the amount of drug needed for induction of anesthesia. A lack of sedation may have contributed to the substantial increase in heart rate in the present study, and the magnitude of the increase in heart rate may be mitigated in premedicated dogs.

Overall, Do_2 after induction with tiletamine-zolazepam was higher than after induction with propofol and was similar to that after induction with alfaxalone and ketamine-diazepam. The Do_2 paralleled the increase in heart rate detected after induction with tiletamine-zolazepam. This can be explained by the concomitant decrease in SAP, MAP, DAP, and SVRI detected for this induction regimen, which is consistent with findings from a study[12] on the cardiorespiratory effects of IV administration of tiletamine-zolazepam to dogs with residual isoflurane anesthesia.

In the dogs of the present study, propofol resulted in a higher stroke volume than did tiletamine-zolazepam from M_{20} to the end of the experiment. This can be explained by the lower heart rate after induction with propofol, which allowed longer diastolic filling times that consequently resulted in higher stroke volumes. Cardiac index and CO were not significantly different among induction regimens at any time point. This finding may have been surprising, although even in the presence of initial sympathetic stimulation with ketamine-diazepam and tiletamine-zolazepam, these drugs have negative inotropic effects.[22,23] In addition to these cardiodepressant effects, vasodilation and myocardial depression from isoflurane administration may have affected the effects of each induction regimen, possibly masking significant differences. However, the intent of the design used for the present study was to replicate common clinical situations in which these induction agents are used in conjunction with inhalation anesthesia to provide balanced anesthesia. Heart rate returned to baseline values over time, although for tiletamine-zolazepam, the observed progressive decrease in heart rate at M_{10} did not correspond to an expected proportional increase in stroke volume, perhaps because of a decrease in myocardial contractility.[24] This may explain the decrease in Do_2 and CO seen with the combinations of dissociative agents at the final time points of the experiments. Because CO is dependent on stroke volume and heart rate, failure of one of these variables to compensate for changes in the other variable results in an overall decrease in CO, which will ultimately affect Do_2.

Although SVRI did not differ significantly among induction regimens, the pattern for SVRI was worth noting. Only alfaxalone and tiletamine-zolazepam caused a significant decrease in SVRI after induction, although absolute values were still comparable among induction regimens. Systemic vascular resistance represents left ventricular afterload. Systemic vascular resistance decreases in nonpremedicated dogs in which anesthesia is induced with tiletamine-zolazepam and maintained with isoflurane.[12] The authors of that study[12] hypothesized that this finding may have been a direct vasodilatory effect of tiletamine-zolazepam, a change in vasomotor tone, or a residual vasodilatory effect of isoflurane. These findings support those of the present study because SVRI was not different among induction regimens, probably owing to the contribution of isoflurane rather than a direct effect of the induction regimen. The SVRI is derived from RAP.[11] Our statistical analysis suggested that changing the brand of transducer significantly affected RAP values; thus, values for this variable should be interpreted carefully. Pulmonary vascular resistance represents right ventricular afterload and reportedly increases after ketamine injection.[24]

Measuring CO in clinical settings is often difficult and expensive. Therefore, MAP has been adopted as a more practical variable to use in clinical practice. However, it should be kept in mind that there can be large variations in CO with no absolute variation in MAP. After anesthesia was induced, MAP decreased for all induction regimens, but this change was significant only for tiletamine-zolazepam and propofol. Hypotension occurred primarily after induction with propofol or ketamine-diazepam. These effects were a result of the combination of the direct effects of these induction agents on vasomotor tone, preload, and contractility. At the end of the anesthetic episode, MAP returned to values similar to those detected after induction but lower than those detected at baseline. This may be explained by the vasodilatory and negative inotropic effects of isoflurane, even at minimum alveolar concentrations,[24] despite the IV administration of lactated Ringer solution.

Respiratory profiles differed among the induction regimens. Although changes in respiratory rate were not significant because of high variability for induction with propofol, 3 dogs had apnea after induction with alfaxalone, whereas 1 dog had apnea after induction with tiletamine-zolazepam, and 1 dog had apnea after induction with propofol. This finding is in contrast to those of a study[10] that involved the use of escalating doses of propofol and alfaxalone in which propofol and alfaxalone did not cause apnea at doses and rates of administration similar to those of the

present study. This finding may have been affected by the rate of administration of the induction regimens, and the outcome may differ in premedicated patients receiving alfaxalone at a slower rate of injection. The high incidence of apnea explains the wide variability in Pa_{O_2}, $P_{ET}CO_2$, and $P_{ET_{ISO}}$ during the first 10 minutes after induction of anesthesia with alfaxalone and the hypoxemia detected after induction with alfaxalone and propofol. However, by M_{10}, hypoventilation had resolved for all induction regimens. Interestingly, hypoxemia also occurred in the absence of apnea in 1 dog after induction with ketamine-diazepam, whereas the apneic dog after induction with tiletamine-zolazepam was not hypoxemic. Apnea was not encountered after ketamine-diazepam administration, which confirmed its low potential to cause respiratory depression when used at clinical doses. Respiratory depression during general anesthesia is commonly estimated by evaluating Pa_{CO_2}. Clinically important respiratory depression can be seen at Pa_{CO_2} > 60 mm Hg, whereas normocarbia can be accompanied by some degree of hypoxemia (arterial O_2 saturation < 90% and Pa_{O_2} < 60 mm Hg).[7] In the present study, substantial respiratory depression was not detected for any of the induction regimens, although ventilation was decreased after induction until the end of the experimental period for all induction regimens, perhaps as a result of the depressant effects of isoflurane on the respiratory system.[25]

All induction regimens had little effect on measured metabolic variables, with only minor differences in base excess. Acid-base changes observed for the present study reflected mild respiratory acidosis associated with induction and maintenance of anesthesia. A significant decrease in pH was detected after induction of anesthesia with tiletamine-zolazepam and propofol. However, these changes were not clinically relevant, and they were consistent with the effects after IV administration of tiletamine-zolazepam to nonsedated dogs.[26] Overall serum concentrations of sodium, potassium, calcium, and lactate were higher in dogs after anesthetic induction with tiletamine-zolazepam than after induction with propofol, although values were still within reference limits. It is unlikely that infusion of lactated Ringer solution caused this change because such infusions during short-term procedures have no effect on blood electrolyte composition.[27] Lactate concentration > 2.5 mmol/L in anesthetized dogs reportedly indicates impaired tissue perfusion.[28] In the present study, lactate concentrations remained within the physiologic range for all induction regimens. The patterns for hemoglobin concentration and total protein concentration in the dogs of the present study (which had a time-dependent decrease in Hct, arterial hemoglobin concentration, and total protein concentrations in arterial and mixed-venous blood) were consistent with those reported in another study.[27] These changes were ascribed to hemodilution in the presence of no fluid loss via evaporation or conduction.

A limitation of the present study was the inconsistency in absolute values of RAP owing to the change in the brand of pressure transducer during the study, which limited the comparison of this variable among induction regimens. However, we were able to detect variations in RAP among time points within the same induction regimen. Cardiorespiratory and metabolic indices were measured in dogs in a light plane of anesthesia that were not subjected to any noxious stimuli. Therefore, it must be remembered that the results reported here may differ from those in clinical situations in which surgical procedures require a deeper anesthetic plane or administration of analgesics. Finally, although the thermodilution method is considered the criterion-referenced standard for use in validating other methods of measuring CO, that method has an inherent error rate of 10% to 20%,[29,30] which should be considered when interpreting hemodynamic data collected via the thermodilution method.

The induction regimens evaluated in the present study provided satisfactory induction of anesthesia and uncomplicated recovery from anesthesia. In subjects that did not receive preanesthetic sedatives and in which a light plane of anesthesia was maintained with isoflurane, cardiovascular and metabolic effects after induction with tiletamine-zolazepam were similar to those after induction with alfaxalone and ketamine-diazepam. The most striking difference in cardiovascular variables was between tiletamine-zolazepam and propofol with regard to heart rate after induction and during the anesthetic episode. The anesthetic regimens were administered IV in this study, and tiletamine-zolazepam induced minor respiratory changes, compared with changes after administration of alfaxalone, whereas metabolic variables were stable and within physiologic limits for all tested induction regimens. Results of the study reported here may guide veterinary anesthetists in the choice of anesthetic induction regimen for healthy dogs that do not receive preanesthetic sedatives. However, studies are needed on the cardiorespiratory effects of these induction regimens in patients with cardiovascular and respiratory compromise.

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Footnotes

a. Microsoft Excel, version 16.10, Microsoft Corp, Redmond, Wash.
b. Telazol, Zoetis Inc, Kalamazoo, Mich.
c. Alfaxan, Jurox Inc, Kansas City, Mo.
d. Zetamine, VetOne, Boise, Idaho.

e. Hospira Inc, Lake Forest, Ill.
f. PropoFlo, Abbott Laboratories, North Chicago, Ill.
g. Sevoflo, Abbott Laboratories, North Chicago, Ill.
h. Excel 210 MRI Compatible, Ohmeda, Madison, Wis.
i. Unilimb, Midmark, Dayton, Ohio.
j. Spectrum, Datascope Corp, Mahawah, NJ.
k. Masimo Technology, Irvine, Calif.
l. Gas Module GE, Datascope Corp, Mahawah, NJ.
m. Mindray Calibration Gas, Airgas Specialty Gases Inc, Lenexa, Kan.
n. Bair Hugger, Arizant Inc, Eden Prairie, Minn.
o. Surflo ETFE, Terumo Medical Corp, Somerset, NJ.
p. Performer Introducer Access Set, Cook Medical LLC, Bloomington, Ind.
q. West-Ward Pharmaceuticals Corp, Eatontown, NJ.
r. 0.9% for irrigation, Baxter Healthcare Corp, Deerfield, Ill.
s. Edwards Lifesciences Corp, Irvine, Calif.
t. P23XL-1, Becton Dickinson, Franklin Lakes, NJ.
u. DTXPlus, BD Medical Systems, Sandy, Utah.
v. RAPIDlab 1200 Systems, Siemens AG, Munich, Germany.
w. Protein/urine refractometer, Henry Schein Medical Inc, Dublin, Ohio.
x. Mac-Lab TRAM 451 Marquette, GE Medical Systems, Chicago, Ill.
y. Isoflo, Abbott Animal Health, Abbott Park, Ill.
z. Isotec 5, Datex-Ohmeda Inc, Helsinki, Finland.
aa. VetDAR, Dimple Hill Software LLC, Corvallis, Ore.
bb. JMP Pro, version 13.0.0, SAS Institute Inc, Cary, NC.

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