Effects of sevoflurane dose and mode of ventilation on cardiopulmonary function and blood biochemical variables in horses

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Objective—To quantitate effects of dose of sevoflurane and mode of ventilation on cardiovascular and respiratory function in horses and identify changes in serum biochemical values associated with sevoflurane anesthesia.

Animals—6 healthy adult horses.

Procedure—Horses were anesthetized twice: first, to determine the minimum alveolar concentration (MAC) of sevoflurane and second, to characterize cardiopulmonary and serum biochemical responses of horses to 1.0, 1.5, and 1.75 MAC multiples of sevoflurane during controlled and spontaneous ventilation.

Results—Mean (± SEM) MAC of sevoflurane was 2.84 ± 0.16%. Cardiovascular performance during anesthesia decreased as sevoflurane dose increased; the magnitude of cardiovascular depression was more severe during mechanical ventilation, compared with spontaneous ventilation. Serum inorganic fluoride concentration increased to a peak of 50.8 ± 7.1 µmol/L at the end of anesthesia. Serum creatinine concentration and sorbitol dehydrogenase activity reached their greatest values (2.0 ± 0.8 mg/dL and 10.2 ± 1.8 U/L, respectively) at 1 hour after anesthesia and then returned to baseline by 1 day after anesthesia. Serum creatine kinase, aspartate aminotransferase, and alkaline phosphatase activities reached peak values by the first (ie, creatine kinase) or second (ie, aspartate aminotransferase and alkaline phosphatase) day after anesthesia.

Conclusions and Clinical Relevance—Sevoflurane causes dose-related cardiopulmonary depression, and mode of ventilation further impacts the magnitude of this depression. Except for serum inorganic fluoride concentration, quantitative alterations in serum biochemical indices of liver- and muscle-cell disruption and kidney function were considered clinically unremarkable and similar to results from comparable studies of other inhalation anesthetics. (*Am J Vet Res* 2005;66:606–614)

Sevoflurane is the newest volatile anesthetic approved for use with human and, more recently, canine patients. It has received widespread publicity and is now used in private and university-based clinical practice[1-3] and in laboratory (quasi-clinical) settings[4-6] to anesthetize horses. Cardiovascular properties of sevoflurane have been studied in horses[7-10,a] and appear similar to those reported for isoflurane,[10-12] currently the most popular inhalation anesthetic for horses. With 2 exceptions,[8,10] all prior studies of sevoflurane were conducted with concurrent use of anesthetic adjuvant drugs. Added drugs confound interpretation of actions by sevoflurane. In the single report[8] in which only sevoflurane was used at multiple doses, cardiovascular and respiratory performances were studied on different occasions and in different horses and mode of ventilation was different for each study (eg, cardiovascular data were obtained only under conditions of **controlled ventilation [CV]**).

In the presently reported study of 6 horses, anesthesia was induced and maintained with only sevoflurane in O_2 and the cardiovascular effects were determined during CV (iso-$Paco_2$) and **spontaneous ventilation (SV)**. At the same time sevoflurane dose-response effects on respiratory function were collected during SV, selected serum biochemical (including serum fluoride ion) parameters associated with prolonged anesthesia with sevoflurane were measured.

Materials and Methods

Horses—Six healthy nonmedicated horses (2 females and 4 geldings) that were a mean ± SEM of 6.0 ± 0.6 (range, 3 to 8) years of age and weighed 513 ± 17 (range, 461 to 559) kg were studied. The group included 3 Standardbreds, 2 Thoroughbreds, and 1 Appaloosa.

Study conditions—The University of California, Davis, Animal Use and Care Administrative Advisory Committee approved the study. Horses were anesthetized on 2 occasions that were ≥ 20 days apart. The first time each horse was anes-

Received April 23, 2004.
Accepted July 14, 2004.

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Supported by the School of Veterinary Medicine's Center for Equine Health with funds provided by the Oak Tree Racing Association and the State of California satellite wagering fund and contributions by private donors.

Presented in part in abstract form at the Association of Veterinary Anaesthetists Semi-annual Meetings, New Castle-upon-Tyne, UK, March 1999 and Madrid, Spain, September 1999.

The authors thank Dr. Neil Willits for statistical assistance and Messrs. Ramon Cervantes, Don Hermes, Richard Morgan, M. (Bill) Perkins, Vince Long, and Larry Melton for technical assistance.

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thetized, the **minimal alveolar concentration (MAC)** of sevoflurane was determined, and during the second anesthesia, cardiovascular and respiratory systems performance was measured at 1.0, 1.5, and 1.75 multiples of the MAC of sevoflurane; the dose order was randomized. Responses were recorded during conditions of CV first and then SV at each multiple of MAC.

Anesthesia was always induced in the morning, following 8 to 12 hours of withholding food but not water; techniques were similar to those previously described.[11-13] Briefly, preanesthetic medication was not administered, and horses received only sevoflurane in O_2 for induction and maintenance of general anesthesia. Sevoflurane was administered first via a face mask and then by an endotracheal tube (internal diameter of 30 mm) connected to a standard large animal semiclosed anesthetic circle system. Sevoflurane was delivered from an agent-specific precision vaporizer[b] with a minimum O_2 delivery rate of 6 L/min. Following induction of anesthesia, horses were positioned in left lateral recumbency on a thick foam pad on a cart.

Inspired and end-expired gas concentrations of O_2 and CO_2 and sevoflurane were analyzed with polarographic[c] and infrared[d] gas analyzers, respectively. Analyzers were calibrated with multiple standards each day before induction of anesthesia, and the calibration was frequently monitored throughout the study day. Measured concentrations were corrected mathematically by use of the gas-specific calibration curves. Pharyngeal-esophageal temperature was monitored with a calibrated thermistor.[c] Lactated Ringer's solution was infused at a rate of 3 mL/kg/h by way of a catheter positioned in the left medial saphenous vein. The urinary bladder was catheterized to maintain an empty bladder during anesthesia and prior to recovery.

Heart rate (HR) and rhythm were obtained from a base-apex ECG tracing on a pen recorder.[f] Direct systolic arterial pressure and diastolic arterial pressure measurements were made on the same pen recorder via a strain gauge-transducer attached to a heparinized saline (0.9% NaCl) solution–filled catheter that was placed in the facial (MAC studies) or carotid (dose-response studies) arteries. The strain gauge was calibrated at the beginning of each experimental day by use of a mercury column, and during the studies, it was positioned level with the midsternum. The arterial pressure was averaged electronically. During the dose-response studies, a catheter was also percutaneously positioned in the main pulmonary artery trunk via the right jugular vein. The location of the pulmonary artery catheter was confirmed by observing a ventricular trace[f] and then advancing the catheter until a **pulmonary arterial pressure (PAP)** trace was obtained. Similar to carotid pressure, systolic PAP and diastolic PAP were measured and mean PAP was obtained by electronic dampening of the PAP signal. The carotid and pulmonary artery catheters also were necessary to measure cardiac output. Cardiac output was determined by the indocyanine green dye dilution technique according to procedures used in this laboratory for horse studies previously described.[11,12] A dose of 12.5 mg of green dye was injected via the pulmonary artery catheter for each cardiac output determination. The emerging dye curve was obtained from blood sampled via the carotid artery catheter and analyzed by a calibrated densitometer.[g] Cardiac output was then hand-calculated from the resultant dye curves. The mean value of ≥ 2 cardiac output determinations (usually 3) that did not differ by more than 10% was recorded for each anesthetic concentration. The green dye was always injected at the beginning of expiration and never during a breath administered by positive pressure ventilation (ie, the ventilator was briefly turned off for the time necessary to measure cardiac output). Stroke volume, total peripheral resistance, and cardiac output referenced to body mass (ie, cardiac output per kilogram and cardiac index) were computed by use of standard equations.

During SV, a calibrated pneumotachograph[h] positioned in the air inlet-outlet of a bag-in-barrel system was used to record respiratory rate and flow and time according to a previously described technique.[12] Expired minute volume was obtained by electronic integration of the expired flow signal recorded on the pen writer.[f] **Tidal volume (V_t)** was calculated, and expired minute volume and V_t were mathematically corrected from ambient conditions to that of body temperature, pressure, and water vapor saturated (BTPS). The mean value of analyses of 5 consecutive breaths was recorded.

Blood was anaerobically obtained at various times from either the arterial or the arterial and pulmonary artery catheters for P_{O_2}, P_{CO_2}, and pH analyses[g] (including assessment of Pa_{O_2}, Pa_{CO_2}, arterial pH, partial pressure of O_2 in pulmonary artery [mixed venous] blood, partial pressure of CO_2 in pulmonary artery [mixed venous] blood, pH value of pulmonary artery [mixed venous] blood, and arterial blood base balance). When arterial and pulmonary artery blood was withdrawn, it was done so simultaneously. Blood was slowly drawn into heparinized syringes over the course of 1 minute, and analysis was usually performed immediately. In the few cases where immediate analysis was not possible, the capped syringes were stored in ice and analysis was performed within 15 minutes of sample collection. Resulting values were corrected to the body temperature of the horse. The blood gas machine was used to calculate arterial base balance on the basis of a nomogram for human blood. The Hct and plasma protein concentration (via refractometer) were also determined.

MAC measurements—The MAC of sevoflurane that just prevented movement in response to ≥ 60 seconds of electrical stimulation (50 V; 5 cycles/s; 10 milliseconds in duration[e]) of oral mucous membranes was determined for each spontaneously ventilating horse according to usual techniques in our laboratory.[13] Alveolar sevoflurane concentration was determined from hand-drawn end-tidal gas samples, and end-tidal concentration was held constant for ≥ 20 minutes prior to stimulation. Body temperature changes and other known modifiers of MAC were avoided. The mean value of ≥ 3 MAC determinations of sevoflurane was reported for each horse. Following the determination of MAC, anesthesia was discontinued and the horses recovered in a padded recovery stall.

Dose-response cardiovascular measurements—At least 20 days following MAC determination, horses were again similarly anesthetized and prepared. During the 30 minutes following induction of anesthesia and tracheal intubation, the horse was prepared for study while the end-tidal sevoflurane concentration was maintained at the equivalent of 1.2 to 1.5 MAC. During this preparation phase, horses breathed spontaneously. Approximately 45 minutes after the first breath of anesthetic, the inspired sevoflurane concentration was either increased or decreased to attain the first study concentration. Doses studied were 1.0×, 1.5×, and 1.75× the MAC of sevoflurane for each horse, and the order was randomized for each horse before studying the first horse. Doses of 1.0 and 1.5 were selected because they spanned usual clinical doses of inhalation anesthesia. They also were common to a previous study[11] of isoflurane in horses and thus facilitated eventual indirect comparison of actions of the 2 agents. A sevoflurane dose of 1.75 MAC was selected as the highest dose because it was concluded from a general literature review and results of a preliminary sevoflurane trial in a horse not included in the presently reported group that at least some subsequently studied horses would likely not survive a sevoflurane dose of 2.0 MAC.

By 1 hour of anesthesia (determined from the time of the first breath of sevoflurane), **intermittent positive pressure ventilation (IPPV)** was instituted to attain and maintain a $Paco_2$ of 45 ± 3 mm Hg via a peak inspiratory pressure of 18 to 22 cm H_2O (conditions of CV). The peak inspiratory pressure was measured with a calibrated strain-gauge transducer attached to a port at the proximal (mouth) end of the endotracheal tube. Constant conditions of IPPV and end-tidal sevoflurane concentration were maintained for 20 minutes before making cardiopulmonary measurements. Procedural order was always as follows: blood sample collection, followed by measurements of vascular pressures, respiratory gas flow and pressures, and finally cardiac output. At the completion of these measurements, the end-tidal anesthetic concentration was maintained but IPPV was discontinued. Spontaneous ventilation began after a brief time as $Paco_2$ increased to breathing threshold. Following ≥ 10 minutes of constant conditions of anesthetic dose and SV, measurements were repeated. At the end of measurements during SV, IPPV was similarly reinstituted and a new anesthetic concentration established. Once arriving at the appropriate sevoflurane dose and $Paco_2$, conditions were again maintained constant for 20 minutes before the second set of measurements during CV. This was then followed by similarly maintaining end-tidal dose of sevoflurane and again reestablishing conditions of SV. Again, after ≥ 10 minutes of constant conditions, measurements during SV were repeated. When these measurements were completed, CV was again started and the third and final anesthetic dose was established. After the appropriate period of constant conditions, measurements at this dose were similarly conducted during CV and SV.

Recovery from anesthesia—On both occasions after anesthesia, the endotracheal tube was disconnected from the breathing circuit and the horse was moved to a padded recovery stall. Oxygen was insufflated via the endotracheal tube at 15 L/min. Each horse was monitored for signs of arousal, including first move, first attempt to sternal recumbency, first attempt to stand, time of standing, and time at tracheal extubation. The senior author, according to a previous scheme, subjectively graded recovery.[14,15]

Blood sample collection and chemical analysis—Between 30 and 60 minutes before anesthesia, blood from the jugular vein was collected percutaneously from 5 of the 6 horses for biochemical and fluoride ion analyses. Samples for analysis were also obtained at 2 hours and the end of anesthesia (fluoride ion analysis only) and at 1 hour and 1, 2, and 4 days following recovery from anesthesia. Serum from these samples was obtained within 1 hour of venipuncture and stored at –20°C until analyzed (usually within a day, but at least by the fourth day after venipuncture) at the Clinical Pathology Laboratory of the University of California, Davis, Veterinary Medical Teaching Hospital. Samples were analyzed for serum aspartate transaminase; creatine kinase; alkaline phosphatase; γ-glutamyltransferase; and sorbitol dehydrogenase activities and total bilirubin, direct bilirubin (from which indirect bilirubin was calculated), BUN, creatinine, glucose, inorganic phosphate, and calcium concentrations.

Serum was also obtained from blood samples collected within 1 hour of induction of anesthesia (baseline), at 2 hours of anesthesia, at the end of anesthesia, and at 1 hour and 1 and 2 days after anesthesia for analysis of inorganic fluoride. The serum was harvested within 1 hour of venipuncture, and all samples were stored at –70°C. At the time of inorganic fluoride analysis, 1 mL of serum was mixed thoroughly with 1 mL of fluoride analysis diluent[j] in a plastic test tube. Each sample was then analyzed by use of an ion-specific electrode-digital ion analyzer.[k] Serum inorganic fluoride concentration was determined against a fluoride calibration curve consisting of 0.05-, 0.1-, 0.3-, 1-, 3-, and 10-ppm (mg/L) fluoride standards. The lower limit of detection was considered 0.05 ppm or 2.63 µmol/L. Each standard was prepared by serial dilution from stock fluoride standard (100 ppm) in distilled-deionized water and then diluted with fluoride analysis diluent and analyzed the same as serum samples. Recoveries of 96%, 96% to 104%, and 90% to 100% were obtained for serum fluoride over spikes of 0.05, 0.10, and 1 ppm, respectively.

Data analysis—Data were grouped, and mean (± SEM) values were calculated for cardiopulmonary, serum biochemical, and recovery data. Repeated-measures ANOVA was used to test for differences on the basis of anesthetic dose and ventilation type. Raw and logarithmically transformed data were used for the chemical and the cardiopulmonary data. Preanesthetic values served as baseline for the biochemical analyses. A paired *t* test or Wilcoxon signed rank test was used to analyze data describing events of anesthetic recovery. Significance for all tests was set at $\alpha = 0.05$.

Results

MAC—Horses were anesthetized for 3.24 ± 0.27 hours for determination of MAC. The MAC of sevoflurane in these horses was 2.84 ± 0.16 **volume percent (vol%)**. The inspired concentration of sevoflurane at MAC was 3.03 ± 0.19%, and body temperature was

Table 1—Mean (± SEM) values of respiratory function indices, hematologic variables, and esophageal temperature in 6 horses anesthetized with various doses (ie, multiples of the minimum alveolar concentration [MAC]) of sevoflurane in O_2 during controlled or spontaneous ventilation.

	Controlled ventilation			Spontaneous ventilation		
Variables	**1.0 MAC**	**1.5 MAC**	**1.75 MAC**	**1.0 MAC**	**1.5 MAC**	**1.75 MAC***
Pao_2 (mm Hg)	476 ± 37	447 ± 40	381 ± 67	348 ± 60	242 ± 38	261 ± 39
$Paco_2$ (mm Hg)	42.4 ± 1.3	44.0 ± 1.1	45.2 ± 0.9	69.9 ± 4.4	84.8 ± 6.3	67.4 ± 4.4
pHa	7.42 ± 0.02	7.40 ± 0.02	7.39 ± 0.01	7.26 ± 0.02	7.18 ± 0.03	7.25 ± 0.02
BB (mEq/L)	2.48 ± 1.17	1.88 ± 0.98	2.38 ± 0.89	2.80 ± 0.99	1.90 ± 1.13	2.02 ± 0.79
$Ppao_2$ (mm Hg)	40.2 ± 1.3	35.9 ± 1.5	30.3 ± 1.8	47.9 ± 4.0	46.5 ± 1.9	44.8 ± 7.7
$Ppaco_2$ (mm Hg)	52.5 ± 1.5	55.7 ± 1.2	59.0 ± 2.2	75.6 ± 4.6	88.5 ± 5.4	76.8 ± 2.2
Hct (%)	33.5 ± 1.7	33.9 ± 1.4	32.0 ± 1.8	34.5 ± 2.1	36.5 ± 2.3	35.2 ± 1.0
PP (g/dL)	5.95 ± 0.20	5.60 ± 0.17	5.57 ± 0.09	5.95 ± 0.20	5.82 ± 0.25	5.63 ± 0.08
Temp (°C)	37.2 ± 0.2	37.1 ± 0.2	37.2 ± 0.2	37.3 ± 0.2	37.1 ± 0.2	37.2 ± 0.2

*n = 5.

Pao_2 = Arterial partial pressure of oxygen. $Paco_2$ = Arterial partial pressure of carbon dioxide. pHa = Arterial pH. BB = Arterial base balance. $Ppao_2$ = Pulmonary arterial (mixed venous) partial pressure of oxygen. $Ppaco_2$ = Pulmonary arterial (mixed venous) partial pressure of carbon dioxide. PP = Plasma protein concentration. Temp = Esophageal temperature.

37.8 ± 0.3°C. This value for MAC was greater than that reported earlier for horses.[16]

Respiratory responses to sevoflurane doses—One horse (ie, horse 6) became apneic during an attempt to reach steady state at 1.75 MAC, and as a result, measurements were not made in this horse at this anesthetic concentration during SV. During CV, ventilation was mechanically maintained constant. For example, the peak inspiratory pressure was 20 ± 0.36 cm H_2O, and the $Paco_2$ was maintained in a narrow reference range of values for unmedicated healthy horses at sea level (43.8 ± 0.7 mm Hg).[12] During CV, the $Paco_2$ was always less and the arterial partial pressure of oxygen and arterial pH were always greater than values obtained during SV (**Tables 1 and 2**). No significant differences were found on the basis of anesthetic dose for a given mode of ventilation. Contrary to these observations, mixed-venous (pulmonary artery) blood gas values were less during CV, compared with conditions of SV. Minute and V_t decreased with increasing anesthetic dose during SV, but the differences were not significant ($P = 0.067$ and 0.066, respectively; **Table 3**). The Hct, plasma protein concentration, and body temperature did not change in relation to anesthetic dose or mode of ventilation.

Table 2—Summary of analysis of cardiopulmonary data from 6 horses anesthetized with various doses of sevoflurane in O_2.

	Factors evaluated for the determination of significant* differences				
Variables	**Mode of ventilation versus sevoflurane MAC**	***P* value**	**MAC multiples of sevoflurane versus mode of ventilation**	***P* value**	**Ventilation × MAC *P* value**
SAP	SV > CV	0.005	(Both) 1.0 > 1.5 > 1.75	< 0.001	0.045
	MAC 1.0	0.020	(CV) 1.0 > 1.5 > 1.75	< 0.001	—
	MAC 1.5	0.019	(SV) 1.0 > 1.5, 1.75	< 0.001	—
	MAC 1.75	0.009	—	—	—
DAP	SV > CV	0.034	(Both) 1.0 > 1.5 > 1.75	< 0.001	0.073
	MAC 1.0	0.028	(CV) 1.0 > 1.5 > 1.75	< 0.001	—
	MAC 1.75	0.028	(SV) 1.0 > 1.5, 1.75	< 0.001	—
MAP	SV > CV	0.013	(Both) 1.0 > 1.5 > 1.75	< 0.001	0.054
	MAC 1.0	0.012	(CV) 1.0 > 1.5 > 1.75	< 0.001	—
	MAC 1.5	0.047	(SV) 1.0 > 1.5, 1.75	< 0.001	—
	MAC 1.75	0.015	—	—	—
HR	NS	0.085	(Both) 1.75 > 1.0	0.012	0.569
SV					
	SV > CV	0.003	(Both) 1.0, 1.5 > 1.75	< 0.001	0.003
	MAC 1.5	0.007	(CV) 1.0 > 1.5 > 1.75	< 0.001	
	MAC 1.75	0.006	(SV) 1.0, 1.5 > 1.75	0.008	
CO	SV > CV	0.002	(Both) 1.0, 1.5 > 1.75	0.003	0.003
	MAC 1.5	0.005	(CV) 1.0 > 1.5 > 1.75	< 0.001	—
	MAC 1.75	0.003	—	—	—
CI	SV > CV	0.005	(Both) 1.0, 1.5 > 1.75	0.003	0.003
	MAC 1.5	0.005	(CV) 1.0 > 1.5 > 1.75	< 0.001	—
	MAC 1.75	0.003	—	—	—
TPR	CV > SV	0.010	(Both) 1.0 > 1.5	0.005	0.009
	MAC 1.5	0.007	(SV) 1.0 > 1.5, 1.75	0.002	—
	MAC 1.75	0.022	—	—	—
SPAP	SV > CV	< 0.001	NS	0.252	0.789
DPAP	SV > CV	0.002	NS	0.832	0.879
MPAP	SV > CV	< 0.001	NS	0.819	0.813
Pao_2	CV > SV	0.008	NS	0.361	0.107
$Paco_2$	SV > CV	< 0.001	NS	0.063	0.136
pHa	CV > SV	< 0.001	NS	0.083	0.134
BB	NS	0.966	NS	0.575	0.244
$Ppao_2$	SV > CV	0.016	(Both) 1.0 > 1.75	0.019	0.359
$Ppaco_2$	SV > CV	< 0.001	(Both) 1.5 > 1	0.013	0.075
	MAC 1.0	0.003	(SV) 1.5 > 1.75, 1.0	0.014	—
	MAC 1.5	< 0.001	—	—	—
	MAC 1.75	0.002	—	—	—
Hct	NS	0.148	NS	0.560	0.485
PP	NS	0.098	NS	0.068	0.184
Temp	NS	0.447	NS	0.670	0.011

*Values of $P < 0.05$ considered significant.

SAP = Systolic arterial pressure. SV = Spontaneous ventilation. CV = Controlled ventilation. DAP = Diastolic arterial pressure. MAP = Mean arterial pressure. HR = Heart rate. CO = Cardiac output. CI = Cardiac index. TPR = Total peripheral resistance. SPAP = Systolic pulmonary arterial pressure. NS = Not significant. DPAP = Diastolic pulmonary arterial pressure. MPAP = Mean pulmonary arterial pressure. — = NA. *See* Table 1 for remainder of key.

Table 3—Mean ± SEM values of respiratory function indices in 6 horses anesthetized with various doses of sevoflurane in O_2 during spontaneous ventilation.

	Spontaneous ventilation		
Variables	**1.0 MAC**	**1.5 MAC**	**1.75 MAC***
f (breaths/min)	3.2 ± 0.6	2.7 ± 0.3	3.9 ± 0.5
V_t (L/breath)	9.85 ± 1.28	8.04 ± 0.76	6.66 ± 0.52
V_E (L/min)	28.10 ± 5.00	22.37 ± 3.19	25.16 ± 2.43
Peak inspiratory gas flow (L/min)	438 ± 55	364 ± 37	318 ± 40
Peak expiratory gas flow (L/min)	562 ± 46	516 ± 42	451 ± 52

*n = 5.
f = Respiratory frequency. V_t = Tidal volume. V_E = Expired minute volume.

Table 4—Mean ± SEM values of cardiovascular function in 6 horses anesthetized with various doses of sevoflurane in O_2 during controlled or spontaneous ventilation.

	Controlled ventilation			Spontaneous ventilation		
Variables	**1.0 MAC**	**1.5 MAC**	**1.75 MAC**	**1.0 MAC**	**1.5 MAC**	**1.75 MAC***
SAP (mm Hg)	108.8 ± 7.8	67.2 ± 5.4	53.5 ± 3.0	121.0 ± 8.2	87.2 ± 8.2	75.6 ± 4.8
DAP (mm Hg)	78.0 ± 5.9	47.3 ± 3.3	39.3 ± 2.5	84.5 ± 7.1	56.2 ± 6.6	53.0 ± 5.4
MAP (mm Hg)	88.2 ± 6.5	53.8 ± 3.9	44.0 ± 2.7	96.7 ± 7.4	66.3 ± 7.1	60.6 ± 5.1
HR (beats/min)	40.9 ± 2.1	45.2 ± 1.7	45.9 ± 2.1	42.5 ± 2.5	45.0 ± 1.9	47.6 ± 2.6
SV (mL/beat)	747 ± 63	494 ± 56	323 ± 28	850 ± 86	899 ± 99	605 ± 99
CO (L/min)	30.1 ± 1.9	22.2 ± 2.2	14.7 ± 1.1	36.1 ± 4.7	40.2 ± 4.4	28.1 ± 4.0
CI (mL/kg/min)	59.0 ± 4.4	43.6 ± 4.9	28.5 ± 1.7	70.6 ± 9.2	77.5 ± 7.0	55.2 ± 6.7
TPR (dynes·sec/cm^5)	240 ± 25	202 ± 22	249 ± 30	230 ± 36	142 ± 23	193 ± 40
SPAP (mm Hg)	28.2 ± 1.5	27.3 ± 1.0	28.5 ± 0.9	35.3 ± 2.4	35.7 ± 1.3	33.4 ± 1.8
DPAP (mm Hg)	18.3 ± 1.8	18.2 ± 0.7	18.2 ± 0.7	22.0 ± 2.0	23.5 ± 2.5	23.0 ± 1.2
MPAP (mm Hg)	21.6 ± 1.6	21.2 ± 0.8	20.7 ± 0.7	26.4 ± 2.1	27.6 ± 1.9	26.5 ± 1.3

*n = 5.
See Table 2 for key.

Cardiovascular responses to sevoflurane doses—The cardiovascular changes produced by altering the end-tidal concentration of sevoflurane during CV and SV were determined (**Table 4**). In general, cardiovascular performance decreased as end-tidal sevoflurane concentration increased and the magnitude of depression for a given dose of sevoflurane was greater during CV, compared with SV.

As mentioned, 1 horse (horse 6) became apneic during SV before the 1.75 MAC steady state condition was realized (during CV at 1.75 MAC, this horse had an MAP of 33 mm Hg and a cardiac output per kilogram of 26 mL/min/kg). Therefore, the resulting composite number of observations for 1.75 MAC during SV is 5 instead of 6. The order of anesthetic doses studied in this horse was 1.0, 1.75, and 1.5 MAC. As a result of the 4 minutes of apnea prior to the development of the 1.75 MAC steady state condition, the decision was made to abort measurements at this stage. The inspired concentration of sevoflurane was rapidly decreased, and after reaching a lower alveolar concentration and improved cardiovascular performance, CV was reinstituted. Subsequent measurements made at the third and final level of anesthesia (ie, 1.5 MAC) proceeded without incidence.

Overall arterial pressure decreased in a dose-dependent manner and was always greater during SV, compared with during CV (Table 4; **Figure 1**). Changes in arterial pressure were largely caused by changes in cardiac output because total peripheral vascular resistance did not change considerably. Total peripheral resistance was significantly greater during CV, compared with SV.

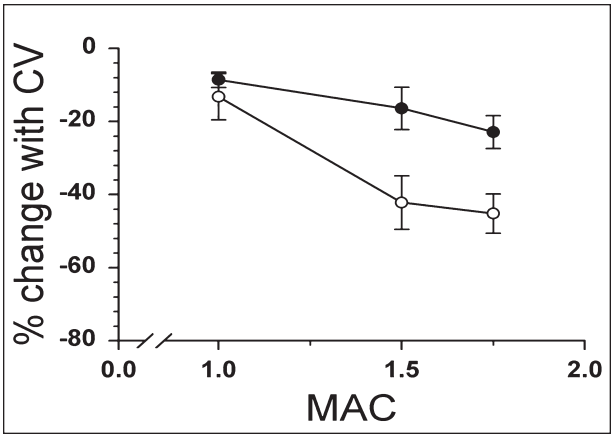

Figure 1—Mean (± SEM) decreases in mean arterial pressure (closed circles) and cardiac output per kilogram (open circles) contributed by conditions of controlled ventilation (CV) relative to conditions of spontaneous ventilation at given doses of sevoflurane (expressed as multiples of the minimum alveolar concentration [MAC]).

Cardiac output (absolute and indexed) decreased with increasing anesthetic dose, and the effect was greatest during CV (Table 4; Figure 1). The depression was notably consistent during CV (eg, values at 1.0 MAC > 1.5 MAC > 1.75 MAC), whereas during SV, values at

1.0 and 1.5 MAC were similar to each other but both values were greater than at 1.75 MAC. Cardiac output decreased as a result of a decrease in stroke volume, regardless of the mode of ventilation. Heart rate increased at the highest sevoflurane dose during CV and SV. The absolute HR was consistently in the higher end of reference range values for anesthetized horses over the entire course of anesthesia. The PAP was lower during CV, compared with SV, but regardless of the mode of ventilation, the PAP did not change in response to variation in anesthetic dose.

Recovery from anesthesia with sevoflurane—Anesthetic duration averaged 5.2 hours for the second anesthesia period (**Table 5**). The only significant differences observed between the recovery of horses after the first anesthesia in comparison to after the second anesthesia was that anesthetic duration, MAC hours of sevoflurane exposure, time from anesthetic circuit disconnection to the ability of the horse to stand, and the time to tracheal tube extubation were all greater following the second anesthesia. In all instances, the response time following the second anesthesia was approximately double that of the first. Quality of recovery for the 6 horses was subjectively graded as follows for the first and second anesthesia periods, respectively: excellent for 2 and 0 horses, good for 3 and 3 horses, and fair for 1 and 3 horses.

The horse (horse 6) that became apneic during SV awoke from the second anesthesia with some signs of muscle soreness and general malaise. This horse did not have an especially violent recovery, although it received an overall subjective recovery behavior grade of fair (in part related to the number of attempts [6] to attain and maintain a sternal and standing [3] posture). Following recovery, this horse appeared stiff and reluctant to move. Although the horse ate hay shortly following recovery, it was less interested than usual in eating for a day following anesthesia. Because of the muscle soreness and reluctance to move that was observed immediately after standing, a clinical diagnosis of anesthesia-associated myopathy was made and an early decision was made to therefore not include subsequent results of postanesthesia serum biochemical analysis in the summarized responses (**Table 6**). This horse was given a nonsteroidal anti-inflammatory drug for 3 days. Recovery of this horse from the first anesthesia with sevoflurane was unremarkable.

Serum biochemical analysis—All preanesthesia values were within reference ranges for our clinical pathology laboratory except for bilirubin (total and indirect bilirubin). As a result of complications with the horse (horse 6) with suspected postanesthesia myopathy, serum biochemical analysis results are summarized without including data from this horse (Table 6). An increase in mean serum creatine kinase and sorbitol dehydrogenase activities and creatinine, glucose, and inorganic phosphorous concentrations and a decrease in mean calcium concentration were observed at 1 hour after anesthesia. By 1 day after anesthesia, serum sorbitol dehydrogenase activity and creatinine and calcium concentrations had returned to baseline. Serum glucose and inorganic phosphorous concentrations decreased; glucose concentration approached baseline but was still significantly greater than baseline, whereas inorganic phosphorous concentration decreased to a significantly less than baseline value. Serum creatine kinase and alkaline phosphatase activities increased further from baseline by 1 day after anesthesia, and by this time, aspartate transaminase activity was also significantly increased. Aspartate transaminase, creatine kinase, and alkaline phosphatase activities were highest on postanesthesia day 2. Although values for all 3 analytes were still significantly greater than baseline on postanesthesia day 4, all had been substantially decreased. Selected control and some postanesthesia results for the horse with suspected postanesthesia myopathy (horse 6) include the following for control, 1-hour, and 1-day samples, respectively: creatinine, 1.2, 2.7, and 1.2 mg/dL; BUN, 23, 29, and 23 mg/dL; creatine kinase, 172, 3,720, and 12,516 U/L; and sorbitol dehydrogenase, 4, 90, and 13 U/L.

Serum fluoride ion analysis—Results of fluoride analysis before, during, and following anesthesia with sevoflurane were recorded (**Table 7**). Unfortunately, samples for 1 horse (ie, horse 1) were inadvertently discarded and therefore not analyzed. Samples from the horse with suspected postanesthesia myopathy (horse 6) are included because any notable influence on bio-

Table 5—Mean ± SEM values of recovery events for 6 horses anesthetized with various doses of sevoflurane in O_2.

Event	Anesthetic periods	
	First	Second
Anesthetic duration (h)*	3.24 ± 0.27	5.21 ± 0.13†
MAC•h (h)†	3.43 ± 0.27	6.97 ± 0.24†
Time to first move (min) §	5.00 ± 1.61	8.33 ± 1.56
Time to first attempt to sternal posture (min)	6.25 ± 1.28	15.50 ± 3.17
Time to first attempt to stand (min)	10.50 ± 1.88	20.83 ± 3.11
Time to standing (min)	14.33 ± 1.48	26.17 ± 3.98†
Attempts to maintain sternal (No.)	1.83 ± 0.31	3.50 ± 0.89
Attempts to stand (No.)	2.33 ± 0.56	3.00 ± 0.68
Time to extubation (min)	11.67 ± 1.54	22.33 ± 4.15†
Quality of recovery score‖	4.12 ± 0.31	3.50 ±0.22

*Time from first breath of sevoflurane to time of endotracheal tube disconnect from the anesthetic breathing circuit. †Significantly ($P < 0.05$) higher values after the second anesthesia, compared with the first anesthesia. ‡Summary of periods at multiples of MAC. §Time from disconnect from the anesthetic breathing circuit and stable level of anesthesia ‖Determined on a scale of 1 to 5 for poor to excellent, respectively.

Table 6—Mean ± SEM values of serum biochemical analysis results in 5 horses before and after anesthesia with sevoflurane in O_2.

Analyte	Reference values*	Baseline	Sample collection times following standing			
			1 h	1 d	2 d	4 d
AST (U/L at 37°C)	138–409	212 ± 26	209 ± 26	803 ± 261†	830 ± 249†	701 ± 213†
CK (U/L at 37°C)	119–287	227 ± 42	941 ± 324†	4,435 ± 1,595†	2,392 ± 880†	716 ± 183†
ALP (U/L at 37°C)	86–285	80 ± 7	80 ± 6	98 ± 9†	101 ± 9†	96 ± 8†
TBil (mg/dL)	0.5–2.3	2.92 ± 0.48	2.94 ± 0.48	4.12 ± 0.88	2.56 ± 0.41	1.88 ± 0.35
IBil (mg/dL)	0.3–1.7	2.88 ± 0.61	2.85 ± 0.61	3.96 ± 0.87	2.42 ± 0.40	1.70 ± 0.36
GGT (U/L at 37°C)	8–22	10.6 ± 0.5	9.4 ± 0.5	10.8 ± 0.8	11.6 ± 0.7	11.6 ± 0.9
SDH (U/L at 37°C)	0–8	4.2 ± 0.7	10.2 ± 1.8†	3.6 ± 0.7	2.8 ± 0.2	2.6 ± 0.2
BUN (mg/dL)	12–27	20.8 ± 1.4	23.4 ± 1.9	21.2 ± 1.2	19.8 ± 1.5	20.4 ± 1.5
Creatinine (mg/dL)	0.9–2.0	1.16 ± 0.13	2.02 ± 0.33†	1.24 ± 0.18	1.16 ± 0.15	1.22 ± 0.20
Glucose (mg/dL)	59–122	92 ± 3	149 ± 17†	118 ± 1†	98 ± 8	98 ± 8
Pi (mg/dL)	2.1–4.7	3.2 ± 0.3	5.4 ± 0.4†	1.6 ± 0.3†	2.5 ± 0.2	4.2 ± 0.4
Ca (mg/dL)	12.1–13.7	11.0 ± 0.4	9.6 ± 0.6†	10.8 ± 0.6	11.2 ± 0.5	11.5 ± 0.5

*Source: Clinical Pathology Laboratory, Veterinary Medical Teaching Hospital, University of California, Davis. †Significantly ($P < 0.05$) different from baseline values.

AST = Aspartate aminotransferase. CK = Creatine kinase. ALP = Alkaline phosphatase. TBil = Total bilirubin. IBil = Indirect bilirubin. GGT = γ-glutamyltransferase. SDH = Sorbitol dehydrogenase. Pi = Inorganic phosphorus. Ca = Calcium.

Table 7—Individual and mean ± SEM values of serum inorganic fluoride test results in 5 horses before, during, and after anesthesia with sevoflurane in O_2.

Horse No.*	MAC·h	Baseline value	Serum inorganic fluoride (mmol/L)				
			Anesthesia time		Time after anesthesia		
			2 h	End	1 h	1 d	2 d
2	7.27	2.63	32.63	42.11	37.37	13.16	6.32
3	6.92	3.68	28.42	63.16	63.16	18.95	6.32
4	6.49	3.16	33.16	31.05	21.05	12.63	4.21
5	8.01	2.11	36.84	70.05	68.42	16.32	7.37
6	6.66	2.63	22.11	47.37	50.00	10.53	3.16
Mean	7.07 ± 0.27	2.84 ± 0.27	30.63 ± 2.51†	50.75 ± 7.07†	48.00 ± 8.63†	14.32 ± 1.48†	5.48 ± 0.77†

*Horse numbers assigned in order of study; fluoride concentrations not determined for horse number 1. †Significantly ($P < 0.05$) different from baseline value.

transformation of sevoflurane as a result of the adverse circumstances associated with this horse was unlikely. However, if there had been an influence, the effect would be to likely decrease, not increase, serum inorganic fluoride concentration. Therefore, any resultant bias would be against the expected anesthesia-related increase in serum inorganic fluoride ion concentration.

Baseline serum inorganic fluoride concentrations in this study were within the reference range of the laboratory for clinically normal horses. Serum inorganic fluoride concentration significantly increased by 2 hours of anesthesia and reached a peak in most horses by the end of anesthesia. Little change was found during the first hour after anesthetic recovery, but by 1 day after anesthesia, fluoride concentrations had decreased by approximately 70% from the concentration found at the end of anesthesia. Serum fluoride concentrations remained significantly increased from baseline for 2 days after anesthesia.

Discussion

Reports[7,16] on the use of sevoflurane in horses first appeared in 1994. During the next few years, numerous reports[1,4,8,9,a]describing the use of sevoflurane under differing conditions (which usually included anesthetic adjuvant drugs) added to our knowledge on its use in horses.During this period, Aida et al[16] first described the anesthetic potency (ie, MAC) of sevoflurane in unmedicated horses and then reported on its cardiopulmonary effects during conditions of eucapnia and CV in various groups of horses.[8] Because adjuvant drugs were not used and therefore did not confound interpretation, results of these investigations[8,16] have been of fundamental importance and have been used as baseline data to guide further study and clinical use of sevoflurane for nearly a decade. Purposes of our study included comparison of our results to those of previous notable studies[8,16] and to add new information where there have been important gaps in our basic knowledge of sevoflurane use in horses. To accomplish these goals, we purposely included some overlap in study method and protocol to provide a basis of comparison with some portions of the earlier work.[8,16] Results of our study confirm most of the previous similarly derived findings but also provide data that support a modified view of some aspects of sevoflurane action in horses. Finally, additional new data from our study extends knowledge of sevoflurane baseline information.

The MAC of sevoflurane determined in our study was 2.84 ± 0.16 vol%, which is approximately 23% greater than that reported for horses in the study by

Aida et al[16] (2.31 ± 0.04 vol%). Although the difference between these 2 values is substantial, these limited data do not provide the requisite evidence to determine that these differences represent an important biological difference. Regardless, evidence exists that MAC of sevoflurane in horses is greater than originally reported and closer to the value determined in our study. For example, Aida et al[16] reported that during induction of anesthesia with only sevoflurane, their horses went from a standing to a recumbent posture at 2.54 ± 0.7 (end-tidal)%. This is 10% greater than the MAC they reported for these horses. From broader experience, it is reasonable to assume that MAC would be greater (perhaps 10% to 20% greater) than the concentration that would allow a horse to stand. Such information suggests that the MAC was underestimated. Clarke et al[a] reported the MAC of sevoflurane in Welsh Mountain Ponies as 2.46 ± 0.38%. However, general anesthesia was first induced in these ponies with xylazine (1.1 mg/kg, IV) and ketamine (2 mg/kg, IV). This dose of xylazine would be expected to have a decreasing effect on MAC for ≥ 3 hours in horses.[17] Ketamine also decreases the MAC in horses.[18] The duration of effect of this dose of ketamine (by itself or in combination with other drugs) on MAC in horses is unknown but is prolonged in rats.[19] Consequently, all things considered, the MAC value determined in the aforementioned ponies also likely underestimates the true MAC of sevoflurane in healthy, otherwise unmedicated equines.

Similar to results of a past report,[8] we found that horses anesthetized with only sevoflurane typically breathe at a low frequency and are hypercapnic. The magnitude of respiratory frequency and $Paco_2$ observed, especially with a low dose of sevoflurane, in horses (eg, 1.0 MAC) is similar to findings when horses are anesthetized with isoflurane.[11,12] When the sevoflurane dose was increased to 1.5 MAC, the $Paco_2$ increased by a mean value of 15 mm Hg, suggesting a more potent respiratory depressant effect (ie, steeper slope to the plotted anesthetic dose vs $Paco_2$ line) than for isoflurane. A further increase to a sevoflurane dose of 1.75 MAC caused apnea in 1 horse of our study and an unexplained mean $Paco_2$ that is similar to that found with 1.0 MAC; the pulmonary arterial (mixed venous) partial pressure of carbon dioxide values are in support of the accuracy of these data. Our $Paco_2$ data at 1.0 to 1.5 MAC fit closely with data of Aida et al,[8] especially when compared on the basis of absolute sevoflurane concentration as opposed to data referenced to MAC multiples. Regardless, the relative potency of sevoflurane (compared with other inhalation anesthetics) as a respiratory depressant is unresolved from the results of our and other studies.[8,12,13]

Our findings compare closely (especially on the basis of absolute sevoflurane concentration) to the reported data of Aida et al[8] and indicate that sevoflurane causes cardiovascular depression on a dose-related basis during CV and that at least following indirect comparison, sevoflurane action is less depressing than halothane but similar to isoflurane at least up to 1.5 MAC.[11] Beyond 1.5 MAC, our results suggest that sevoflurane is of greater insult to cardiovascular performance than is isoflurane. For example, mean arterial pressure and cardiac output per kilogram were both greater at an isoflurane dose of 2.0 MAC than at a sevoflurane dose of 1.75 MAC; for cardiac output, the magnitude of depression was notable. It is also interesting to mention that in horses anesthetized with sevoflurane, HR was often increased and total peripheral resistance decreased, compared with values from horses similarly anesthetized with isoflurane.[11]

Spontaneous ventilation favorably modifies the dose-depressing effect of sevoflurane on cardiovascular function. Variables such as arterial pressure and cardiac output per kilogram during SV are less depressed, compared with conditions of CV. Mode of ventilation did not appear to markedly influence absolute values of HR and total peripheral resistance because like our experience with CV, HR was often greater and total peripheral resistance was less than that generally experienced with other contemporary volatile anesthetics in horses. On the other hand, indirect comparison with results of another investigation of horses suggests that the use of adjuvant drugs lessens the increase in HR during anesthesia with sevoflurane.[9,20]

Times for various events during recovery from anesthesia with sevoflurane were consistent and, perhaps not surprisingly, influenced by duration of anesthesia.[21] Our current data, compared with that of a prior study[22] of recovery behavior of horses anesthetized with isoflurane in our laboratory, support those of Matthews et al,[20] who found that recovery times following similar times of anesthesia with sevoflurane are usually shorter than events following anesthesia with isoflurane. It is important to distinguish that such comparisons were made in the absence of recovery-modifying drugs because use of such drugs would minimize or abolish any difference related to the physical characteristics of the volatile agents.

Results of prior studies reveal little change in serum biochemical variables following short-term exposure to sevoflurane (ie, approx 1.5 and 2.6 hours during the studies of Hikasa et al[7] and Aida et al,[8] respectively). Results from our study were more remarkable. Serum biochemical evidence of hepatic and skeletal muscle cellular disruption and altered kidney function was found immediately following anesthetic recovery, and especially evidence of muscle-cell damage was found for some days to follow. However, the magnitude and temporal responsiveness of these serum biochemical changes are not unlike responses reported following similar exposure to other inhalation anesthetics.[23,24] The influence of profound arterial hypotension and perhaps decreased O_2 delivery to tissues, especially during portions of deep anesthesia, is likely an important etiologic factor for these changes.[25-27]

Inorganic fluoride is a known degradation product of sevoflurane.[28-30] Serum inorganic fluoride concentrations exceeding 50 µmol/L have been of particular interest with regard to human patients because prior investigations with methoxyflurane indicate that the incidence and severity of postanesthetic renal dysfunction correlate with serum fluoride concentration and first observable signs of toxic effects occur at approximately the concentration of 50 µmol/L.[31] Although the importance of systemic versus local (ie, renal) defluoridation of an inhalation anesthetic in causing toxic effects remains unresolved[32] and the accuracy of a similar correlation of serum concentration between fluoride and toxic effects in horses is unknown, the 50 µmol/L serum fluoride ion concentration bench-

mark seems a reasonable concentration to consider when evaluating the potential for toxic effects. Aida et al[8] reported a peak fluoride ion concentration of 29.6 µmol/L by the end of 2.6 hours of anesthesia with sevoflurane. The duration of anesthesia in our study was approximately twice that in the study of Aida et al.[8] During the mean 5.2-hour duration of the second anesthesia of our study, these horses were exposed to approximately 7 MAC hours of sevoflurane. Serum inorganic fluoride concentration reached 50.8 ± 7.1 µmol/L by the end of anesthesia and then rapidly decreased to near baseline by the next day. No renal dysfunction or toxic effects measured by BUN and serum creatinine and inorganic phosphate concentrations beyond that commonly associated with a similar duration of general anesthesia in horses[23,24] were observed in our study. In addition, our results are in agreement with results of prior horse studies[7,8] of similar or less sevoflurane exposure. Thus, our results along with those of Aida et al[8] indicate that higher concentration or longer time of exposure (or both) to sevoflurane results in higher serum inorganic fluoride concentration; the increase in serum fluoride concentration from baseline is short-lived (ie, returning to near baseline by 1 day and back to baseline sometime between 1 and 2 days post-sevoflurane exposure), and no evidence exists of kidney damage being directly attributable to increased serum fluoride ion concentration in young healthy horses anesthetized only with sevoflurane for approximately 5 hours.

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c. Model OM-11, Sensormedics Corp, Anaheim, Calif.
d. Model LB-2 CO_2 and anesthetic analyzers, Sonsormedics Corp, Anaheim, Calif.
e. YSI Tele-thermometer model 43, Yellow Springs Instrument Co, Yellow Springs, Ohio.
f. Model 7 polygraph, Grass Instruments, Quincy, Mass.
g. Lyons Medical Instrument Co, Van Nuys, Calif.
h. Fleisch No. 4, Instrumentation Associates Inc, New York, NY.
i. Model ABL 330, Radiometer America, Cleveland, Ohio.
j. Fluoride analysis diluent, Corning Inc, Corning, NY.
k. Orion Mode 601a digital ionanalyzer, Thermo Electron Corp, Waltham, Mass.

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