Comparison of the cardiovascular effects of equipotent anesthetic doses of sevoflurane alone and sevoflurane plus an intravenous infusion of lidocaine in horses

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Objective—To compare cardiovascular effects of sevoflurane alone and sevoflurane plus an IV infusion of lidocaine in horses.

Animals—8 adult horses.

Procedures—Each horse was anesthetized twice via IV administration of xylazine, diazepam, and ketamine. During 1 anesthetic episode, anesthesia was maintained by administration of sevoflurane in oxygen at 1.0 and 1.5 times the minimum alveolar concentration (MAC). During the other episode, anesthesia was maintained at the same MAC multiples via a reduced concentration of sevoflurane plus an IV infusion of lidocaine. Heart rate, arterial blood pressures, blood gas analyses, and cardiac output were measured during mechanical (controlled) ventilation at both 1.0 and 1.5 MAC for each anesthetic protocol and during spontaneous ventilation at 1 of the 2 MAC multiples.

Results—Cardiorespiratory variables did not differ significantly between anesthetic protocols. Blood pressures were highest at 1.0 MAC during spontaneous ventilation and lowest at 1.5 MAC during controlled ventilation for either anesthetic protocol. Cardiac output was significantly higher during 1.0 MAC than during 1.5 MAC for sevoflurane plus lidocaine but was not affected by anesthetic protocol or mode of ventilation. Clinically important hypotension was detected at 1.5 MAC for both anesthetic protocols.

Conclusions and Clinical Relevance—Lidocaine infusion did not alter cardiorespiratory variables during anesthesia in horses, provided anesthetic depth was maintained constant. The IV administration of lidocaine to anesthetized nonstimulated horses should be used for reasons other than to improve cardiovascular performance. Severe hypotension can be expected in nonstimulated horses at 1.5 MAC sevoflurane, regardless of whether lidocaine is administered. (Am J Vet Res 2011;72:452–460)
lidocaine is frequently administered to reduce the requirement for isoflurane during anesthesia in horses.\textsuperscript{6,8,9} Sevoflurane is gaining popularity for anesthesia of equids because its use may result in rapid and smooth recovery from anesthesia, but to our knowledge, the combination of sevoflurane and lidocaine has not been fully investigated in horses.\textsuperscript{7} In another study,\textsuperscript{10} our laboratory group determined that lidocaine administered IV as a bolus of 1.3 mg/kg during a 15-minute period followed by a constant rate infusion at 50 µg/kg/min decreased the sevoflurane MAC in horses from a mean of 2.42% to a mean of 1.78%.

The objective of the study reported here was to compare the cardiovascular effects of anesthesia in horses achieved by the administration of sevoflurane alone with the effects of an equivalent plane of anesthesia achieved by use of sevoflurane combined with IV infusion of lidocaine. The hypothesis was that at equipotent anesthetic doses, the combination of sevoflurane plus IV administration of lidocaine would cause less cardiovascular depression (decrease in CO and blood pressure) in horses than would result from the use of sevoflurane alone.

**Materials and Methods**

**Animals**—Eight healthy adult horses were used in the study. The horses consisted of 4 geldings and 4 mares that ranged from 3 to 13 years of age (mean ± SD, 9 ± 5 years) and that weighed between 334 and 482 kg (mean ± SD, 417 ± 59 kg). Each horse had been anesthetized once for determination of sevoflurane MAC with and without lidocaine infusion in another study.\textsuperscript{10}

Horses were maintained in a large paddock with shelter and had access to grass hay and water at all times, except the morning of an experiment. The study protocol was approved by the Colorado State University Institutional Animal Care and Use Committee.

**Anesthetic protocol**—For the cardiovascular evaluations reported here, each horse was anesthetized 2 times; a minimum interval of 6 days between anesthetic episodes was allowed for full recovery and drug washout between experiments. To limit feed intake before each experiment, each horse that was to be used on that given day was removed from the paddock early in the morning before hay was provided. Body weight, rectal temperature, heart rate, and respiratory rate were recorded. Hair overlying the right jugular furrow was clipped, and the skin was aseptically prepared. Approximately 3 mL of 2% mepivacaine\textsuperscript{e} was infiltrated SC in 2 sites, and two 8F catheter introducers\textsuperscript{d} were inserted into the right jugular vein. A 7F, 110-cm thermistor tip catheter\textsuperscript{b} and another 7F, 110-cm catheter\textsuperscript{e} were inserted as far as possible into the right jugular vein; the external portions of these catheters were then covered with bandage material to protect them during induction of anesthesia. The mouth of each horse was rinsed with water.

Xylazine hydrochloride\textsuperscript{c} (0.7 mg/kg, IV) was administered. Five minutes later, induction was achieved by IV administration of ketamine hydrochloride\textsuperscript{c} (2 mg/kg) and diazepam\textsuperscript{e} (0.02 mg/kg). After anesthetic induction, tracheal intubation was performed with a 26-mm cuffed endotracheal tube, which was connected to a standard large animal anesthesia circle breathing system that delivered sevoflurane\textsuperscript{h} in 100% oxygen. When depth of anesthesia for a horse was judged to be sufficient, the endotracheal tube was briefly disconnected from the anesthesia machine and the horse was transported to a surgery room; the tube then was reconnected to the anesthesia machine for delivery of sevoflurane in 100% oxygen. Horses were positioned in left lateral recumbency on a thick foam pad. Samples of airway gas were obtained continuously from the distal portion of the trachea via a catheter placed within the endotracheal tube; these samples were analyzed for end-tidal sevoflurane and CO\textsubscript{2} concentrations via an automated agent analyzer.\textsuperscript{i} The agent analyzer was calibrated before and after each experiment by use of 3 external sevoflurane standards (1.5%, 2.5%, and 3.5%). During the instrumentation period, anesthesia was maintained with sevoflurane administered at an end-tidal concentration of approximately 1.2 times the MAC for sevoflurane published elsewhere\textsuperscript{11} (adjusted for local barometric pressure). Horses were allowed spontaneous ventilation; periodic expansion of the lungs to prevent atelectasis was manually provided during this time.

**Instrumentation**—On arrival in the surgery room, all horses were instrumented by insertion of a calibrated temperature probe into the rectum, and mean ± SD body temperature was maintained at 35.8 ± 0.2°C by use of blankets and heat lamps. A balanced electrolyte solution was infused IV at a rate of 5 mL/kg/h throughout anesthesia. An ECG (base-apex lead) was recorded continuously for each horse and used to assess heart rate and rhythm.\textsuperscript{j} A 20-gauge, 5-cm catheter\textsuperscript{a} was placed in a transverse facial artery and connected to a calibrated pressure transducer\textsuperscript{l} for measurement of systolic arterial blood pressure, diastolic arterial blood pressure, and MAP and to facilitate collection of arterial blood samples for blood gas and plasma lidocaine analyses.

The bandages were removed from the previously placed jugular catheters. The position of the thermistor tip catheter was adjusted so that its tip was in the pulmonary artery, whereas the other jugular catheter was positioned so that its tip was in the right atrium, as determined by observation of characteristic pressure waveforms and values. All blood pressure measurements were obtained via appropriately calibrated pressure transducers, with the sternal midline considered as the zero reference point. Arterial blood samples were obtained anaerobically from the catheter in the transverse facial artery and analyzed for Pa\textsubscript{O\textsubscript{2}}, Pa\textsubscript{CO\textsubscript{2}}, and pH within 10 minutes after collection.\textsuperscript{m} The urinary bladder was aseptically catheterized, and the urinary catheter was connected to a collection bag to permit continuous drainage of urine throughout anesthesia to minimize distention of the urinary bladder during recumbency and prior to anesthetic recovery.

Once instrumentation was completed, mechanical (controlled) ventilation was instituted with a bag-in-barrel system powered by a pressure-limited ventilator.\textsuperscript{n} During anesthesia, mean ± SD Pa\textsubscript{CO\textsubscript{2}} was maintained at 45 ± 3 mm Hg by maintaining peak inspiratory pressure.
between 20 and 24 cm H₂O and adjusting the respiratory rate as needed. Breath-to-breath tracking of end-tidal sevoflurane and CO₂ concentrations was facilitated by use of the automated, calibrated agent analyzer.

**Determination of CO**—The thermodilution method was used to measure CO. For each measurement, a bolus of 50 mL of ice-cold (0.1° to 0.2°C) saline (0.9% NaCl) solution was rapidly injected into the right atrial catheter by use of a specially fabricated power injector. The change in pulmonary artery blood temperature was detected by use of a CO computer connected to the thermistor tip catheter, and the reported CO was corrected in accordance with a correction factor provided for use with this system. At least 2 measurements with values within 10% of each other were obtained at each measurement period, and the mean value for each pair of measurements was calculated.

**Experimental procedures**—After induction of anesthesia in experiment 1, half the horses received sevoflurane alone and the other half received sevoflurane plus lidocaine. Treatments were reversed for the second experiment. Approximately 1 hour after induction of anesthesia, which allowed for instrumentation and washout of induction drugs, end-tidal sevoflurane concentration for the horses receiving sevoflurane alone was adjusted to 1.0 or 1.5 times the MAC obtained for that specific horse in the previous study. For horses receiving sevoflurane plus lidocaine, a syringe pump was used to deliver lidocaine IV (a bolus injection of 1.3 mg/kg administered over a 15-minute period followed by a continuous rate infusion at 50 µg/kg/min), and the end-tidal sevoflurane concentration was reduced to provide an equipotent anesthetic dose (in combination with the lidocaine infusion) equivalent to 1.0 or 1.5 times each horse’s MAC. For 1.5 MAC sevoflurane, an end-tidal sevoflurane concentration of 1.5 times the horse’s sevoflurane MAC was targeted; for 1.5 MAC sevoflurane plus lidocaine, the target was an end-tidal sevoflurane concentration of 1.5 times the individual horse’s sevoflurane MAC minus the difference between 1.0 MAC sevoflurane and 1.0 MAC sevoflurane plus lidocaine, which was considered to represent the contribution of the lidocaine infusion. For example, in a horse with a sevoflurane MAC of 2.42% and sevoflurane plus lidocaine MAC of 1.61%, lidocaine was considered to contribute 0.81% sevoflurane or 0.33 MAC equivalent. Therefore, 1.5 MAC sevoflurane for that horse would be 1.5 times 2.42% = 3.63%, whereas 1.5 MAC sevoflurane plus lidocaine would be 3.63% – 0.81% = 2.82%.

For all experiments (sevoflurane alone or sevoflurane plus lidocaine), horses were randomly allocated such that half the horses received the 1.0 MAC multiple first followed by the 1.5 MAC multiple, whereas the other half received the 1.5 MAC multiple followed by the 1.0 MAC multiple.

After a 30-minute equilibration period at each MAC multiple, end-tidal sevoflurane concentration, body temperature, heart rate, respiratory rate, systemic arterial blood pressures, and CO were recorded. Cardiac index and TPR were calculated from these values via standard equations. Heparinized arterial and mixed-venous blood samples were anaerobically collected and used for pH, Pco₂, and Po₂ analysis and PCV and total protein measurements. For experiments in which lidocaine was administered, arterial blood samples were collected at the time of each set of measurements during the lidocaine infusion for subsequent determination of plasma lidocaine concentrations.

It was deemed important to gain insights into the effect of spontaneous and controlled ventilation on the measured variables. The 2 sets of measurements (1.0 and 1.5 MAC) were determined during controlled ventilation. Controlled ventilation then was discontinued, each horse was maintained at the second sevoflurane concentration (1.0 or 1.5 MAC, with or without lidocaine infusion), and horses were allowed spontaneous ventilation for 20 minutes before cardiovascular measurements were repeated. Because only 1 set of measurements were performed during spontaneous ventilation, there were only 4 sets of measurements for each treatment (sevoflurane alone at 1.0 [n = 4 horses] and 1.5 MAC [4] and sevoflurane plus lidocaine at 1.0 [4] and 1.5 MAC [4]).

After the final set of measurements, lidocaine infusion (if applicable) was discontinued. Sevoflurane delivery was adjusted to 1.2 MAC, and all instrumentation was disconnected and all catheters (except for the catheter introducers in the jugular vein) were removed. Twenty minutes after the final measurements (and discontinuation of lidocaine infusion, if applicable), anesthesia was discontinued and the endotracheal tube disconnected from the anesthetic machine. Horses were moved to a padded and darkened recovery stall and allowed to recover without assistance, but they were constantly observed. Oxygen was insufflated at a rate of 15 L/min via the endotracheal tube until a horse began to move. One of 2 observers (THF or MLR), who were aware of the treatment administered to each horse, evaluated all recoveries. Intervals were recorded beginning at the time of disconnection from the anesthetic machine. Variables recorded included time to first movement, time to sternal recumbency, and time to standing. In addition, the number of attempts required to successfully stand was recorded and the overall quality of recovery was subjectively scored by the 2 observers (THF and MLR) by use of a 5-point scale (5 = excellent [single coordinated effort to stand with minimal or no ataxia], 4 = very good [single attempt to stand, with some ataxia], 3 = good [quiet recovery with > 1 attempt to stand], 2 = fair [uncoordinated attempts to stand with or without minor injury, such as a superficial laceration], 1 = poor [multiple, uncoordinated attempts to stand resulting in major or life-threatening injury, such as a fractured limb]). After a horse achieved a standing position, the endotracheal tube was removed and phenylbutazone (4 mg/kg, IV) was administered to minimize any inflammation or soreness related to recumbency.

**Plasma lidocaine analyses**—Plasma concentrations of lidocaine were measured by use of an HPLC system with mass spectral detection. The HPLC system consisted of a binary pump, vacuum degasser, thermostatted column compartment, and system autosampler. The HPLC column was a phenyl column (internal diameter, 4.6 × 50 mm; bead size, 5.0 µm) protected by a
C18 cartridge (internal diameter, 4 × 2.0 mm) and was maintained at approximately 21°C. The mobile phase consisted of an aqueous component (solution A, 0.1% formic acid in water) and an organic component (solution B, acetonitrile). Each 4.0-minute assay consisted of the following linear gradient elution: 98% solution A and 2% solution B at 0 minutes, 2% solution A and 98% solution B at 2.5 minutes, 2% solution A and 98% solution B at 3.2 minutes, 98% solution A and 2% solution B at 3.5 minutes, and 98% solution A and 2% solution B at 4.0 minutes. The system operated at a flow rate of 1.5 mL/min.

Mass spectrometric detection was performed on a triple quadrupole instrument via multiple reaction monitoring. Ions were generated in positive ionization mode by use of an electrospray interface. Lidocaine compound-dependent settings were as follows: declustering potential, 35 V; entrance potential, 5 V; collision cell entrance potential, 11 V; collision energy, 28 V; and collision cell exit potential, 2.5 V. Trazodone (internal standard) compound-dependent settings were as follows: declustering potential, 56.86 V; entrance potential, 4.08 V; collision cell entrance potential, 20.56 V; collision energy, 32.75 V; and collision cell exit potential, 2.72 V. Source-dependent settings were as follows: nebulizer gas, 483 kPa; auxiliary (turbogas) gas, 414 kPa; turbo gas temperature, 600°C; curtain gas, 345 kPa; collision-activated dissociation gas (nitrogen), 41 kPa; ionspray voltage, 5,500 V; and interface heater, 100°C. Peak areas ratios obtained from multiple reaction monitoring of lidocaine (mass-to-charge ratio, 235.3 → 176.1) were used for quantification.

Standard solutions of lidocaine and trazodone were prepared in acetonitrile. Lidocaine was extracted from plasma by adding 300 µL of 2% formic acid in acetonitrile to 100 µL of plasma, vortexing for 10 minutes, and centrifuging at 18,000 g for 10 minutes. An aliquot of 50 µL of the resulting supernatant was injected into the liquid chromatography–mass spectrometry–mass spectrometry system for analysis.

**Results**

Immediately after induction, anesthetic depth in some horses was insufficient to achieve endotracheal intubation or to safely transport those horses to the surgery room; therefore, 3 horses received sevoflurane via a facemask before intubation and most of the horses were not moved to the surgery room until sevoflurane had been delivered for 5 minutes to result in a sufficiently deep plane of anesthesia. The interval from induction of anesthesia to the first measurement period ranged from 90 to 104 minutes (mean, 93 minutes), which included at least 30 minutes of constant conditions. The interval from induction to the second measurement period ranged from 134 to 160 minutes (mean, 142 minutes). Interval from induction to the final set of measurements under conditions of spontaneous ventilation ranged from 133 to 205 minutes (mean, 169 minutes).

Cardiovascular measurements were summarized (Table 1). In general, there were significant differences in measurements related to dose (1.0 vs 1.5 MAC) and to mode of ventilation (controlled vs spontaneous), but there were no significant differences attributable to anesthetic protocol (sevoflurane alone vs sevoflurane

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controlled ventilation</th>
<th></th>
<th>Spontaneous ventilation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Sevoflurane (n = 8)</td>
<td>Sevoflurane plus lidocaine (n = 8)</td>
<td>Sevoflurane (n = 4)</td>
<td>Sevoflurane plus lidocaine (n = 3)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>40 ± 2</td>
<td>43 ± 2</td>
<td>37 ± 2</td>
<td>39 ± 2</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>96 ± 4</td>
<td>80 ± 4</td>
<td>96 ± 4</td>
<td>83 ± 4</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>73 ± 4</td>
<td>60 ± 4</td>
<td>76 ± 4</td>
<td>64 ± 4</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>62 ± 4</td>
<td>51 ± 4</td>
<td>62 ± 4</td>
<td>52 ± 4</td>
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<tr>
<td>MPAP (mm Hg)</td>
<td>27 ± 2</td>
<td>27 ± 2</td>
<td>29 ± 2</td>
<td>29 ± 2</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>16 ± 2</td>
<td>18 ± 2</td>
<td>19 ± 2</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>23.1 ± 2.0</td>
<td>19.2 ± 2.0</td>
<td>22.4 ± 2.0</td>
<td>18.5 ± 2.0</td>
</tr>
<tr>
<td>CI (L/min/kg/min)</td>
<td>53.8 ± 4.3</td>
<td>44.8 ± 4.3</td>
<td>53.9 ± 4.3</td>
<td>44.1 ± 4.3</td>
</tr>
<tr>
<td>TPR (dynamics/s/cm²)</td>
<td>282 ± 33</td>
<td>280 ± 33</td>
<td>282 ± 33</td>
<td>314 ± 33</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>35.5 ± 0.2</td>
<td>35.5 ± 0.2</td>
<td>35.8 ± 0.2</td>
<td>35.7 ± 0.2</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>29 ± 1</td>
<td>29 ± 1</td>
<td>28 ± 1</td>
<td>29 ± 1</td>
</tr>
</tbody>
</table>

DAP = Diastolic arterial blood pressure, MPAP = Mean pulmonary artery blood pressure, n = Number of horses, RAP = Right atrial pressure. 

*Within each row, values with different superscript letters differ significantly (P < 0.05).
plus lidocaine at a given MAC multiple. Heart rate, TPR, body temperature, and PCV did not change significantly with any treatment. Arterial blood pressures were significantly altered by anesthetic dose and mode of ventilation; they were highest during spontaneous ventilation at 1.0 MAC and lowest during controlled ventilation at 1.5 MAC, regardless of whether sevoflurane alone or sevoflurane plus lidocaine was used. Right atrial pressure was unchanged, except for a significant increase during spontaneous ventilation at 1.5 MAC sevoflurane plus lidocaine. There was only 1 significant change in CO attributable to dose (a higher CO at 1.0 MAC sevoflurane plus lidocaine than at 1.5 MAC sevoflurane plus lidocaine), and there were no significant differences in CO or CI related to lidocaine infusion or to mode of ventilation.

It should be mentioned that the mean MAP during anesthesia at 1.5 MAC was < 70 mm Hg, regardless of whether sevoflurane or sevoflurane plus lidocaine was used and whether there was controlled or spontaneous ventilation. Five of the 8 horses had MAP < 60 mm Hg during anesthesia at 1.5 MAC (3 horses had this degree of hypotension with both anesthetic protocols, 1 horse had it only with 1.5 MAC sevoflurane, and 1 horse had it only with 1.5 MAC sevoflurane plus lidocaine). Two of the 5 hypotensive horses had MAP ≤ 50 mm Hg (both during 1.5 MAC sevoflurane) and were treated with dobutamine (0.5 to 2 µg/kg/min IV, for 15 and 25 minutes, respectively). In these 2 horses, dobutamine infusion was terminated 20 minutes before cardiovascular measurements were obtained. One of these horses became so hypotensive (MAP, 47 mm Hg) after termination of dobutamine treatment during conditions of controlled ventilation that the remaining portion of that experiment was cancelled and the horse allowed to recover without attempting measurements for conditions of spontaneous ventilation; therefore, the 1.5 MAC sevoflurane plus lidocaine spontaneous ventilation group consisted of only 3 horses.

Blood gas results were summarized (Table 2). There were no significant changes in arterial blood pH, PaCO\(_2\), or PaO\(_2\), associated with treatment (sevoflurane vs sevoflurane plus lidocaine) or anesthetic dose (1.0 vs 1.5 MAC). However, there were significant differences in blood gas variables between controlled and spontaneous ventilation. Mean ± SE arterial pH ranged from 7.42 ± 0.01 to 7.43 ± 0.02 during controlled ventilation and was significantly higher than the mean pH (range, 7.23 ± 0.01 to 7.32 ± 0.01) during spontaneous ventilation. Mean PaCO\(_2\) ranged from 34 ± 1 mm Hg to 46 ± 1 mm Hg during controlled ventilation. Mean elapsed time from termination of controlled ventilation to first spontaneous breath ranged from 119 ± 31 seconds to 329 ± 83 seconds, and mean arterial PaCO\(_2\) at first breath ranged from 68 ± 2 mm Hg to 74 ± 5 mm Hg. During spontaneous ventilation, mean PaCO\(_2\) increased significantly (range, 61 ± 6 mm Hg to 83 ± 4 mm Hg), compared with mean PaCO\(_2\) during controlled ventilation. Mean PaO\(_2\) ranged from 341 ± 14 mm Hg to 394 ± 36 mm Hg during controlled ventilation and was significantly higher than mean PaO\(_2\) (range, 196 ± 50 mm Hg to 278 ± 13 mm Hg) during spontaneous ventilation.

Mean plasma total protein concentration varied from 5.1 to 7.0 g/dL throughout the experiments. However, these values did not differ significantly for anesthetic protocol, anesthetic dose, or mode of ventilation.

Results for analysis of plasma lidocaine concentrations indicated that there were no significant differences in lidocaine concentrations at the time of measurements during 1.0 and 1.5 MAC sevoflurane plus lidocaine or at the time the lidocaine infusions were terminated. Mean ± SE plasma lidocaine concentrations were 2,138 ± 128 ng/mL, 2,248 ± 116 ng/mL, and 2,570 ± 233 ng/mL at 1.0 MAC, 1.5 MAC, and the end of lidocaine infusion, respectively.

All horses recovered satisfactorily from anesthesia (Table 3). Analysis of recovery data revealed that there

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### Table 2: Mean ± SE values for arterial blood gas results for 8 horses anesthetized with sevoflurane at 1.0 or 1.5 MAC and sevoflurane plus lidocaine at 1.0 or 1.5 MAC for conditions of controlled or spontaneous ventilation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controlled ventilation</th>
<th>Spontaneous ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sevoflurane (n = 8)</td>
<td>Sevoflurane plus lidocaine (n = 8)</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 ± 0.01*</td>
<td>7.43 ± 0.02*</td>
</tr>
<tr>
<td>PaCO(_2) (mm Hg)</td>
<td>46 ± 1*</td>
<td>44 ± 1*</td>
</tr>
<tr>
<td>PaO(_2) (mm Hg)</td>
<td>341 ± 14*</td>
<td>355 ± 12*</td>
</tr>
</tbody>
</table>

*Within each row, values with different superscript letters differ significantly (P < 0.05).

### Table 3: Mean ± SE values for recovery time, number of attempts to stand, and score for overall quality of recovery for 8 horses anesthetized with sevoflurane and with sevoflurane plus a lidocaine infusion.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sevoflurane</th>
<th>Sevoflurane plus lidocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Time to first movement (min)</td>
<td>14.2 ± 0.4</td>
<td>17.4 ± 0.8</td>
</tr>
<tr>
<td>Time to sternal recumbency (min)</td>
<td>33.0 ± 1.1</td>
<td>42.0 ± 1.8</td>
</tr>
<tr>
<td>No. of attempts to stand</td>
<td>4.7 ± 0.1</td>
<td>4.5 ± 0.1</td>
</tr>
<tr>
<td>Overall quality of recovery*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For all variables, values did not differ significantly (P > 0.05) between treatments.

*Recovery scores were graded on a 5-point scale (5 = excellent [single coordinated effort to stand with minimal or no ataxia], 4 = very good [single attempt to stand, with some ataxia], 3 = good [quiet recovery with > 1 attempt to stand], 2 = fair [uncoordinated attempts to stand with or without minor injury, such as a superficial laceration], and 1 = poor [multiple, uncoordinated attempts to stand resulting in major or life-threatening injury, such as a fractured limb]).
were no significant differences between treatments with regard to recovery times, although time to standing typically was longer (but not significantly \( P = 0.056 \) different) in horses that received sevoflurane plus lidocaine. There were no significant differences between treatments in the number of attempts to stand or quality of recovery.

Discussion

Horses appear to be more sensitive to the cardiovascular and respiratory depressant effects of inhalation anesthetics, compared with the sensitivity of dogs. Therefore, minimizing the doses of inhalation anesthetics by augmenting analgesia and sedation with other drugs would appear to be a rational approach to anesthetic management of equids. Unfortunately, some MAC-sparing drugs (particularly the opioids) commonly used in dogs do not have similar MAC-sparing effects in horses, probably because of central excitatory effects. For this reason, balanced anesthesia in horses has focused mainly on nonopioid drugs such as \( \alpha \)-adrenoceptor agonists, ketamine, and lidocaine to supplement inhalation anesthetics. It has generally been assumed that use of such MAC-sparing drugs would be beneficial in reducing the dose-dependent depression of cardiovascular function associated with inhalation anesthesia. Because of the potential benefits of IV administration of lidocaine on both gastrointestinal tract motility and MAC reduction, the use of lidocaine infusions during anesthesia in horses is increasing. This trend inspired researchers to conduct studies of the pharmacokinetics of IV administration of lidocaine in horses under a variety of conditions (healthy awake horses vs healthy anesthetized horses vs horses anesthetized for colic surgery). These studies as well as results for clinical use of IV infusions of lidocaine in anesthetized horses have suggested that lidocaine administration allows a lower anesthetic vaporizer setting to be used and has not been associated with significant alterations in heart rate or MAP. However, most studies have not involved the measurement of CO or calculation of TPR, both of which may greatly affect tissue perfusion. To our knowledge, the only full-length report of IV administration of lidocaine during sevoflurane anesthesia was a clinical study, which was confounded by various vaporizer settings, surgical stimulation, and administration of dobutamine.

Lidocaine infusions in isoflurane-anesthetized dogs have been associated with a 40% decrease in CI\(^{17,18}\) or no change in CI\(^{19}\). In a 2005 study, investigators determined that lidocaine administered at various infusion rates during isoflurane-induced anesthesia in cats caused only a 10% to 15% decrease in heart rate and a slight increase in MAP at the highest infusion rate but was associated with a decrease of nearly 40% in CO, compared with results for an equipotent dose of isoflurane alone. An increase in vascular resistance was responsible for the increase in MAP, despite a decrease in CO.\(^{17}\) This finding raised concern that the increasingly widespread use of IV infusions of lidocaine during anesthesia might be associated with similarly detrimental effects on CO and tissue perfusion in horses, which may not be detected with routine clinical monitoring of heart rate and MAP. The study reported here assures that concern because MAP and CO or CI in anesthetized horses were not significantly altered by lidocaine infusion, provided anesthesia was maintained at an equipotent depth by adjusting the sevoflurane concentration appropriately. Cardiac output and CI typically were higher at 1.0 MAC than at 1.5 MAC, but peripheral resistance did not change significantly between treatments. Values for CI were similar to those reported for anesthesia with sevoflurane under conditions of controlled ventilation.

Because the primary objective of the study reported here was to evaluate the direct cardiovascular effects of IV administration of lidocaine combined with sevoflurane, horses were not subjected to any surgical stimulation during the experiments. Results of this study may apply to horses anesthetized for noninvasive procedures such as magnetic resonance imaging or computed tomography. However, surgical stimulation has been reported to alter cardiovascular measurements in halothane- and isoflurane-anesthetized horses; therefore, the effects of IV administration of lidocaine during surgery may differ from those reported here.

For similar reasons, most of the measurements were obtained during conditions of controlled ventilation. Changes in \( \text{Paco}_2 \) can alter cardiovascular measurements during both halothane- and isoflurane-induced anesthesia, with halothane-anesthetized horses having the greatest increases in CI and MAP in association with hypercapnia, likely as a result of increased circulating concentrations of catecholamines. To ensure consistent blood gas variables in the present study, controlled ventilation was used throughout most of each experiment. However, a limited number of measurements were obtained during spontaneous ventilation at the end of each experiment. As expected, horses typically hypoventilated (mean \( \text{Paco}_2 \), 61 to 83 mm Hg), and the resulting hypercapnia was associated with increased arterial blood pressures (but minimal change in CO), compared with results for conditions of controlled ventilation. Whether the degree of hypercapnia or the cardiovascular findings would be different during surgical stimulation or during a prolonged period of spontaneous ventilation is uncertain.

Sevoflurane has cardiovascular and respiratory effects similar to those of isoflurane, but it is becoming the anesthetic of choice in horses because its lower blood gas partition coefficient has the potential to result in more rapid, and possibly smoother, recovery characteristics, compared with those for isoflurane. However, when used clinically with protocols that involve IV administration of sedatives and induction agents, sevoflurane may not provide any advantage over isoflurane for recovery. At low doses (approx 1 MAC), sevoflurane causes respiratory and cardiovascular depression in horses comparable to that associated with isoflurane; at higher doses (\( \geq 1.5 \) MAC), sevoflurane causes greater depression of respiratory and cardiovascular performance than does isoflurane. Because CO, MAP, and perfusion of muscles are critical to the prevention of postanesthetic myopathy in horses, the effect of IV infusion of lidocaine during sevoflurane-induced anesthesia warrants more critical investigation.
to determine whether these cardiovascular variables are improved as a result of the MAC-sparing properties of lidocaine or, conversely, whether they are reduced as a result of the cardiovascular depressant effects of lidocaine. Results of the study reported here confirmed that lidocaine caused no significant improvement or deterioration in cardiovascular variables during sevoflurane-induced anesthesia in horses but that there may be clinically important hypotension at 1.5 MAC sevoflurane during anesthesia, regardless of whether lidocaine was used.

The IV administration of lidocaine to anesthetized horses has increased during the past few years as various benefits have been proposed or proven. Lidocaine has long been used as an antiarrhythmic in many species, but it also has analgesic and anti-inflammatory properties. In anesthetized ponies, IV administration of lidocaine can decrease the MAC for halothane and augment analgesia during castration. In conscious horses, IV administration of lidocaine can increase thermal threshold, which suggests somatic analgesic effects, and it reportedly reduces the risk of postoperative ileus after abdominal surgery. Because of the latter favorable effect on equine gastrointestinal tract motility, equine surgeons and critical care specialists frequently request IV administration of lidocaine be initiated during colic surgery and continued postoperatively. The lidocaine loading and infusion dosages used in the study reported here were the same as those that have been found to result in steady-state plasma concentrations in healthy anesthetized horses within 30 minutes. Analysis of results of the present study confirmed that plasma lidocaine concentrations were similar for each horse at the time of each set of measurements (1.0 or 1.5 MAC) and at the termination of lidocaine infusion.

As mentioned previously, results of the present study indicated that lidocaine infusion was not associated with significant cardiovascular depression; however, the concomitant decrease in sevoflurane concentration was not associated with significant improvement in cardiovascular measurements. Therefore, the decision for IV administration of lidocaine to anesthetized horses should be made because of improvements in analgesia, promotility effects, or antiarrhythmic effects and not for improvements in blood pressure or perfusion.

Arterial blood pressures were significantly decreased in association with an increased anesthetic dose and with controlled ventilation, which is similar to results of other studies of anesthesia with sevoflurane. It should be mentioned that arterial hypotension was severe enough at 1.5 MAC (MAP < 70 mm Hg) to be considered clinically unacceptable, particularly during controlled ventilation. All of the horses in this study may have benefited from dobutamine administration during anesthesia at 1.5 MAC, but only the 2 most severely hypotensive horses were treated in an attempt to minimize the influence of dobutamine on cardiovascular measurements. In addition, dobutamine administration was terminated at least 20 minutes prior to measurements in an attempt to minimize its influence on the results. Fortunately, none of the horses had any clinical signs of myopathy or other hypotension-related problems following the experiments.

Cardiac output and Cl were similar to values reported for horses anesthetized with sevoflurane alone. As expected, they were typically higher with a lower dose and with spontaneous ventilation, although the difference was significant only for 1.0 MAC sevoflurane plus lidocaine during controlled ventilation, compared with 1.5 MAC sevoflurane plus lidocaine during controlled ventilation.

Arterial blood gas values were similar regardless of whether sevoflurane alone or sevoflurane plus lidocaine was used and were similar at 1.0 and 1.5 MAC, which indicated that gas exchange was not significantly affected by the addition of lidocaine to sevoflurane. As expected, Pco2 was significantly higher and pH and Paco2 were significantly lower when horses had spontaneous ventilation, compared with results for controlled ventilation. Therefore, nonstimulated horses maintained at a surgical plane of anesthesia with sevoflurane or sevoflurane plus lidocaine are unlikely to ventilate well enough spontaneously to maintain a clinically acceptable Paco2 of ≤ 65 mm Hg, and controlled ventilation should be strongly considered whenever sevoflurane is used in horses.

Although from a purely scientific standpoint it would have been ideal to avoid administering any drugs other than the 2 drugs of interest (sevoflurane and lidocaine), the IV administration of xylazine, ketamine, and diazepam for induction mimics clinical situations and facilitates rapid and smooth induction of anesthesia, which is safer for both horses and veterinary personnel, compared with induction via inhalation of sevoflurane alone. An attempt was made to minimize the dosages of the induction drugs, which likely was the reason that most horses appeared to be lightly anesthetized after induction until sevoflurane had been administered for several minutes. One horse (an Arabian gelding) did not become recumbent after the initial anesthesia induction; therefore, the dosages of xylazine, ketamine, and diazepam for that horse had to be increased to 1.1, 2.7, and 0.05 mg/kg, respectively. It has been reported that the cardiovascular effects associated with various induction drugs are not significantly different by 28 to 38 minutes of inhalation (halothane) anesthesia. Because the first cardiovascular measurements in the study reported here were not obtained until a mean of 95 minutes after induction, the effect of the induction drugs on the results of the present study should have been fairly minimal and, at the least, consistent between treatments.

The loading dose (1.3 mg/kg) and infusion rate (50 µg/kg/min) for lidocaine used in the present study are the same as those used clinically in our hospital and result in steady-state plasma lidocaine concentrations within 20 minutes. In another study of the effect of IV administration of lidocaine on halothane MAC in ponies, investigators used higher loading doses (2 and 5 mg/kg) and infusion rates (up to 100 µg/kg/min). However, steady-state plasma lidocaine concentrations were never attained in that study. It is possible that administration of higher doses of lidocaine would result in even greater reductions of the sevoflurane requirement, but they may be associated with an increased risk of lidocaine toxicosis. Lidocaine toxicosis often
manifests as neurologic signs (eg, weakness or ataxia), which would be masked by anesthesia.

Cardiovascular variables are subject to temporal changes during inhalation anesthesia (increases in MAP and CO after the first hour, which stabilize after 2 to 4 hours), and these changes have been described elsewhere.20,31,32 Had we attempted to measure cardiovascular variables for both sevoflurane alone and sevoflurane plus lidocaine infusion within a single anesthetic episode, the measurements for sevoflurane plus lidocaine would have had to be made after the measurements for sevoflurane alone, which would have exacerbated the potential for temporal influences. However, the study was conducted as 2 separate experiments, with half the horses receiving sevoflurane alone and the other half receiving sevoflurane plus lidocaine during the first experiment (treatments were reversed during the second experiment), to ensure that the temporal effects were similar for both treatments. Although this was a more time-consuming approach, it minimized the potential for temporal cardiovascular changes to confound the results.20,31,32

Horses became hypothermic during the experiments, despite all efforts to maintain body temperature by use of blankets, forced warm air blankets, and heat lamps. Although the experiments were conducted during the summer, they were performed in an air-conditioned room, which likely contributed to the problem. The effect of decreased body temperature on anesthetic requirements has been discussed in greater detail elsewhere, but briefly, sevoflurane MAC was likely altered by <10% to 15% in these horses. In fact, the mean sevoflurane MAC determined for these horses was 2.42%,10 which is similar to that reported in a previous study11 conducted by another laboratory group. Because body temperatures were similar in all experiments, temperature would not have had any greater effect on one treatment than on another treatment.

It has been suggested7 that IV infusions of lidocaine during inhalation anesthesia of horses may result in worse ataxia and a decreased quality of recovery; therefore, it was suggested that lidocaine infusion be discontinued 30 minutes before the end of anesthesia to minimize these problems. In the study reported here, lidocaine infusion was discontinued 20 minutes before sevoflurane delivery was terminated and no additional sedatives were administered before or during recovery. For these conditions, no significant or clinically relevant differences in recovery quality or times were found. Although it appeared that when horses received lidocaine infusions they required more time until standing (42 minutes), compared with the time for horses when they received sevoflurane alone (33 minutes), the difference of 9 minutes in recovery after approximately 3 hours of anesthesia was not significant and unlikely to be clinically important.

We concluded that supplementation of anesthesia with sevoflurane by IV administration of lidocaine in nonstimulated horses did not result in deterioration or improvement of cardiovascular and respiratory measurements, compared with results for an equivalent dose (1.0 or 1.5 MAC) of sevoflurane alone. Clinically important hypotension is likely to develop in nonstimulated horses at 1.5 MAC, whether sevoflurane is used alone or in conjunction with lidocaine. Therefore, the decision for IV administration of lidocaine to nonstimulated anesthetized horses should be made because of improvements in analgesia, promotility effects, or antiarrhythmic effects and not because of improvement in blood pressure or perfusion. Whether the cardiovascular effects of lidocaine infusions in sevoflurane-anesthetized horses at other MAC multiples or during surgical stimulation are different from those reported here remains to be determined.

References

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