Effects of ventilation and isoflurane end-tidal concentration on intracranial and cerebral perfusion pressures in horses

Robert J. Brosnan, DVM, PhD; Eugene P. Steffey, VMD, PhD; Richard A. LeCouteur, BVSc, PhD; Ayako Imai, DVM, MS; Thomas B. Farver, PhD; Gregg D. Kortz, DVM

Objective—To measure the effects of isoflurane end-tidal concentration and mode of ventilation (spontaneous vs controlled) on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) in horses.

Animals—6 adult horses of various breeds.

Procedures—Anesthesia was induced and maintained with isoflurane in O2 in 6 healthy, unmedicated adult horses. Using a subarachnoid strain gauge transducer, CPP was measured. Blood gas tensions and carotid artery pressures also were measured. Four isoflurane doses were studied, corresponding to the following multiples of the minimum alveolar concentration (MAC): 1.0 MAC, 1.2 MAC, 1.4 MAC, and 1.6 MAC. Data were collected during controlled ventilation and spontaneous ventilation at each dose.

Results—Increasing isoflurane end-tidal concentration induced significant dose-dependent decreases in mean arterial pressure (MAP) and CPP but no change in ICP. Hypercapnic spontaneous ventilation caused significant increases in MAP and ICP, compared with normocapnic controlled ventilation; no change in CPP was observed.

Conclusions and Clinical Relevance—Hypercapnia likely increases cerebral blood flow (CBF) by maintaining CPP in the face of presumed cerebral vasodilation in healthy anesthetized horses. The effect of isoflurane dose on CBF, however, remains unresolved because it depends on the opposing influences of a decrease in CPP and cerebral vasodilation. (Am J Vet Res 2003;64:21–25)

Cerebral blood flow (CBF) is the quotient of cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR) and normally remains fairly constant over a wide range of CPP via cerebrovascular autoregulation. However, CO2 and the potent inhalant anesthetics produce dose-dependent and heterogeneous cerebral vasodilation and thus have the potential to alter cerebral hemodynamics. Increasing isoflurane dose in neurologically normal cats and baboons decreases CPP as a result of a decrease in mean arterial pressure (MAP) and, in the former study, an increase in intracranial pressure (ICP); nevertheless, CBF is preserved as a result of a decrease in CVR. In fact, isoflurane-mediated cerebral vasodilation can even lead to an increase in CBF over awake values in healthy dogs. Hypercapnia, first shown to decrease CVR and increase CBF in resting humans, produces similar effects under isoflurane anesthesia in rats, rabbits, cats, and dogs. Intracranial pressures also are inclined to increase, although increases in MAP that accompany respiratory acidosis preserve or even increase CPP.

The cerebral circulation in horses is subject to large changes in hydrostatic pressure concomitant with vertical changes in head position relative to the heart. Although head elevation in awake horses has minimal effect on ICP,12 isoflurane-anesthetized horses have substantial intracranial hypertension during head-dependent postures. Moreover, anesthetic dose-dependent systemic hypotension14,15 may further compromise CPP and perhaps CBF, although increased arterial pressures in hypercapnic horses during spontaneous ventilation might ameliorate these effects, compared with normocapnic horses during controlled ventilation. Possible increases in ICP and decreases in CPP associated with isoflurane anesthesia may lead to cerebral hypoperfusion and substantively contribute to anesthetic and postanesthetic morbidity (ie, violent or atactic recovery, delayed return to performance).

The purpose of the study reported here was to measure the effects of isoflurane end-tidal concentration and mode of ventilation (spontaneous vs controlled) on ICP and CPP in horses. Our study was designed to test the following hypotheses: (1) CPP in horses anesthetized with isoflurane decreases in a dose-dependent manner as a primary function of dose-dependent decreases in MAP and (2) spontaneous ventilation with associated hypoventilation causes increases in ICP and MAP that oppose change to CPP.

Materials and Methods

Animals—Our study was conducted at Davis, California (located near sea level) and included 1 Holsteiner, 1 Quarter Horse, 2 Thoroughbreds, and 2 warmblood horses with an equal number of mares and geldings. Horses were 3 to 8 years old (mean ± SD, 5.5 ± 1.9 years old) and weighed from 453 to 603 kg (558 ± 59 kg). The Animal Use and Care Committee at the University of California-Davis approved this protocol.

Anesthesia—Food was withheld 12 hours prior to the experiment; water was available ad libitum. Anesthesia was induced in unpremedicated horses with isoflurane in O2 delivered via a face mask by use of a protocol that has been
published previously. Following intubation with a 30-
mml-diameter cuffed orotracheal tube, horses were placed in
left lateral recumbency and connected to a standard large-
animal, semi-closed anesthetic circuit; the head was orientated
in the sagittal plane, level with the thoracic inlet. For the first
hour of each experiment, anesthesia was maintained with
spontaneous ventilation of 1.7 to 2.0% isoflurane in O2 to
prevent gross, purposeful movement during surgical instru-
mament and catheter placement. Lactated Ringer’s solution
was administered at 3 mL • kg⁻¹ • h⁻¹ through a left medial
saphenous vein catheter to replace insensible and urinary
fluid losses. Blankets and heat lamps were used as needed to
maintain normothermia.

Instrumentation—Systolic and diastolic arterial blood
pressures were measured from a percutaneous, 14-gauge,
17.6-cm-long, polytetrafluoroethylene right carotid artery
catheter connected to a strain gauge transducer that was cali-
brated against a mercury manometer; MAP was obtained as
the electronic signal mean. Central venous pressure was mea-
sured from a second percutaneous, 6.5-F, 110-cm-long, poly-
ethylene catheter connected to a strain gauge transducer that
was calibrated with a water manometer and advanced from
the right jugular vein into the right atrium, as confirmed by
pressure waveform tracings. Heart rate was determined from
a single axis (base-apex) EKG. Airway pressure and respira-
tory rate were quantified with a water manometer-calibrated
differential pressure transducer. Respiratory airflow was
measured with a Silverman style pneumotachometer and dif-
ferential pressure transducer that was calibrated with a
rotameter of certified accuracy. Electronic integration of the
expiratory flow curve yielded tidal volume; the integrator
signal was calibrated against a volumetric syringe. Gas vol-
umes measured at ambient temperature (20.2 to 23.0°C)
were corrected to body temperature and pressure saturated
with water (BTPS) by use of Charles’ Law. Body temperature
was measured with a calibrated nasopharyngeal electronic
thermometer. End-tidal isoflurane and end-tidal CO₂ were
measured with infrared gas analyzers, and fraction of
inspired O₂ (FiO₂) was measured with a polarographic O₂
sensor; all analyzer readings were corrected to standard
curves derived from multiple certified standard gases.
Arterial partial pressures of O₂ and CO₂ (PaO₂, PaCO₂)
and arterial pH (pHₐ) were obtained by use of an automated
blood gas analyzer with values corrected to standard curves
derived via tonometry of equine blood with certified gas mix-
tures. Direct ICP measurements were obtained from a sub-
arachnoid strain-gauge transducer placed through a right
parietal craniotomy according to a published surgical proce-
dures; transducers were electronically calibrated prior to
placement, and accuracy was verified after each experiment
by use of a graduated water column. Cerebral perfusion pres-
sure was calculated as the difference between MAP and ICP
(CPP = MAP – ICP).

Experimental protocol—After completion of instru-
mament during the first hour of anesthesia, horses were
studied at each of the following multiples of the minimum
alveolar concentration (MAC) of isoflurane in randomized
order: 1.0 MAC (1.31%), 1.2 MAC (1.57%), 1.4 MAC
(1.83%), and 1.6 MAC (2.10%). At the first dose, breathing
was controlled to provide normocapnia by use of intermittent
positive pressure ventilation such that peak inspiratory and
end-expiratory pressures were 20.6 ± 0.7 and 1.7 ± 0.4 cm
H₂O (mean ± SD), respectively. Responses were measured
following 30 minutes maintenance at this constant (steady-
state) end-tidal concentration. Next, the horse was permitted
to breathe spontaneously at the same steady-state isoflurane
concentration, and responses were measured 10 minutes fol-
lowing the first spontaneous breath at identical constant end-
tidal isoflurane concentrations. This protocol for measure-
ments during controlled and spontaneous ventilation was
repeated for each subsequent isoflurane dose. At the end of
our study, all instruments were removed and horses were
recovered from anesthesia.

Data analysis—Data were analyzed by use of a 2-factor
dose (dose and ventilation mode) repeated-measures ANOVA with
dose × ventilation mode interaction included in the
model. Bonferroni adjustments were made for treatment
comparisons; contrasts were deemed significant at P < 0.05.
Two horses became hypoxic (Pao₂ < 80 mm Hg) during at
least 1 measurement in our study; analyses were therefore
repeated on the remaining 4 horses to assess whether this
might be a confounding factor. Two-tailed post hoc tests were
used for analysis of the response variables for all horses. One-
tailed probabilities were used for repeat post hoc analysis of
response variables for normoxic horses, because these
tests were designed to determine whether significant differ-
ences had the same sign as counterpart analyses that includ-
ed all horses.

Results

Individual ICP and CPP values ranged from high
values of 81 and 113 mm Hg to low values of 21 and
24 mm Hg, respectively (Table 1). Isoflurane caused
significant dose-dependent decreases in MAP and CPP
of similar magnitude (Table 2). Worsening hypoventi-
ation, as evidenced by an increase in PaCO₂ resulting
from a decrease in expired volume per unit time, also
was observed during spontaneous ventilation; however,
these changes were not significant given the sample
size used in this study. Spontaneous ventilation, com-
pared with controlled ventilation, resulted in an
increase in MAP and ICP, which averaged 0.7 mm Hg
for each mm Hg increase in PaCO₂; no effect on CPP
was observed. Central venous pressure and heart rate
were affected by neither isoflurane dose nor ventilation
mode. Spontaneous ventilation resulted in a decrease in
blood pH and caused a significant increase in base
excess (0.88 ± 0.54 mEq/L), compared with controlled
ventilation.

Two horses became hypoxic toward the end of
the study, with O₂ tensions in each horse reaching a
nadir of 47 and 68 mm Hg. An analysis that included
data from only normoxic horses produced similar
results to those obtained from using data from all hors-
es (Table 2). In fact, contrasts using normoxic horses
resulted in slightly greater differences with smaller SD
than when all horses were included. Nevertheless,
some contrasts with only normoxic horses were not
significant (range, P = 0.056 to 0.062), most likely as a
consequence of insufficient power rather than con-
 founding effects of hypoxemia.

Discussion

Although isoflurane and CO₂ are reputed cerebral
vasodilators, these compounds differ in their effects on
systemic and cerebral hemodynamics in horses. Isoflurane
causes a dose-dependent decrease in MAP
without affecting ICP, thereby resulting in a decrease in
CPP. These changes are most apparent at higher MAC
multiples (1.4 and 1.6) than at lower multiples (1.0
and 1.2). In contrast, hypercapnia causes increases in
MAP and ICP of approximately equal magnitude at all
isoflurane anesthetized rats decreases CBF.11

There also is evidence to indicate that an increase in cerebral hypoperfusion and ischemic damage, especially given previous measurements of CPP in awake horses of 101 ± 22 mm Hg.12 Furthermore, profound intracranial hypertension (> 70 mm Hg) present in 1 horse during spontaneous ventilation at all isoflurane doses may augment intracranial elastance which, in turn, could cause factors that lower CBF (such as an increase in cerebral blood volume and systemic hypotension) to outweigh factors that otherwise would promote CBF (eg, a decrease in CVR) during isoflurane anesthesia and hyperventilation. Hence, in the absence of adequate physiologic compensation, increases in blood vessel caliber and blood volume that decrease resistance to flow also would increase ICP and decrease CPP. Given high intracranial elastance, the magnitude of CPP decrease may exceed the magnitude of CVR decrease, resulting in an overall decrease in CBF.

An increase in the alveolar-arterial difference in partial pressure of oxygen (PaO₂ - PaO₂) from ventilation-perfusion mismatching is common in horses during anesthesia23-25 and can lead to hypoxemia and compromised cerebral O₂ delivery. The repeated analysis excluding 2 horses that became hypoxic during part of our study despite a FIO₂ > 0.9 did not substantially change our results. Results of studies in sheep26,27 and

### Table 1—Mean (± SD) pressure and ventilation measurements at 4 isoflurane doses during controlled ventilation and spontaneous ventilation in 6 laterally recumbent horses

<table>
<thead>
<tr>
<th>Isoflurane dose</th>
<th>1.0 MAC</th>
<th>1.2 MAC</th>
<th>1.4 MAC</th>
<th>1.6 MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>CV (n = 6)</td>
<td>SV (n = 6)</td>
<td>CV (n = 6)</td>
<td>CV (n = 6)</td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>128 ± 28</td>
<td>154 ± 9</td>
<td>127 ± 26</td>
<td>147 ± 25</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>105 ± 25</td>
<td>120 ± 9</td>
<td>108 ± 26</td>
<td>116 ± 24</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>32 ± 2.9</td>
<td>49 ± 17</td>
<td>30 ± 4</td>
<td>49 ± 16</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>74 ± 19</td>
<td>70 ± 19</td>
<td>78 ± 24</td>
<td>67 ± 19</td>
</tr>
<tr>
<td>CPR (mm Hg)</td>
<td>10 ± 5</td>
<td>9 ± 6</td>
<td>8 ± 3</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>36 ± 19</td>
<td>37 ± 5</td>
<td>37 ± 2</td>
<td>36 ± 4</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>12 ± 2</td>
<td>7 ± 5</td>
<td>11 ± 1</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>V̇E (mL/kg)</td>
<td>NA</td>
<td>22 ± 9</td>
<td>NA</td>
<td>20 ± 8</td>
</tr>
<tr>
<td>V̇̇E (mL/kg/min)</td>
<td>NA</td>
<td>248 ± 65</td>
<td>NA</td>
<td>74 ± 18</td>
</tr>
<tr>
<td>Pao₂ (mm Hg)</td>
<td>299 ± 113</td>
<td>254 ± 124</td>
<td>261 ± 129</td>
<td>189 ± 87</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>46 ± 3</td>
<td>64 ± 13</td>
<td>44 ± 2</td>
<td>64 ± 8</td>
</tr>
<tr>
<td>pHa</td>
<td>7.41 ± 0.04</td>
<td>7.31 ± 0.07</td>
<td>7.42 ± 0.02</td>
<td>7.30 ± 0.05</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>34 ± 5</td>
<td>37 ± 8</td>
<td>34 ± 4</td>
<td>37 ± 5</td>
</tr>
<tr>
<td>T3 (µg/dL)</td>
<td>6.4 ± 0.5</td>
<td>6.4 ± 0.4</td>
<td>6.3 ± 0.4</td>
<td>6.3 ± 0.4</td>
</tr>
</tbody>
</table>

*Values exclude 2 hypoxic horses.

### Table 2—Mean (± SD) significant (P < 0.05) isoflurane dose (MAC) and ventilation mode treatment differences for all horses (n = 6) and for horses that remained normoxemic throughout the study (4, values in parentheses)

<table>
<thead>
<tr>
<th>Contrasts*</th>
<th>1.0 MAC – 1.6 MAC</th>
<th>1.2 MAC – 1.6 MAC</th>
<th>CV – SV</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>27 ± 10 (32 ± 3)</td>
<td>26 ± 14</td>
<td>−15 ± 9 (−15 ± 11)</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>NS</td>
<td>NS</td>
<td>−17 ± 10 (−19 ± 11)</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>27 ± 8 (30 ± 7)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Pao₂ (mm Hg)</td>
<td>NS</td>
<td>NS</td>
<td>62 ± 47</td>
</tr>
<tr>
<td>HbO₂ (mm Hg)</td>
<td>NS</td>
<td>NS</td>
<td>−23 ± 9 (−26 ± 10)</td>
</tr>
<tr>
<td>pHa</td>
<td>0.13 ± 0.04 (0.14 ± 0.04)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Contrasts of 1.0 to 1.2 MAC, 1.0 to 1.4 MAC, 1.2 to 1.4 MAC, and 1.4 to 1.6 MAC resulted in no significant differences in variable measurements.
NS = Not significant.
See Table 1 for remainder of key.

isofoflurane doses and, therefore, does not produce a net change in CPP. Thus, hypoventilation may be expected to increase CBF in horses by maintaining CPP in the face of a presumptive decrease in CVR. The effects of isoflurane dose on CBF would depend on the opposing magnitudes of systemic hypotension and cerebral vasodilatation, although results of studies on rats16 and humans19 suggest a greater role for the latter.

There also is evidence to indicate that an increase in CBF during isoflurane anesthesia is accompanied by a dose-dependent decrease in cerebral metabolic rate, whereas increased MAP in isoflurane-anesthetized dogs has been shown to increase CBF highly dependent on CPP. For instance, increasing MAP in isoflurane-anesthetized dogs may render the cerebral circulation a pressure-passive system with CBF highly dependent on CPP. For instance, increasing MAP in isoflurane-anesthetized dogs has been shown to increase CBF likely delivery, particularly at high doses, whereas hypotension in hypercarbic isoflurane-anesthetized rats decreases CBF.11 In this study, 2 horses anesthetized with isoflurane at 1.6 MAC had CPP values of 28 and 38 mm Hg; a third horse at this same dose had a MAP of 57 mm Hg and a CPP of 24 mm Hg during spontaneous ventilation. Given a pressure-passive cerebral vascular response, these horses might likewise be at greater risk for cerebral hypoperfusion and ischemic damage, especially given previous measurements of CPP in awake horses of 101 ± 22 mm Hg.12 Furthermore, profound intracranial hypertension (> 70 mm Hg) present in 1 horse during spontaneous ventilation at all isoflurane doses may augment intracranial elastance which, in turn, could cause factors that lower CBF (such as an increase in cerebral blood volume and systemic hypotension) to outweigh factors that otherwise would promote CBF (eg, a decrease in CVR) during isoflurane anesthesia and hyperventilation. Hence, in the absence of adequate physiologic compensation, increases in blood vessel caliber and blood volume that decrease resistance to flow also would increase ICP and decrease CPP. Given high intracranial elastance, the magnitude of CPP decrease may exceed the magnitude of CVR decrease, resulting in an overall decrease in CBF.
dogs have shown that ICP increases and CPP decreases with hypoxia; a decrease in CVR permits a compensatory increase in CBF. Similar changes in ICP and CPP might not have been observed in these hypoxic horses, either because too few horses were affected to detect a difference or because the degree and duration of hypoxemia were insufficient to produce a detectable difference. Nevertheless, for most horses and most anaesthetic doses, significant differences in PaO$_2$ difference. Nevertheless, for most horses and most of hypoxemia were insufficient to produce a detectable difference. Nevertheless, for most horses and most 

Differences in cerebral hemodynamics between controlled ventilation and spontaneous ventilation cannot be entirely attributed to changes in PaCO$_2$. Peak inspiratory pressure and respiratory rates were generally higher during controlled ventilation than spontaneous ventilation, and intrathoracic pressure differences between ventilatory modes can alter systemic (and likely cerebral) blood flow. In addition, metabolic compensation during spontaneous ventilation, as indicated by an increase in base excess, may have attenuated increases in cardiac output, carotid artery flow, and ICP, resulting in underestimation of the cerebrovascular response to PaCO$_2$.

Results of our study indicate that isoflurane anesthesia in horses decreases CPP as a function of anesthetic dose and that permissive hypercapnia during spontaneous ventilation increases ICP and MAP. At present, CBF in horses has not been quantified; therefore, the effects of drugs and ventilation mode on cerebral perfusion must be inferred from relationships to CPP and ICP as well as from extrapolation from data in other species. However, a predilection for concurrent intracranial hypertension, low perfusion pressure, and hypoxemia may place even healthy anesthetized horses at far greater risk for cerebral ischemic damage than is currently appreciated in other species. It is quite conceivable that such profound alterations in cerebral hemodynamics in horses may yet prove to be a contributing factor to common perianesthetic challenges (eg, violent recovery, slow return to performance) as well as to overt, but rare, postanesthetic complications (eg, blindness, seizures).

References

Correction: Detection of a genetic mutation for myotonia congenita among Miniature Schnauzers and identification of a common carrier ancestor

In the article "Detection of a genetic mutation for myotonia congenita among Miniature Schnauzers and identification of a common carrier ancestor" (AJVR, Oct 2002, pp 1443-1447), the figure on page 1444 should appear as follows:

![Figure 2—Polyacrylamide gel documenting results of genomic DNA amplified by use of a PCR technique and digested by use of *Hpy CH4 III*. Lanes were as follows: M, molecular-weight markers; A, homozygous affected (myotonic) dogs; C, heterozygous dogs (carriers); N, dogs with normal alleles. Notice the fragments of 175, 135, and 30 bp for the normal allele, whereas fragments for the mutant allele were 175 and 165 bp.](image)