



Influence of changing lateral recumbency and mode of ventilation on the alveolar-arterial oxygen tension gradient and selected laboratory analytes in adult isoflurane anesthetized horses

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ABSTRACT. This study investigated the influence of changing recumbency and mode of ventilation over repeated anesthetics on the alveolar to arterial oxygen tension gradient ($P_{A-a}O_2$) and laboratory analytes in eight horses during a year-long imaging study. Anesthesia was induced with xylazine, diazepam or guaifenesin, and ketamine and maintained with isoflurane. Horses were positioned in right or left lateral recumbency for computed tomography. Ventilation was controlled during 47% of the anesthetics. Blood was sampled from an arterial catheter prior to (30 ± 5 min from connection to anesthetic circuit), within 5 min of changing lateral recumbency, and prior to circuit disconnection (24 ± 6 min after second sample) for measurement of pH, partial pressure of arterial oxygen (PaO_2) and partial pressure of arterial carbon dioxide, blood glucose and electrolytes. $P_{A-a}O_2$ was calculated. Data from five anesthetic episodes for each horse were summarized as mean \pm standard error and analyzed using a mixed-model ANOVA. *t* tests were used for pairwise comparisons ($P < 0.05$). PaO_2 decreased after turning (198 vs. 347 mmHg), then increased to 291 mmHg prior to disconnection. Correspondingly, $P_{A-a}O_2$ was wider (252 vs. 120 mmHg), and improved before disconnection (190 mmHg). Body temperature, ionized- Ca^{2+} and blood glucose were lower, and Na^+ was higher at the last time point. In conclusion, turning anesthetized horses decreases PaO_2 and results in a widening $P_{A-a}O_2$ suggesting a cautious approach in animals with pre-existing hypoxemia.

KEY WORDS: altitude, alveolar-arterial oxygen gradient, anesthesia, changing position, horse

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General anesthesia is associated with a reduction of oxygenation and ventilation in human beings [9, 21, 26, 30] and animals [40]. Hypoxemia is commonly described in anesthetized horses and maintained in both dorsal and lateral recumbency at sea level [6, 15, 17, 19, 24, 33]. Major causes of the lowered partial pressure of arterial oxygen (PaO_2) include drug induced hypoventilation, and ventilation/perfusion (V/Q) mismatching due to postural and gravitational effects [8, 20, 23, 31].

Prior reports in anesthetized horses also indicate that PaO_2 decreases are exacerbated when horses are turned from dorsal to lateral recumbency [16], from left to right lateral recumbency [23] and from right lateral to dorsal recumbency [12]. The influence of the ventilation mode on oxygenation has also been demonstrated [6, 12, 36]. However, factors influencing oxygenation such as arterial carbon dioxide tension ($PaCO_2$) or fraction of inspired oxygen (FiO_2) were either not measured or not standardized in these studies. Therefore, we elected to measure these factors and assess mode of ventilation, recumbency and the influence of changing the same in horses anesthetized at 1,525 m above sea level while undergoing computed tomography (CT) imaging for another study.

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The primary objective of the present study was therefore to evaluate the influence of initial lateral recumbency, changing recumbency and mode of ventilation on the alveolar to arterial oxygen gradient ($P_{A-a}O_2$). The study also adds to limited data of horses anesthetized at elevations above sea level. Selected laboratory analytes were also assessed.

MATERIALS AND METHODS

Animals

Two geldings and six female horses ranging between 2 and 6 years of age (mean \pm standard deviation, 3 ± 1 years) and weighing between 374 and 557 kg (mean \pm standard deviation, 453 ± 46 kg) were used in the study. The horses were group housed in a paddock with a shelter and fed a diet of grass hay. Food was withheld on the morning of each study; water was available at all times. The study was performed at approximately 1,525 m above sea level.

Experimental protocol

Following approval by the Colorado State University Institutional Animal Care and Use Committee, each horse was anesthetized five times for CT as part of a distal limb imaging study. Due to the position assigned for the CT scans, horses were turned from left lateral (LL) to right lateral (RL) recumbency for the first, third and fifth anesthetics and from RL to LL recumbency during the second and fourth anesthetics. An interval of at least one month was allowed between anesthesia episodes in each horse. Prior to each anesthetic the horses' body weight, heart rate (HR), respiratory rate (RR) and rectal temperature (T) were recorded. Horses were then sedated in a padded stall adjacent to the CT scanner with xylazine (0.5–1 mg/kg, IV; Sedazine, Fort Dodge Animal Health, Fort Dodge, IA, U.S.A.) and anesthesia induced with ketamine (2 mg/kg, IV; Ketaset, Fort Dodge Animal Health) and diazepam (0.1 mg/kg, IV; Diazepam injection USP, Hospira Inc., Lake Forest, IL, U.S.A.) or 5% guaifenesin (dose range, 200–400 ml or 10–20 g; Guaifenesin, VEDCO, St. Joseph, MO, U.S.A.) via a 14-gauge catheter in a jugular vein. Following intubation with a cuffed 26 mm orotracheal tube, the horse was hoisted and positioned in lateral recumbency on a CT table modified for equine use and the endotracheal tube connected to the anesthetic breathing circuit. Anesthesia was maintained with isoflurane in oxygen (5–6 l/min) based on clinical assessment of anesthetic depth by the anesthetist. The starting lateral recumbency was assigned based on the primary study as mentioned previously and alternated between anesthetics.

Prior to the study, an oxygen analyzer (5125 MRI Compatible Oxygen Meter; Ohmeda, CO, U.S.A.) was placed at the level of the inspiratory valve of the large animal anesthetic breathing circle to measure FiO_2 . This was calibrated at 21 and 100% oxygen prior to each anesthetic event and accuracy verified at the conclusion of each anesthesia. A balanced electrolyte solution was administered intravenously at a rate of 10 ml/kg/hr during anesthesia. HR and rhythm were monitored using a physiologic monitor (Escort II; MDE, Arleta, CA, U.S.A.). T was measured at the time of blood sampling and used to correct blood gas values. A 20-gauge catheter was placed in the facial or transverse facial artery for direct arterial blood pressure monitoring (Escort II; MDE) and to facilitate sampling for blood gas analysis. Dobutamine was infused if necessary, at a rate of 1–2 μ g/kg/min to maintain mean arterial blood pressure (MBP) greater than or equal to 70 mmHg. The use of mechanical ventilation was assigned in attempt to have an equivalent sample size between spontaneous ventilation and controlled ventilation groups. RR was set between 6 and 8 breath/min and peak airway pressure maintained between 24 and 30 cmH₂O during controlled ventilation.

Arterial blood was sampled three times during anesthesia from each horse for measurement of pH and blood gases. Blood glucose, lactate and sodium, potassium and calcium ions were also measured. The first sample was taken just prior to turning the horse from the initial lateral position to the opposite side; the second sample was taken 5 min after turning and the last sample collected just prior to anesthetic circuit disconnection from the endotracheal tube. Blood samples were anaerobically collected and placed in ice water and analyzed (ABL800Flex; Radiometer, Copenhagen, Denmark) within 30 min. Barometric pressure (P_{BAR}), and FiO_2 were recorded and along with blood gas values used to calculate the $P_{A-a}O_2$ gradient using the following equation:

$$P_{A-a}O_2 \text{ gradient} = [(FiO_2) * (P_{BAR} - P_{H_2O}) - (PaCO_2/R)] - PaO_2$$

where P_{H_2O} was the water vapor pressure (assumed to be 47 mmHg) and R the respiratory quotient, assigned a value of 0.8.

At the time of each blood sample HR, FiO_2 , T, systolic (SBP), MBP and diastolic blood pressure (DBP) were also recorded.

At the end of the study, animals were disconnected from the anesthetic machine and transferred to a padded recovery stall where they were extubated in lateral recumbency upon swallowing and continuously observed until standing; recovery was not assisted. They were then returned to their paddock.

Statistical analysis

Data were summarized as mean \pm standard error by use of SAS statistical software (PROC GLIMMIX), version 9.3 (SAS institute, Inc., Cary, NC, U.S.A.). A mixed model 2 factor analysis of variance with 2 levels including fixed and random effects was used for comparing data at the three measurement periods. Residuals from the analysis of variance were plotted to confirm that they were normally distributed and independent. The response variables included in the model were FiO_2 , pH, blood gas and acid base values, electrolytes and physiological parameters. The effects of the initial lateral recumbency (right or left), ventilation mode (spontaneous or controlled) and interactions were included in the model. Hence, we estimate and compare mean responses for the four combinations of ventilation and recumbency as described. Specifically, pairwise comparisons for ventilation mode and initial lateral recumbency were examined between sampling times by use of *t* tests (least-squares means). Tukey adjusted pairwise comparisons were performed for comparisons between all four groups. Values of $P < 0.05$ were considered statistically significant for all analyses.

Table 1. Mean \pm standard error for pH, blood gases, electrolytes and physiological parameters at three different sampling times (prior to and after changing lateral recumbency and prior to disconnection) from eight adult horses undergoing repeated anesthesia

Parameter	Prior to changing lateral recumbency	After changing lateral recumbency	Prior to disconnection	<i>P</i> values
Parameter				
FiO ₂	0.90 \pm 0.01 ^{a)}	0.87 \pm 0.01 ^{b)}	0.93 \pm 0.01 ^{c)}	<0.0001
PaO ₂ (mmHg)	347 \pm 17.4 ^{a)}	198 \pm 17.4 ^{b)}	291 \pm 17.4 ^{c)}	<0.0001
PaCO ₂ (mmHg)	53 \pm 1.6	56 \pm 1.6	55 \pm 1.6	0.41
P _{A-a} O ₂ (mmHg)	120 \pm 16 ^{a)}	252 \pm 16 ^{b)}	190 \pm 16 ^{c)}	<0.0001
pHa (units)	7.35 \pm 0.01	7.33 \pm 0.01	7.34 \pm 0.01	0.37
Base excess (mmol/l)	2 \pm 0.4	1.8 \pm 0.4	1.9 \pm 0.4	0.88
HCO ₃ ⁻ (mmol/l)	28.4 \pm 0.4	28.8 \pm 0.4	28.7 \pm 0.4	0.68
P _{BAR} (mmHg)	639 \pm 0.9	639 \pm 0.9	639 \pm 0.9	0.99
Electrolytes				
Na ⁺ (mEq/l)	136 \pm 0.5 ^{a)}	136 \pm 0.5 ^{a)}	137 \pm 0.5 ^{b)}	0.045
K ⁺ (mEq/l)	3.32 \pm 0.06	3.39 \pm 0.06	3.24 \pm 0.06	0.09
Cl ⁻ (mEq/l)	97.5 \pm 0.6	97.6 \pm 0.6	98.1 \pm 0.6	0.39
Anion gap (mmol/l)	13.1 \pm 0.4	13.2 \pm 0.4	13.3 \pm 0.4	0.82
Ionized Ca ²⁺ (mmol/l)	1.41 \pm 0.02 ^{a)}	1.42 \pm 0.02 ^{a)}	1.38 \pm 0.02 ^{b)}	0.012
Glucose (mg/dl)	137 \pm 3.4 ^{a)}	135 \pm 3.4 ^{a)}	121 \pm 3.4 ^{b)}	<0.0001
Lactate (mmol/l)	1.08 \pm 0.08	1.16 \pm 0.08	1.08 \pm 0.08	0.31
Physiological parameters				
T (°C)	36.6 \pm 0.2 ^{a)}	36.6 \pm 0.2 ^{a)}	35.7 \pm 0.2 ^{b)}	<0.0001
HR (beats/min)	38 \pm 1.8	36 \pm 1.8	39 \pm 1.8	0.19
SBP (mmHg)	112 \pm 4.2	105 \pm 4.2	106 \pm 4.2	0.51
MBP (mmHg)	75 \pm 2.5	73 \pm 2.5	73 \pm 2.5	0.65
DBP (mmHg)	60 \pm 2.4	60 \pm 2.4	59 \pm 2.4	0.87

Different letters denote significant differences for a given parameter at the three measurement time points (*P*<0.05).

RESULTS

Data from 28 anesthetics were included for analysis and were equivalently distributed from each of the 5 consecutive anesthetic periods: 20, 19, 22, 19 and 20%, respectively. Twelve anesthetic events were excluded for varying reasons such as exceeding the time allocated for sample collection or malfunction of the oxygen analyzer. Ventilation was controlled in 47% (n=13) of anesthetics; 53% (n=15) breathed spontaneously. Horses were first positioned in LL recumbency 61% or 17 times and in RL recumbency 39% or 11 times. Horses breathed isoflurane for 62 \pm 18 min (mean \pm standard deviation). Duration between anesthetic induction and the first blood sample was 30 \pm 5 min; 24 \pm 6 min (mean \pm standard deviation) elapsed between the second and third blood samples. Dobutamine (1 μ g/kg/min) was administered (for 30 and 40 min) during two anesthetic episodes.

FiO₂, P_{BAR}, calculated P_{A-a}O₂, temperature-corrected PaO₂ and PaCO₂, pH, HCO₃⁻, base excess, electrolytes and physiological parameters in horses prior to and after changing lateral recumbency and prior to circuit disconnection are reported in Table 1. The overall (regardless of initial recumbency) PaO₂ decreased from 347 mmHg to 198 mmHg (*P*<0.0001) after turning and then increased to 291 mmHg prior to disconnection (198 vs. 291 mmHg, *P*<0.0001); however, PaO₂ prior to disconnection remained lower than the pre-turning value (*P*=0.0024). Correspondingly, compared to the initial value (120 mmHg), the P_{A-a}O₂ was greater after turning (252 mmHg, *P*<0.0001) and remained elevated compared to the initial values prior to disconnection (190 vs. 120 mmHg, *P*=0.0002). However this improved (190 vs. 252 mmHg, *P*=0.0006) over time from post-turning to pre-disconnection. PaCO₂, P_{BAR}, pH, HCO₃⁻ and base excess did not change significantly.

Sodium, ionized calcium and glucose obtained from the third blood sample (prior to disconnection) were different from those of the first and second samples. Potassium, chloride, anion gap and lactate did not change at all time. T decreased significantly from 36.6°C at the first and second blood sampling to 35.7°C before disconnection (*P*<0.0001). HR, SBP, MBP and DBP did not vary over time.

Regardless of the effects of initial position or turning, PaCO₂ and HCO₃⁻ were higher and pH lower in horses breathing spontaneously as compared to those being mechanically ventilated. Horses rotated from LL to RL recumbency had a lower PaO₂ and higher P_{A-a}O₂, PaCO₂, and HCO₃⁻ than those rotated from RL to LL recumbency averaged over all-time points. (Table 2) PaO₂ values prior to and after changing lateral recumbency and prior to disconnection were 365, 208 and 334 mmHg, respectively in horses starting in RL recumbency and 329, 187 and 249 mmHg, respectively in horses starting in LL recumbency. Correspondingly, the P_{A-a}O₂ in horses starting in RL were 100, 242 and 150 mmHg while values in horses starting with LL were 141, 261 and 229 mmHg prior to and after turning and prior to disconnection, respectively. While of potential clinical relevance, neither the PaO₂ nor P_{A-a}O₂ were statistically different at any time point. Additionally, no statistical difference was seen in the PaO₂ or P_{A-a}O₂ when the interaction of recumbency and ventilation mode were considered (Table 3).

Table 2. Mean \pm standard error of blood gas values averaged over all time points for spontaneous (SV) and controlled (CV) ventilation, and for horses starting in left (LL) or right (RL) lateral recumbency

	PaO ₂ (mmHg)	PaCO ₂ (mmHg)	P _{A-a} O ₂ (mmHg)	pHa (units)	HCO ₃ ⁻ (mmol/l)
Ventilation					
SV	276 \pm 17	61 \pm 1.6	182 \pm 16	7.30 \pm 0.009	29.3 \pm 0.37
CV	281 \pm 16	49 \pm 1.4	193 \pm 15	7.38 \pm 0.008	28.1 \pm 0.33
<i>P</i> values	0.73	<0.0001	0.54	<0.0001	0.0075
First lateral recumbency					
LL	255 \pm 15	57 \pm 1.3	211 \pm 14	7.34 \pm 0.008	29.4 \pm 0.3
RL	302 \pm 17	52 \pm 1.7	164 \pm 17	7.35 \pm 0.01	28 \pm 0.4
<i>P</i> values	0.0071	0.0223	0.0075	0.2643	0.0009

Table 3. Mean \pm standard error comparisons of pH, blood gas values and the alveolar to oxygen gradient between all four-treatment group (right [RL] and left [LL] lateral, spontaneous [SV] and controlled [CV] ventilation) combinations

	PaO ₂ (mmHg)		PaCO ₂ (mmHg)		P _{A-a} O ₂ (mmHg)		pHa (units)	
	LL	RL	LL	RL	LL	RL	LL	RL
CV	265 \pm 21	297 \pm 19	51 \pm 2 ^{a,b}	46 \pm 1.8 ^a	211 \pm 20	175 \pm 18	7.37 \pm 0.01 ^a	7.39 \pm 0.01 ^a
SV	245 \pm 17	307 \pm 26	63 \pm 1.5 ^c	58 \pm 2.8 ^{b,c}	210 \pm 15	153 \pm 25	7.30 \pm 0.01 ^b	7.30 \pm 0.02 ^b

Different letters denote significant differences ($P < 0.05$).

DISCUSSION

Lateral recumbency in the anesthetized horse reduces lung volume in dependent (lowermost) lung regions [34], and can result in ventilation perfusion mismatching or pulmonary shunting [31] and impaired gas exchange. A decrease in PaO₂ and increasing P_{A-a}O₂ gradient are therefore commonly described in equine anesthesia from horses at sea level. These data suggest that similar effects are observed in horses anesthetized at altitude albeit the magnitude may differ.

This study supports that at least a transient decrease in PaO₂ and corresponding increase in P_{A-a}O₂ gradient (which accounts for the influence of P_{BAR}, FiO₂ and PaCO₂) after turning horses is likely. Atelectasis and changes in ventilation and perfusion ratios are likely to influence this as has been previously proposed. [8, 20, 23, 31]. While a slight decrease in measured FiO₂ from 0.90 to 0.87 due to disconnection of the circuit during the position change may have played a role in the decreased PaO₂ value, the P_{A-a}O₂ gradient, which accounts for changes in FiO₂ indicates this was not a major factor.

One study reports radiopacity of the uppermost lung persists for more than 20 min after changing lateral recumbency in ponies [23]. Improvement in PaO₂ was however seen in the current study within this period as reflected in pre-disconnection values. Interestingly, in the eight samples collected from horses in both RL and LL recumbency between 6–10 min after turning (and therefore not included in the overall analysis) the PaO₂ had already improved to 241 mmHg and P_{A-a}O₂ decreased to 205 mmHg. Compared to PaO₂ of 198 mmHg and P_{A-a}O₂ of 252 mmHg obtained from blood collected within 5 min of turning this suggests a rapid improvement in pulmonary function.

To minimize well-documented adverse effects of hypotension in horses, we aimed to maintain a mean blood pressure greater than 70 mmHg. As mentioned dobutamine was infused in two anesthesia periods to two different horses for 30 and 40 min. It is hard to ascertain the influence of this limited data on blood gas values, but arterial blood pressure remained consistent over time.

PaCO₂ did not change significantly in response to changing recumbency. This is in agreement with a previous study in foals [4] and not surprising as PaCO₂ is more likely to be influenced by anesthetic depth in spontaneously breathing animals and less affected by ventilation perfusion changes [32]. The pH, HCO₃⁻ and base excess were also unchanged.

Of clinical interest results of the current study showed that horses starting in RL recumbency had consistently (but not significantly) higher PaO₂ values and a lower A–a gradient than horses starting in LL recumbency. While this represents only a limited number of horses these findings are in agreement with prior study [6] and literature that suggests LL recumbency in horses provides a better V/Q relationship than RL recumbency during anesthesia [18]. However, the opposite is also reported in a study using radioactive gas for investigation of the V/Q relationship [22]. Interestingly this study reports a larger A–a difference regardless of whether the right side was the first or second side down. The cause for these differences remains unknown but may relate to differences in methodology, potential lack of power in some studies, the breed and body shape of horses, etc.

PaCO₂ and HCO₃⁻ were higher and pH was lower in spontaneously breathing as compared to mechanically ventilated horses. This is consistent with prior reports [6, 28, 36, 41]. However, unlike some prior reports in anesthetized horses and ponies, the PaO₂ and P_{A-a}O₂ in the current study did not differ between the two ventilation modes [6, 12, 36]. The reasons for this are unknown but there is the possibility of the impact of different anesthesia protocols since ventilation parameters were similar. It is interesting that

radiographic evidence suggests that the distribution of inspired gas or ratio of dependent and independent tidal volume does not change with mechanical ventilation alone [3, 25].

Ionized calcium (pH corrected), sodium and glucose in the final blood sample differed significantly from earlier values, but both the ionized calcium (1.38 mmol/l) and sodium (137 mEq/l) remained in the normal range (1.25–1.75 mmol/l and 130–142 mEq/l, respectively; clinical reference intervals from Colorado State University-Veterinary Teaching Hospital). The increase in sodium may be associated with the decrease in T at that time (35.7°C) as is reported in hypothermic-anesthetized humans, rats and rabbits [27]. The mechanism remains unknown. Hypothermia is also associated with increase in intracellular ionized calcium especially in myocardial cells [2], reducing the concentration in blood. An alternative explanation is that the drugs used in the peri-anesthesia period may change the electrolyte concentrations. For example, diazepam has been shown to increase blood calcium, sodium and potassium in rats [11]. Similarly, ketamine and xylazine are shown increase plasma sodium and calcium in rabbits [14], whereas plasma calcium and phosphorus decrease significantly after xylazine injection in white-tailed deer [5]. Specific to the horse, total calcium concentration in serum decreases during halothane anesthesia following xylazine premedication in horses [13].

Although blood glucose values obtained from the pre-disconnection sample (121 mg/dl) were lower than those of prior samples (137 and 135 mg/dl), the glucose level remained within the upper limit of the normal range (70–135 mg/dl; reference intervals from Colorado State University-Veterinary Teaching Hospital). Glucose in the first blood sample was slightly above the normal range and was likely caused by the administration of the α -2 agonist, xylazine given for premedication. This phenomenon is well documented in horses [35, 37–39] and thought to be the result of inhibition of insulin secretion mediated via α -2A adrenoceptors on pancreatic β cells [1, 7, 10, 29].

Despite a small number of horses used in the study, data from 28 anesthetics was available and provided adequate power to assess key outcome variables over the duration of this study. In addition to information related to the influence of position and its change, and mode of ventilation on PaO₂ and the P_{A-a}O₂ gradient, the study provides baseline information about blood gas and electrolyte values in horses anesthetized at an altitude of approximately 1,525 m.

Results confirm that changing lateral recumbency during anesthesia can decrease blood oxygen tension and widen the alveolar to arterial gradient for oxygen in clinically normal horses. While caution is advised when turning animals and especially those with pre-existing hypoxemia, in these normal horses the negative effects resulting from the postural change lessened over time. In these horses, oxygenation was not different with controlled ventilation despite a lower PaCO₂. Due to lack of significant data in the current study and mixed results from prior studies, it remains unclear if lung function would be better supported by placing the horse in a specific lateral recumbency.

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