THE EFFECTS OF A REDUCED FRACTIONAL INSPIRED OXYGEN CONCENTRATION ON VENTILATION AND A-a OXYGEN GRADIENT IN ISOFLURANE ANESTHETIZED HORSES

by

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Abstract

Introduction

Hypoventilation ($PaCO_2$ > 45 mmHg) and large $P_{(A-a)}O_2$ gradients due to V/Q mismatch and shunt, are common during isoflurane anesthesia in horses. A fraction of inspired oxygen < 50% has been shown to improve ventilation and decrease intra-operative atelectasis in humans and some animals. The study compared the effects of two different fractions of inspired oxygen, 50% versus > 95%, on ventilation, respiratory pattern, and $P_{(A-a)}O_2$ gradient in isoflurane anesthetized horses.

Materials and Methods

Eight mature horses were sedated with IV xylazine (1.0 mg/kg) and anesthetized with diazepam (0.05 mg/kg) and ketamine (2.2 mg/kg) twice. Anesthesia was maintained with isoflurane (E_T1.5 vol%) in either 50 or > 95% oxygen for 90 minutes. Both treatments were randomly assigned to each horse with a one week interval in between treatments. Horses were positioned in dorsal recumbency, connected to a preloaded circle breathing system and allowed to spontaneously ventilate. Measurements included inspiratory and expiratory peak flow and time, tidal volume, respiratory frequency, E_TCO_2, $P_{\bar{E}}CO_2$, $P_{\bar{E}}O_2$, PaO_2, $PaCO_2$, pH, SaO_2, heart rate, and arterial blood pressure. Calculated values included PAO_2, $P_{(A-a)}O_2$, $P_{(A-a)}O_2$ rate of change, and physiologic dead space.

Results

FiO_2 of 50% resulted in a lower PaO_2, SaO_2, PAO_2, and $P_{(A-a)}O_2$. No significant change in $PaCO_2$, ventilatory pattern, or any remaining measured variables was observed ($p<0.05$).

Discussion

The use of 50% oxygen and nitrogen as the carrier gas did not significantly change the ventilatory characteristics or improve oxygenation in isoflurane anesthetized horses. Repeatable respiratory rhythms characteristics were observed for horses while inspiring 50% and > 95% oxygen. A high A-a oxygen gradient with an equal rate of change overtime was still observed during both treatments.

Table of Contents

List of Figures

List of Tables

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Chapter 1 - Introduction and Materials and Methods

Introduction

There are several anesthetic related complications that occur with greater frequency or magnitude in horses than with other species. Among these complications are hypoventilation and large alveolar to arterial oxygen gradients ($P_{(A-a)}O_2$), which may result in hypoxemia despite high inspired oxygen concentrations.

Hypoventilation, described as an increase in $PaCO_2$ to greater than 45 mmHg, is a well-recognized problem and has been documented during equine inhalant anesthesia and, to a lesser degree, during total intravenous anesthesia.[1-2] The increased $PaCO_2$, during isoflurane anesthesia, is a result of a lower respiratory rate while tidal volume is maintained or even increased. [1,3] Horses anesthetized with isoflurane in 100% oxygen often show an irregular respiratory pattern, characterized by a low respiratory rate with prolonged periods of apnea.[1,3-4] This irregular pattern and increased $PaCO_2$ may require intermittent positive pressure ventilation, which may decrease cardiac output. [5] Cuvelliez et al. showed that horses anesthetized with halothane in 30% oxygen had a lower $PaCO_2$ when compared to horses anesthetized with halothane in 85% oxygen.[2] Subsequently, Marntell et al. reported that horses anesthetized with tiletamine-zolazepam hypoventilate to a greater degree when maintained on an inspired oxygen concentration of > 95% compared to 21% oxygen.[6]

Large $P_{(A-a)}O_2$ is a common clinical finding in anesthetized horses and has been well documented in spontaneously and mechanically ventilated horses.[7-9] Many patients become hypoxemic (PaO_2 < 60 mmHg) even while breathing 100% oxygen.[7,10] The large $P_{(A-a)}O_2$ is usually the result of ventilation perfusion mismatch and intrapulmonary shunt caused by atelectasis. Pulmonary shunt has been shown to increase to 21-51% (average 34%) while under anesthesia compared to the 4-7% shunt measured while the horses were standing prior to anesthesia.[11-12] Airway closure and atelectasis can be responsible for up to 74% of gas exchange impairment.[13] Administration of a high fraction of inspired oxygen (> 95%) during equine anesthesia has been associated with an increase in intrapulmonary shunt and a decrease in gas exchange.[6]

The use of a lower fraction of inspired oxygen (40-50%) is common in anesthetized humans and has been shown to decrease atelectasis and intrapulmonary shunt, resulting in improved gas exchange.[14] Utilization of air-oxygen mixes in dogs and cats demonstrated improvements in lung aeration and atelectasis when analyzed by computed tomography.[15-16] Atelectasis persists into the postoperative period and may cause decreases in PaO_2 and increase the potential for bacterial accumulation and systemic translocation.[17-19] Staffieri et al. demonstrated that by gradually increasing the fraction of inspired oxygen to > 90% in anesthetized, mechanically ventilated horses, oxygenation was improved compared to immediate use of 100% oxygen.[20]

Studies using a low fraction (30-50%) of inspired oxygen have been performed in many species. [6, 15-16, 20-21] These studies showed improvements in ventilation and reductions of intrapulmonary shunt. When managing isoflurane anesthetized horses, hypoventilation and large A-a oxygen gradients might be improved by using oxygen air mixes. [2, 6] Clinically, the reluctance to using gases other than 100% oxygen may be attributed to occasional hypoxemia (PaO_2 < 60 mmHg) despite delivering 100% oxygen. Additionally most large animal anesthetic machines are equipped with only an oxygen flowmeter and are not equipped to deliver air oxygen mixes.

The objectives of the present study were to evaluate if the use of 50% inspired oxygen compared to > 95% oxygen would, first, alter the respiratory pattern of spontaneously ventilating isoflurane anesthetized horses, by increasing ventilation and generating a more constant respiratory rhythm. A second objective was to examine if 50% inspired oxygen would reduce $P_{(A-a)}O_2$ and improve gas exchange. It was hypothesized that horses breathing 50% inspired oxygen would show an increase in minute ventilation, a decrease in $PaCO_2$, a less irregular breathing pattern, and a smaller $P_{(A-a)}O_2$ than when breathing > 95% oxygen.

List of abbreviations

$P_{(A-a)}O_2$ = Alveolar to arterial oxygen tension gradient

P_aCO_2 = Arterial carbon dioxide tension

$P_{\bar{E}}CO_2$ = Mean expired carbon dioxide tension

E_tCO_2 = End tidal carbon dioxide tension

$\frac{V_D}{V_T}$ = Physiologic dead space

P_IO_2 = Inspired oxygen tension

F_IO_2 = Fractional inspired oxygen concentration

$P_{\bar{E}}O_2$ = Mean expired oxygen tension

$F_{\bar{E}}O_2$ = Fractional expired oxygen concentration

P_AO_2 = Alveolar oxygen tension

Materials and Methods

Animals

Eight healthy horses (6 geldings, 2 mares) were used in the study. The mean ± SD age was 11 ± 4.3 years (range 6-20 years) and the mean body weight was 537 ± 48 kg. Breeds included 5 Quarter horses, 2 Thoroughbreds and 1 Appaloosa. All horses were ASA status I based on a complete blood count (CBC) and physical examination. Food and water was available until the morning of the study. Horses were randomly assigned to receive 2 treatments on separate occasions. Treatments consisted of maintenance of isoflurane (ISO) [a] anesthesia with an inspired oxygen concentration of either 50 % or > 95%. The study was approved by the Institutional Animal Care and Use Committee.

Anesthesia

Each horse was anesthetized twice with 7 days between treatments. A 14-gauge 7.5 cm catheter was placed in the right jugular vein for drug and fluid administration. Xylazine hydrochloride [b] (1.0 mg/kg, IV) was administered 5 minutes prior to anesthetic induction with diazepam [c] (0.05mg/kg IV) and ketamine hydrochloride [d] (2.2 mg/kg IV). Horses were endotracheally intubated with a 26-mm internal diameter cuffed endotracheal tube. Horses were hoisted and positioned in dorsal recumbency on a padded surgery table. If necessary, horses were supplemented with ketamine hydrochloride (0.2 mg/kg IV) prior to hoisting. The endotracheal tube was connected to a large animal anesthesia breathing circuit. [e] The breathing circuit had been preloaded with 2.5% ISO in 100% oxygen or with ISO in 60% oxygen depending on treatment. Preloading of the breathing circuit was done

20 minutes prior to the beginning of anesthesia by circulating 2.5% ISO in 60% oxygen with the balance nitrogen or 2.5% ISO in 100% oxygen until the desired breathing circuit concentration was achieved. Oxygen and ISO concentrations were measured with a previously calibrated multiparameter monitoring system. [f] The breathing system was then sealed until horses were connected to the breathing circuit Y-piece. Horses ventilated spontaneously throughout the study, with no intervention even during prolonged periods of apnea. Anesthesia was maintained with ISO (end tidal concentration [E_TISO] 1.5 %). Inspired oxygen concentration was maintained at 50% or > 95% after the initial 5 minutes necessary to attain the desired oxygen concentration and E_TISO. Preloading the breathing circuit with 2.5% ISO was necessary to attain the desired E_TISO within the first 5 minutes of study. Preloading the breathing circuit with 60% oxygen was necessary to allow for partial denitrogenation of the horse's lungs and to attain a stable inspired concentration of oxygen of 50% for one treatment. Similarly filling the breathing circuit with ISO in 100% oxygen was necessary for denitrogenation and to attain an inspired oxygen concentration > 95% in the first 5 minutes. Carrier gas flow was 8 L/min for 90 minutes. Control of inspired oxygen concentration was achieved by adjusting a calibrated air oxygen blender [g]. Lactated Ringer's Solution was administered IV at 5 ml/kg/hr. For recovery, horses received 0.006 mg/kg of acepromazine maleate IV and were nasotracheally intubated. During recovery, 15L/min oxygen was insufflated via a catheter inserted to the distal tip of the nasotracheal tube. Horses were allowed to recover unassisted in a recovery stall equipped with a rapidly inflating-deflating air pillow.

Instrumentation, Data Collection and Analysis

A multichannel recorder and data acquisition system was used to digitize and record arterial pressure waveforms, ECG tracings, and respiratory flows .[h] A multiparameter monitor was used to display gas concentrations and pulse oximetry readings. Information derived from these systems were observed frequently and gas concentrations and saturation recorded at data acquisition periods.[f] Calibration was accomplished with manufacturer recommended gases.

A 20-gauge, 5 cm Teflon catheter was inserted percutaneously into the mandibular artery for direct arterial blood pressure recording and collection of blood samples. The

blood pressure transducer was positioned at the level of the point of the shoulder. Respiratory flow was acquired using a calibrated pneumotachograph [i] attached to the air inlet/outlet of a bag-in-a-barrel system. [4] The pneumotachograph was connected to a differential pressure transducer interfaced to the data acquisition system. Calibration was performed prior to each experiment and included flow through the pneumotachograph via a precision rotameter. [j] Integration of the flow signal for tidal volume determination was checked using a 7L calibration syringe.[k]

Arterial pressure waveforms, ECG, and respiratory flows were monitored continuously and recorded every 5 minutes for the first 30 minutes and every 10 minutes for the following 60 minutes. Time zero (T0) represents the moment the horses were connected to the preloaded breathing circuit. At T5 the target inspired oxygen concentration and the E_TISO of 1.5% had been attained. Analysis of within treatment variables were referenced to T5 measurements.

Cardiovascular and respiratory data analyzed included systolic, diastolic, and mean arterial pressures, heart rate, inspiratory and expiratory peak flow, inspiratory and expiratory time, tidal volume, respiratory frequency and respiratory rhythm. Tidal volume was automatically integrated from the expiratory flow signal. Respiratory and anesthetic gas measurements included E_TCO_2, $P_{\bar{E}}CO_2$, F_IO_2, $P_{\bar{E}}O_2$, E_TISO and F_IISO. A sampling catheter extending through the lumen of the endotracheal tube to the distal end was used for end tidal and inspiratory gas sampling. Mean expired gas ($P_{\bar{E}}O_2$, $P_{\bar{E}}CO_2$) samples were collected through a multiport sampling catheter extending the entire length of the breathing circuit expiratory corrugated breathing hose. The multi-orifice sampler was constructed of small-bore tubing (2.35 mm OD, 1.25 mm ID) .[l] The distal end of the tubing was sealed. Nine small orifices at 15cm intervals were created along its length (145 cm). Mixed expired gas samples were collected continuously during expiratory flow. Three 20 ml aliquots were aspirated over 3 consecutive respiratory cycles into a 60-ml sampling syringe. All gas analysis was performed using a calibrated gas analyzer.[f]

Arterial blood samples were aspirated from the arterial catheter into heparinized syringes. Sampling occurred during three consecutive respiratory cycles, at 15, 30, 60, and 90 minutes. Samples were immediately sealed and analyzed. Measurements included

PaO_2, $PaCO_2$, pH, hemoglobin oxygen saturation (SaO_2), packed cell volume, and total protein. All gas values were corrected to concurrent body temperature. Body temperature was measured with a calibrated thermistor placed rectally.[m]

Minute ventilation, physiologic dead space, P_AO_2, $P_{(A-a)}O_2$, and rate of change in $P_{(A-a)}O_2$ overtime were calculated. Minute ventilation was calculated by multiplying tidal volume x respiratory rate and correcting to BTPS. Respiratory rate and tidal volume were measured over a five minute period to avoid biased reading. Physiologic dead space was calculated based on the following equation:

$$\frac{V_D}{V_T} = \frac{(P_aCO_2 - P_{\bar{E}}CO_2)}{P_aCO_2}$$

Partial pressure of alveolar oxygen (PAO_2) was calculated based on the alveolar gas equation: [22]

$$P_AO_2 = P_IO_2 - P_aCO_2 \left(\frac{P_IO_2 - P_{\bar{E}}O_2}{P_{\bar{E}}CO_2}\right)$$

The partial pressure difference between alveolar and arterial oxygen [$P_{(A-a)}O_2$] was calculated using the following formula:

$$P(A-a)O_2 = P_AO_2 - P_aO_2$$

Statistical Analysis

General linear mixed models were used to test the effectiveness of the treatment between the two treatment groups. Methodology from Putt and Chinchilli was utilized to determine the effectiveness of the treatment between the two treatment groups for all response variables.[23] An overall F-test p-value was obtained to test if there was a difference in the average responses between the treatment groups. The changes in the

responses over time were also compared between the two treatment groups using an effects-level contrast. Multiple tests were performed to compare the responses at each time point with the response at the T5 within each treatment. A Tukey adjustment was used to adjust the resulting p-values to account for multiple comparisons. Individual t-tests were also performed at each time point to test if there was a difference in average values of the response between the treatments at those specific time points. Significance was declared at $P < 0.05$.

Chapter 2 - Results and Discussion

Results

There were no statistical differences between the two treatments for cardiovascular variables at any measured time. Heart rate averaged 39.2 ± 4.2 bpm and 38.9 ± 3.6 bpm for horses breathing 50% and > 95% oxygen respectively. Mean arterial blood pressure showed a steady decrease between T5 and T40 followed by a steady increase between T40 and T90 for both treatments. Hypotension (MAP < 60 mmHg) was observed with both groups between T20 and T70, with no significant difference between the two groups.

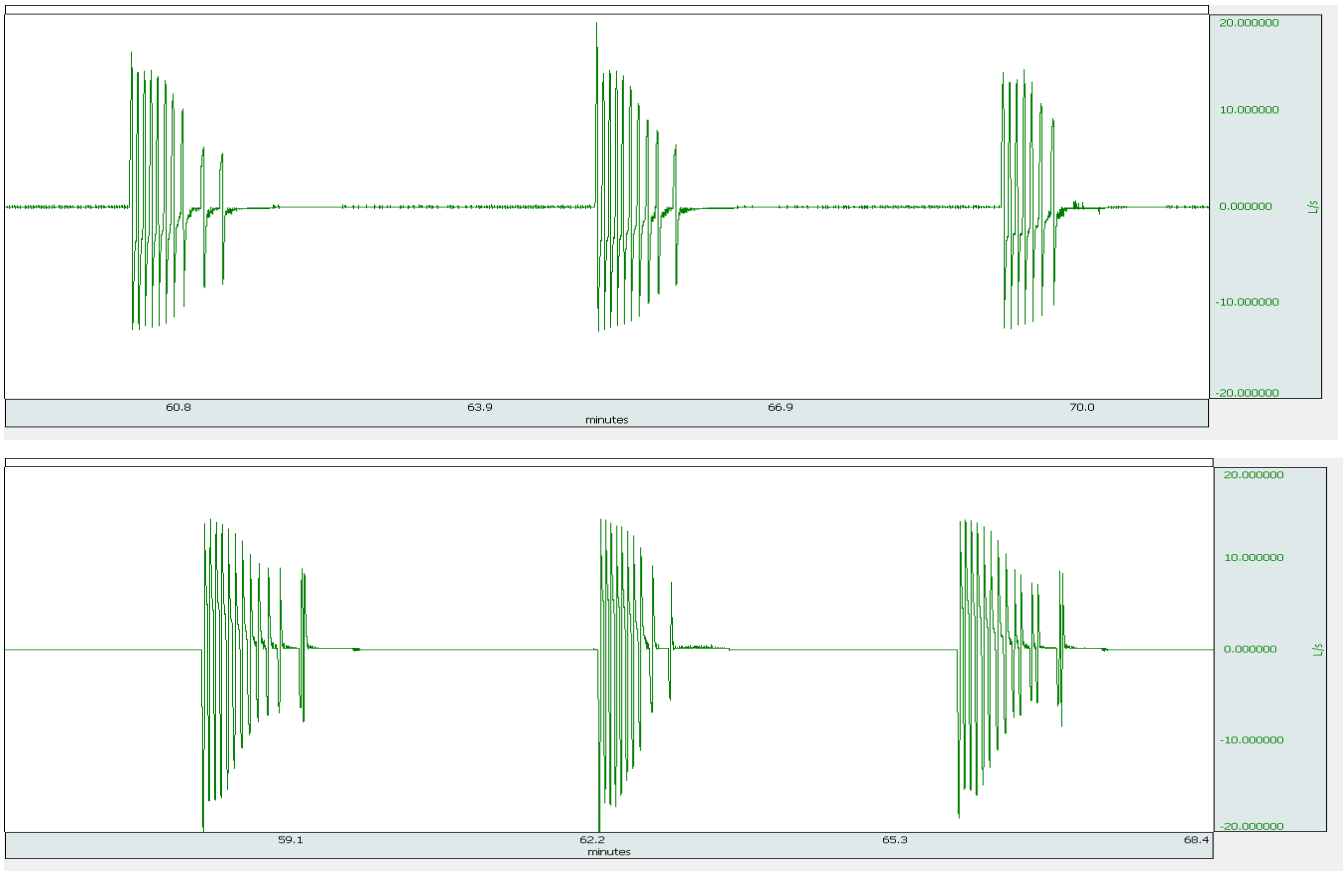
No change in minute ventilation was observed between the two treatments. Hypoventilation was identified with both treatments with no significant difference between them. $PaCO_2$ for horses averaged 51.9 ± 9.5 and 57.5 ± 10.8mmHg for horses breathing 50% and > 95% oxygen respectively. There were no significant differences between tidal volume and respiratory rate between the two treatments. No statistical differences were observed in the inspiratory and expiratory time or inspiratory and expiratory peak flow between treatments at any measured time (Table 1). There were no statistical differences between the two treatments for any of the other respiratory variables at any measurement time (Table 1). A higher expiratory flow was seen within both groups at all measured times when compared to T5. A shorter inspiratory time was seen in horses breathing 50% at all measured times when compared to T5. No difference in inspiratory time was seen with horses breathing > 95% oxygen. Respiratory rhythm incorporated respiratory rate and duration of apnea for each specific animal during both treatments.

Respiratory rhythm for each individual animal was observed and recorded during the entire anesthetic episode. A specific pattern observed during both treatments can be seen in (Fig 2.1). Each horses maintained a repeatable pattern during both treatments from T10 until T90. Apneic periods were horse dependent and ranged from 2 seconds up to 4 minutes.

PaO_2 and SaO_2 were significantly higher in horses anesthetized with Isoflurane in > 95% oxygen than in horses anesthetized with Isoflurane in 50% oxygen at all measurement times (Table 2.2). The average PaO_2 was 203 ± 113.3 mmHg and 77.8 ± 19.7 mmHg respectively. The average SaO_2 was 98.7 ± 1.4% and 92.9 ± 3.6% respectively. A greater A-a oxygen gradient was seen with the use of > 95% oxygen than when 50% oxygen was used. Calculated average $P_{(A-a)}O_2$ was 380.5 ± 113.9 and 194.8 ± 31.6 mmHg respectively. No difference was seen in the rate of change in $P_{(A-a)}O_2$ between the two treatments. No significant difference was seen in the physiologic dead space between the two treatments.

There were no significant difference for PCV, TP, pH, and body temperature between the two treatments.

Figure 2.1 Graphical representation of respiratory rhythm. Inspiratory and expiratory flow measurements for one horse over a 12 minute period while breathig 50% oxygen (top box) and > 95% oxygen (bottom box).



Inspiratory and expiratory flow measured in L/s (y-axis) and time measured in minutes (x-axis).

Table 2.1 Mean ± s.d of respiratory variables of 8 horses anesthetized with Isoflurane in 50% and > 95% oxygen during spontaneous ventilation.

		time (min)												
	treatment	0	5	10	15	20	25	30	40	50	60	70	80	90
PIF (L/s)	50	4.1 ± 1.7	4.2 ± 1.9	5.1 ± 1.4	5.7 ± 2.1†	5.7 ± 2.5	5.9 ± 2.6	5.8 ± 2.4	6.1 ± 3.2	6.0 ± 2.7	6.6 ± 4.0†	6.7 ± 3.9†	6.8 ± 3.5†	6.9 ± 3.7†
PIF (L/s)	100	3.9 ± 1.8	4.0 ± 1.0	5.5 ± 2.6†	4.8 ± 0.9	5.5 ± 1.8	5.5 ± 1.9	6.4 ± 3.9†	5.4 ± 1.5	6.1 ± 3.3†	6.2 ± 3.1†	6.3 ± 3.3†	6.4 ± 2.9†	6.5 ± 3.3†
IT (s)	50	2.2 ± 0.7	3.0 ± 1.5	2.7 ± 1.5†	2.7 ± 1.2†	2.5 ± 1.2†	2.4 ± 1.1†	2.3 ± 0.8†	2.1 ± 0.5†	2.0 ± 0.5†	2.0 ± 0.5†	2.1 ± 0.4†	2.0 ± 0.5†	2.0 ± 0.5†
IT (s)	100	2.5 ± 0.8	3.0 ± 1.0	2.8 ± 1.1	2.7 ± 1.2	2.6 ± 1.1	2.7 ± 1.3	2.6 ± 1.2	2.4 ± 0.9	2.5 ± 1.0	2.5 ± 0.8	2.4 ± 0.6	2.4 ± 0.6	2.5 ± 0.6
PEF (L/s)	50	5.7 ± 1.1	6.8 ± 1.4	7.8 ± 1.2†	8.4 ± 1.4†	8.4 ± 1. 4†	8.6 ± 1.4†	8.7 ± 1.4†	8.9 ± 1.9†	8.9 ± 1.6†	9.2 ± 2.0†	9.6 ± 2.2†	9.5 ± 2.0†	9.5 ± 2.1†
PEF (L/s)	100	5.2 ± 0.6	6.4 ± 0.6	7.8 ± 1.7†	7.6 ± 1.2†	8.2 ± 1.3†	8.4 ± 1.1†	9.0 ± 1.8†	8.6 ± 0.9†	9.1 ± 1.6†	9.2 ± 1.5†	9.2 ± 1.5†	9.2 ± 1.5†	9.5 ± 1.8†
ET (s)	50	0.9 ± 0.3	1.2 ± 0.3	1.4 ± 0.5	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3
ET (s)	100	0.9 ± 0.2	1.2 ± 0.3	1.6 ± 0.2†	1.4 ± 0.4	1.4 ± 0.2	1.4 ± 0.3	1.5 ± 0.4	1.3 ± 0.2	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	1.4± 0.3
TV (L)	50	5.2 ± 2.4	7.8 ± 3.1	9.3 ± 3.6	10.5 ± 2.5	9.9 ± 2.1	10.1 ± 1.8	10.0 ± 1.8	9.6 ± 2.5	9.4 ± 2.1	10.0 ± 3.0	10.4 ± 3.2	10.3 ± 2.7	10.3 ± 2.8
TV (L)	100	5.2 ± 2.2	7.5 ± 2.2	10.2 ± 2.4†	9.1 ± 2.4	9.8 ± 1.7	9.6 ± 1.4	10.4 ± 2.8	9.1 ± 1.0	10.0 ± 2.1	10.2 ± 2.1	10.1 ± 2.3	10.3 ± 2.2	10.5 ± 2.5
RR (bpm)	50	5.4 ± 3.0	3.1 ± 1.6	2.7 ± 1.8	2.2 ± 0.8	2.5 ± 1.2	2.5 ± 1.2	2.7 ± 1.0	2.9 ± 1.0	3.0 ± 0.9	3.0 ± 0.9	3.1 ± 0.9	2.8 ± 1.0	3.0 ± 1.0
RR (bpm)	100	3.4 ± 1.6	2.5 ± 1.3	1.8 ± 1.1	2.1 ± 1.1	2.0 ± 1.0	2.3 ± 1.3	2.1 ± 1.3	2.3 ± 1.0	2.2 ± 0.7	2.4 ± 0.8	2.5 ± 0.8	2.3 ± 0.8	2.2 ± 0.8
MV (L/min)	50	23.0 ± 7.4	21.4 ± 9.3	21.2 ± 8.0	22.2 ± 8.2	23.9 ± 12.4	25.4 ± 13.0	25.8 ± 10.2	26.1 ± 9.3	27.3 ± 8.7	28.1 ±7.3	30.8 ± 11.5	27.7 ± 7.8	30.1 ± 11.0
MV (L/min)	100	14.9 ± 4.0	16.0 ± 4.4	17.9 ± 9.2	16.9 ± 7.4	18.8 ± 8.6	20.3 ± 9.4	20.6 ± 8.9	20.0 ± 7.1	21.5 ± 6.6	23.4 ± 7.6	24.3 ± 7.4	23.3 ± 8.3	21.6 ± 6.8

PIF= peak inspiratory flow; IT= inspiratory time; PEF= peak expiratory flow; ET= expiratory time; TV= tidal volume; RR= respiratory rate; MV= minute ventilation. *Significant difference between the two treatments ($p < 0.05$). †Significant difference between measured time Tn and T5 within each treatment ($p < 0.05$)

Table 2.2 Mean ± s.d. of measured arterial blood gas values and calculated values of 8 horses anesthetized with Isoflurane in 50% and > 95% oxygen during spontaneous ventilation.

		time (min)			
variable	treatment	15	30	60	90
pH	50	7.34 ± 0.1	7.33 ± 0.1	7.35 ±0.1	7.37 ± 0.1
pH	100	7.32 ± 0.1	7.31 ± 0.1	7.33 ± 0.1	7.32± .01
SpO_2 (%)	50	90.9 ± 2.2*	90.4 ± 2.1*	88.8 ± 6.1	85.8 ± 14.3
SpO_2 (%)	100	93.3 ± 2.2*	93.3 ± 2.8*	92.8 ± 2.6	92.6 ± 2.3
SaO_2 (%)	50	92.3 ± 3.0*	93.5 ± 3.2*	93.9 ± 4.0*	92.0 ± 4.2*
SaO_2 (%)	100	98.8 ± 1.5*	99.1 ± 1.0*	98.9 ± 1.2*	97.9 ± 2.1*
$PaCO_2$ (mmHg)	50	51.1 ± 8.5	54.5 ± 8.8	51.4 ± 8.1	50.8 ± 12.5
$PaCO_2$ (mmHg)	100	54.7 ± 8.4	57.5 ± 10.6	57.6 ± 11.7	60.2 ± 12.7
PaO_2 (mmHg)	50	75.2 ± 12.9*	80.4 ± 15.5*	85.1 ± 32.5*	70.45 ± 17.9*
PaO_2 (mmHg)	100	212.7 ± 103.7*	219.6 ± 117.9*	201.8 ± 116.5*	178.5 ± 115.3*
PAO_2 (mmHg)	50	251.2 ± 19.8*	260.9 ± 23.4*	290.9 ± 10.9*	287 ± 18.2*
PAO_2 (mmHg)	100	552.5 ± 42.1*	583.9 ± 17.8*	598.9 ± 8.8*	599.1 ± 9.4*
$P_{(A-a)}O_2$ (mmHg)	50	176.0 ± 28.7*	180.8 ± 25.7*	205.9 ± 39.6*	216.6 ± 32.4*
$P_{(A-a)}O_2$ (mmHg)	100	339.9 ± 107.0*	364.3 ± 112.4*	397.1 ± 120.1*	420.7 ± 116.2*
Δ $P_{(A-a)}O_2$ (%)	50	N/A	3.2 ± 6.3	13.9 ± 18.5	6.5 ± 9.1
Δ $P_{(A-a)}O_2$ (%)	100	N/A	8.9 ± 14.0	9.7 ± 13.8	7.2 ± 7.9
VD/VT	50	0.29 ± 0.09	0.31 ± 0.06	0.35 ± 0.12	0.35 ± 0.13
VD/VT	100	0.30 ± 0.10	0.26 ± 0.10	0.29 ± 0.07	0.32 ± 0.12

SpO_2= hemoglobin oxygen saturation measured with pulse oximeter; SaO_2 = arterial hemoglobin oxygen saturation; $PaCO_2$ = partial pressure of arterial carbon dioxide; PaO_2= partial pressure of arterial oxygen; PAO_2 = partial pressure of alveolar oxygen; $P_{(A-a)}O_2$ = Alveolar-arterial tension gradient; VD/VT = physiologic dead space. *Significant difference between the two treatments ($p < 0.05$).

Discussion

Air-oxygen mixtures are used routinely as a delivery gas during anesthesia for humans. Air-oxygen mixtures are not often used during inhalation anesthesia for horses. Experimentally, a lower fraction of inspired oxygen has been used during canine, feline, ovine, and equine anesthesia. [2, 6, 15-16, 20-21] Advantages demonstrated clinically and experimentally include improved minute ventilation and decreased atelectasis resulting in better gas exchange [2, 15-16, 20] and improvement in oxygenation during the post operative recovery period. [14, 18]

In this study, ventilatory characteristics, oxygenation, and A-a oxygen gradient were analyzed in Isoflurane anesthetized spontaneously ventilating horses inspiring two different oxygen concentrations. Minute ventilation was different during the initial five minutes horses were connected to the breathing circuit, with higher minute ventilation observed when the lower fraction of inspired oxygen was administered. Decreased ventilation following immediate inspiration of a high fraction of inspired oxygen in horses has never been analyzed or documented. Breath holding was not observed during the first five minutes and respiratory rate was actually higher during this period than any other measured time for both treatments. Previous studies using inhalant anesthesia, have not described a difference in minute ventilation shortly after induction when comparing different fractions of inspired oxygen. Previous research in horses that reported a change in ventilation based on measurement of $PaCO_2$, did not sample arterial blood for blood gas analysis until 15 minutes post connection to the breathing circle, therefore any potential difference would had been missed due to timing. [2] Marntell et al. observed a higher minute ventilation, respiratory rate, and a decrease in $PaCO_2$ in horses breathing 21% oxygen vs > 95% oxygen five minutes after induction while using total intravenous anesthesia. [6] This increase in minute ventilation was maintained until animals were placed on > 95% oxygen (15 minutes post induction). In our study, no significant difference between treatments was observed after the initial five minutes.

Ventilatory character showed marked variability between horses. This study used each horse as it's own control allowing for observance of individual breathing patterns twice. Ventilatory rhythm for each individual horse, identified by respiratory rate and duration of apnea, was similar for both treatments. Isoflurane anesthetized horses often show a characteristic breathing pattern associated with a low respiratory rate and an irregular rhythm. [1] The study confirmed that the irregular respiratory pattern is not different when a lower fraction of inspired oxygen is used. The individual horse's respiratory pattern was continuous, starting at T10 until

the end of the anesthetic period, and repeatable while breathing 1.2 MAC Isoflurane in either 50% or > 95% oxygen. Four minute periods of apnea were consistent in one horse. Animals that develop such prolonged periods of apnea present the anesthetist with challenges, including difficulty in maintaining proper plane of anesthesia, hypercarbia, and hypoxemia. Prolonged periods of apnea were accompanied by a steady decrease in SpO_2 until ventilation resumed. Stimulation to breathe likely results from hypercarbia and hypoxemia. An additional arterial blood sample was collected for blood gas analysis from one of the animals to identify the degree of hypercarbia and/or hypoxemia. Arterial blood gas results revealed moderate to severe hypercarbia ($PaCO_2$ 71.7 mmHg) but not hypoxemia (PaO_2 80.0 mmHg), despite a period of apnea greater than 2 minutes. This arterial blood gas was collected as the animal was breathing > 95% oxygen. Unfortunately we did not repeat the arterial blood gas during an apneic period while the same animal was breathing 50% oxygen. It is possible that the same apneic period while breathing the lower oxygen concentration would have resulted in hypoxemia. The irregular respiratory rate and long periods of apnea in some horses emphasizes the need for the availability of a mechanical ventilator when Iso is used as the inhalant anesthetic gas, not only to avoid hypercarbia and hemoglobin desaturation, but to assist in maintaining an appropriate plane of anesthesia.

Administration of a high fraction of inspired oxygen (> 95%) has been associated with a greater degree of atelectasis than when a lower fraction of inspired oxygen (< 50%) is used. [6, 14-16, 20] Anesthetized horses develop severe intrapulmonary shunt as a result of collapsed alveoli (atelectasis) leading to large A-a oxygen gradients. [6, 9, 24] Atelectasis results from loss of surfactant, airway compression, and absorption of gas distal to closed airways.[25] Absorption atelectasis occurs due to the presence of intermittent airway closure (low V/Q zones) followed by absorption of alveolar gas into the capillary blood resulting in collapse of the alveoli. The use of 30-50% inspired oxygen has been described to decrease absorption atelectasis by avoiding the complete collapse of the intermittently closed alveoli by use of an accompanying inert or poorly absorbed gas such as nitrogen.[25] A large A-a oxygen gradient was observed with all horses during both treatments. A significantly lower A-a oxygen gradient resulted from the administration of 50% oxygen. A decrease in A-a oxygen gradient can be a reflection of a decrease in intrapulmonary shunt, but it is not an accurate measurement as it is affected by many physiological factors such as administered fraction of inspired oxygen, hemoglobin concentration, and arterial-venous oxygen content difference.[26] Other measurements have been

proposed to quantify oxygen transfer, and therefore intrapulmonary shunt, including PaO_2/FiO_2, PaO_2/PAO_2, and $P(A\text{-}a)O_2/PaO_2$, with all of them presenting limitations resulting in inaccuracy. [27] The most accurate method to measure oxygen transfer and pulmonary function is through calculating the intrapulmonary shunt by collection of mixed venous as well as arterial blood.[27] A pulmonary arterial catheter was not used in this study, therefore true intrapulmonary shunt could not be calculated and we cannot conclude that the use of 50% inspired oxygen actually resulted in a decrease in intrapulmonary shunt.

A high A-a oxygen gradient was observed shortly after induction in both treatment groups, which supports previous reports detailing the early appearance of atelectasis in anesthetized horses. [6-8, 28] A progressive increase in A-a oxygen gradient was noticed for both groups, but the rate of increase between treatments was not different during the 90 minutes of anesthesia. Laterally recumbent horses anesthetized with halothane in 30% or 85% oxygen, showed a significant increase in A-a oxygen gradient while breathing the higher oxygen concentration when compared to the lower oxygen concentration, but the increase was only detected after 120 minutes of anesthesia.[2] Steffey et al. showed no change in A-a oxygen gradient over time in halothane anesthetized laterally recumbent horses, despite 5 hours of anesthesia.[3]

Post-anesthetic atelectasis may persist in human patients for up to 4 days and it can result in an increased frequency of post operative hypoxemia and possibly pulmonary infection.[17-18] The use of air oxygen mixtures reduces atelectasis, improves gas exchange, and decreases postoperative hypoxia.[18] Studies have demonstrated hypoxemia in horses during postoperative recovery while in lateral recumbency even with administration of supplemental oxygen.[10, 30-31] Use of a lower fraction of inspired oxygen with a decrease in atelectasis and improvement in gas exchange [6] may prove to be beneficial in horses during anesthetic recovery by decreasing hypoxemia. This study did not measure postoperative PaO_2, therefore we do not know the effects of a lower fraction of inspired oxygen during anesthetic recovery in horses.

Use of > 95% oxygen resulted in a significantly higher SaO_2 and PaO_2, The majority of horses breathing 50% oxygen had a hemoglobin saturation > 90%. Hypoxemia was noticed in 12.5% of all measurements taken with half of the hypoxemic events resulting from one horse in particular. No hypoxemia was observed when > 95% oxygen was used. The previously reported decrease in intrapulmonary shunt [6] with the use of a lower fraction of inspired oxygen is an

advantage to the patient, unfortunately the risk of hypoxemia can be greater and should be closely monitored.

Other ventilatory modalities have been attempted in order to decrease atelectasis, increase gas exchange, and improve PaO_2 in horses. The use of recruitment maneuvers and PEEP have been extensively described in the literature for humans as well as animals. Recruitment maneuvers, though effective in horses, require the repetitive use of high pressures (60-80 cmH_2O) and PEEP needs to be instituted in order to maintain the recruited alveoli open. [32] Use of recruitment maneuvers using 100% oxygen without PEEP results in closing of the alveoli shortly after the maneuver followed by gas resorption and the return of atelectasis.[14] Disadvantages associated with repeated recruitment maneuvers and PEEP are barotrauma and possible decrease in cardiac output.[33-34] In humans, use of a lower fraction of inspired oxygen (40%) after recruitment maneuvers results in a diminished and slower reappearance of atelectasis.[14] Use of recruitment maneuver in horses while inspiring a lower fraction of oxygen has not been investigated. Opening and maintenance of collapsed alveoli using 40-50% oxygen may show some of the benefits seen with PEEP without the decrease in cardiac output.

Horses in this study were hypotensive (MAP < 60 mmHg) for an extended period of time. Administration of drugs for treatment of hypotension, such as ephedrine and dobutamine, can increase cardiac output.[35-36] An increase in cardiac output increases oxygen delivery resulting in an increase PvO_2. The increase in PvO_2 consequently decreases venous admixture ultimately increasing PaO_2. [37] In this study we elected not to treat any hemodynamic variables to avoid increases in PaO_2 originating from changes in cardiac output instead of improvement in gas exchange.

The use of 50% oxygen and nitrogen as the carrier gas did not significantly change the ventilatory characteristics in isoflurane anesthetized horses. Horses maintained a low respiratory rate with an irregular respiratory pattern with both inspired oxygen concentrations. This study did demonstrate that the irregular respiratory pattern is continuous and can be repeated at the selected end tidal isoflurane concentration (1.2 MAC). A high A-a oxygen gradient with an equal rate of change overtime was still observed during both treatments. Administration of a lower fraction of inspired oxygen may have resulted in decreased intrapulmonary shunt and increased minute ventilation,[2,6] but based on this study, the risk of moderate to severe hypercarbia and hypoxemia is still present and should not be overlooked.

Footnotes

a. Isoflo® - Abbott Animal Health, Abbott Park, IL

b. AnaSed® - Lloyd Incorporated, Shenandoah, IA

c. Diazepam - Hospira, Inc., Lake Forest, IL

d. Ketaset® - Fort Dodge Animal Health**,** Fort Dodge, IA

e. North American Drager, Telford, PA

f. Datex-Ohmeda Cardiocap/5 gas monitor – General Electric Company – Datex-Ohmeda, Madison, WI

g. BIRD air oxygen blender - VIASYS Respiratory Care Inc., Palm Springs, CA

h. Biopac - Biopac Systems, Inc. - Goleta, CA

i. Fleisch No. 4 - Instrumentation Associates Inc, New York, NY.

j. Rotameter – Fisher Porter, Warminster, PA

k. 7L calibration syringe – Hans Rudolph, inc., Kansas City, MO

l. Gas sampler – United States Catheter and Instrument Corp., Glens Falls, NY

m. YSI 4600 Series Precision Thermometer – YSI, Yellow Springs, OH

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