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Impact of low inspired oxygen fraction on oxygenation in clinical horses under general anesthesia

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Summary: The objective was to compare the use of 0.3 and >0.95 oxygen inspired fraction during general anesthesia in horses. Forty client-owned adult horses were anesthetized in dorsal or in lateral recumbency with isoflurane in oxygen and randomly allocated to receive inspiratory fraction of oxygen >0.95 (group HIGH) or 0.3 (group LOW). Mechanical ventilation was provided using pressure controlled mode. Arterial blood gas analysis was performed before, during and after general anesthesia. The group LOW obtained lower intra-operative PaO_2 values but better indices of venous admixture than the group HIGH. The PaO_2 further decreased during the recovery, without significant differences between groups. Even though the use of lower oxygen inspired fraction (0.3) tended to improve pulmonary function during general anesthesia, it markedly decreased safety as a result of hypoxemia. During the recovery, no difference was observed between groups for the arterial oxygenation such that lower intra-anesthetic oxygen inspired fraction did not provide any advantages.

Keywords: anesthesia, oxygenation, atelectasis, venous admixture, hypoxemia

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Introduction

Application of high FIO_2 (inspired fraction of oxygen) over 0.95 (ie 95%) is common during general anesthesia in veterinary medicine. Increasing the PaO_2 (arterial oxygen partial pressure) is often applied to minimize the risks of inadequate oxygen delivery to the tissues. However, the use of high FIO_2 has also been demonstrated to contribute to intrapulmonary shunt (*Marntell* et al. 2005). General anesthesia induces modifications in lung ventilation and perfusion leading to a decrease in arterial blood oxygenation (*Nyman* and *Hedensternia* 1989). Atelectasis is an important cause of this impairment. Low arterial oxygenation is mainly caused by compression atelectasis, particularly in horses, through loss of respiratory muscle tone and compression of the lungs (*Hedensternia* and *Rothen* 2000). The alveoli further collapse by absorption of gas content from the alveolus into the blood once the alveolus is closed off from the ventilated respiratory tree (*Wagner* et al. 1974). The higher the O_2 concentration within the alveoli, the faster is the rate of absorption atelectasis formation, converting ventilation to perfusion mismatch to a more severe intrapulmonary shunt and venous admixture (*Nyman* and *Hedensternia* 1989).

The beneficial effect of intermediate FIO_2 to limit the development of atelectasis and maintaining pulmonary gas exchange was demonstrated in human subjects (*Duggan* and *Kavanagh* 2007) as well as in dogs (*Staffieri* et al. 2007) and horses (*Marntell* et al. 2005). In horses the development of atelectasis and the resulting arterial hypoxemia is particularly common and marked, even in healthy subjects (*Whitehair* and *Willits* 1999). However, many contributing factors have been identified for the development of peri-anesthetic pulmonary atelectasis in healthy horses, like body weight, thoracic conformation (*Mansel* and *Clutton* 2008, *Moens* et al. 1995), fasting time, abdominal distension and positioning, or mode of ventilation (*Gleed* and *Dobson* 1988). Therefore, the use of intermediate FIO_2 (<0.5) may not be sufficient to improve the pulmonary mismatch between ventilation and perfusion in horses under clinical conditions (*Schulte-Bahrenberg* et al. 2011). It is also not known if less intra-operative atelectasis could contribute to improve blood oxygenation during recovery (*Marntell* et al. 2005).

The present study aimed at determining if the use of intermediate FIO_2 (0.3) under clinical conditions in horses without main cardiorespiratory compromise can be safely administered compared to the traditional use of high FIO_2 (>0.95). The hypothesis tested was that the horses receiving lower FIO_2 would maintain satisfactory values for intra-operative PaO_2 as well as better values for the indices of oxygenation, and that the PaO_2 values during the recovery phase would be higher absence of O_2 supplementation.

Materials and methods

Animals

For each horse, owner consent was obtained before inclusion in the study. Adult warm blood horses scheduled at the veterinary hospital (equine private veterinary clinic) for an elective surgery were recruited for the trial. Horses assigned American Society of Anesthesiologists status IV or V, obese horses, pregnant mares, and horses presenting respiratory diseases or abnormal preoperative values of arterial blood gas analysis (performed in all animals) were not included. Based on the positioning required for the surgical procedure, horses involved for the study were included into two categories: D (dorsal recumbence) or L (lateral recumbence). Horses from each category were then separated into two treatment groups: the group

HIGH received isoflurane (Isoflo, Essex Tierarznei GmbH, Munich, Germany) in FIO_2 higher than 0.95; the group LOW received isoflurane in a mixture of medical air and oxygen with a FIO_2 of 0.3. Allocation to the four subgroups (HIGH-L, HIGH-D, LOW-L, LOW-D) was performed using a computer-generated randomization table divided in two blocks. When the whole anesthetic lasted less than 60 minutes or if an unexpected event (e.g. repositioning) happened, the horse was excluded. Based on sample size analysis, a difference between groups for the main outcome parameters (PaO_2 and indices of oxygenation) equal to their variability requires at least 18 horses per group to reach significance ($P = 0.05$) with a power of 85% (two-tailed hypothesis). Recruitment continued until 40 horses (20 for each treatment group) were successfully enrolled. Food was withheld overnight but access to water was always granted. A 12-gauge, 8 cm catheter was placed in the jugular vein in each horse before anesthesia.

Anesthetic technique

The horses were premedicated with 50 µg/kg of romifidine (Sedivet, Boeringer Ingelheim, Ingelheim, Germany) and 50 µg/kg L-methadone combined to fenpipramide (L-Polamivet, Intervet, Unterschleissheim, Germany), IV. The mouth of each horse was rinsed with water and general anesthesia was induced in a dedicated padded box with 0.1 mg/kg diazepam (Diazepam10, Ratiopharm Gmbh, Ulm, Germany) and 3 mg/kg ketamine (Narketan10, Chassot GmbH, Ravensburg, Germany), IV. Endotracheal intubation was performed. Horses were hoisted onto a surgery table in a preparation room and the endotracheal tube was connected to a large animal anesthetic circle system equipped with a mechanical ventilator (Stephan-Respirator GT, F.Stephan GmbH, Gackenbach, Germany). The mechanical ventilator was modified to perform with a descending accordion bellow within a graduated cylinder housing. Oxygen and air were administered using 2 separate flow meters to reach first a FIO_2 of 0.3 for all the horses with a total fresh gas flow rate of 6 L/min. Intermittent positive pressure ventilation was started immediately after endotracheal intubation with a pressure-controlled mode (time-cycled, with pressure plateau) and set for a ventilator cycling rate of 8 breaths/min, an inspiratory-to-expiratory ratio of 1:2, and a peak inspiratory airway pressure of 25 cmH_2O. The ventilator cycling rate was further adjusted to maintain an end-tidal partial pressure for CO_2 as close as possible to 40 mmHg. The delivered VT (tidal volume) was controlled visually by the anesthetist (graduated excursion of the respiratory bellow) and the horse was excluded from the study if VT was to fall below 10 mL/kg to avoid insufficient lung aeration. An initial end-tidal concentration for isoflurane of 1.2% was targeted and was later adjusted according to the anesthetic depth to allow adequate surgical anesthesia. Shortly after endotracheal intubation, the horses received a loading dose of lidocaine (Lidocain 2%, Albrecht, Aulendorf, Germany) at 1.5 mg/kg, IV, over 10 minutes, followed by a continuous infusion at 2 mg/kg/h, IV. Five minutes after starting inhalational anesthesia, air was discontinued in the group HIGH and high oxygen flow was shortly applied to reach more than 0.95 FIO_2 within 5–10 minutes. After surgical preparation, the horses were transferred in the operating theatre by rolling the surgical table without any disconnection from the breathing system and the ventilator.

Monitoring

Standard hemodynamic parameters were monitored continuously by means of an electrocardiogram and a catheter inserted into the facial artery connected to a calibrated electronic pressure transducer (NovatransII MX860, Medex GmbH, Düsseldorf, Germany). Respiratory gases were continuously sampled from the distal end of the endotracheal tube and respiratory rate, inspired and end-tidal concentration for CO_2, O_2 and isoflurane were automatically analyzed (Dräger PM 8014-8050, Drägerwerk, Lübeck, Germany). The gas analyzer was calibrated before starting the trial. Arterial blood samples were anaerobically collected firstly once before anesthesia by needle puncture at the facial artery (T0, standing), later from the facial artery catheter at 20 (T1), 40 (T2) and 60 (T3) minutes after anesthesia induction, then at 5 (T4), 10 (T5) and 15 (T6) minutes after disconnecting from the breathing system (breathing room air), and finally once 5 minutes after the horse achieved standing position (T7). The samples were immediately analyzed (ABLTM5, Radiometer Medical A/S, Copenhagen, Denmark) for pH, $PaCO_2$ (arterial carbon dioxyde partial pressure) and PaO_2. The values were not corrected for patient body temperature but measured at standard 37 °C. For each time point, PA-aO2 (difference between alveolar and arterial oxygen partial pressure), (ratio between arterial and alveolar oxygen partial pressure), Pa/FIO_2 (ratio between arterial oxygen partial pressure and inspired oxygen fraction) and FSHUNTe (estimated oxygen content-based index) were retrospectively calculated, using the following formula:

$$PAO_2 = [FIO_2 \times (PBAR - PH_2O)] - (PaCO_2 \times 1.2)$$

(*Bigeleisen* 2001)

$$FSHUNTe = \frac{[(1.36 \times Hb \times (1\text{-}S_aO_2)] + (0.0031 \times P_{A\text{-}a}O_2)}{[(1.36 \times Hb \times (1\text{-}S_aO_2)] + (0.0031 \times P_{A\text{-}a}O_2)] + 3.5} \times 100$$

(*Araos* et al. 2012)

A partial pressure of 47 mmHg was used for the water vapor pressure (PH_2O) at 37 °C and was not corrected for patient body temperature. Barometric pressure (PBAR) was obtained once each day of the experiment. To obtain the simplified formula for FSHUNTe, $Pc'O_2$ (the pulmonary end-capillary partial pressure of oxygen) was assumed to be equal to PAO_2, $Sc'O_2$ (the pulmonary end-capillary oxygen saturation) was assumed to be 100% (ie, 1) when $PAO_2 > 120$ mmHg, and $Ca\text{-}O_2$ (arterio-venous difference in oxygen content) was assumed to be 3.5 mL/dL. SaO2 was derived from PaO2 by the blood gas analyser (based on human oxygen hemoglobin dissociation curve). The alveolar dead space fraction (VD%) was estimated using the following formula:

$$VD\% = [(PaCO_2 - PETCO_2)/PaCO_2] \times 100$$

Peak inspiratory airway pressure was monitored at each breath. Dobutamine (Dobutamin solvay, Solvay Arzneimittel, Hannover, Germany) was administered IV when necessary to maintain the mean arterial pressure over 70 mmHg. The lidocaine infusion was stopped 15 minutes before the end of the surgery. Once the procedure was terminated and general anesthesia ended, all horses were weaned from mechanical ventilation by stopping isoflurane administration and decreasing the mechanically delivered respiratory frequency to 2 breaths per minute for some minutes until spontaneous ventilation resumed. Then, the horses were administered romifidine (15 µg/kg, IV), and were softly hoisted and placed in right lateral recumbency in a closed padded recovery stall.

Recovery from general anesthesia

The horses recovered unassisted but under continuous clinical evaluation, and in the absence of additional oxygen (breathing room air). Time elapsed from the end of anesthesia to standing was recorded as recovery time. Recovery quality was scored from 1 (very good) to 5 (very poor). All horses were observed postoperatively for complications until 24 hours after anesthesia.

Statistical analysis

Frequencies for gender, breeds, surgical interventions and quality score of recovery were analyzed with a Chi-square test to detect significant differences between classes. Sample weights, physiological measurements, isoflurane concentration, and time to recover were normally distributed (Kolmogorov-Smirnov test) and were reported for both groups as mean ± standard deviation of individual values or derived from each individual mean for repeated measures. Significant differences between groups and classes for mean values were analyzed with a one-way analysis of variance, a two-way analysis of variance or a two-way repeated measures analysis of variance followed by a Holm-Sidak method for pair-wise multiple comparisons, according to the nature of the data. Sample ages, duration of anesthesia as well as measured and calculated blood gas values were not normally distributed and were reported as median and interquartile range (25%–75%). Significant differences between groups and classes for median values were analyzed with a Mann-Whitney rank sum test, or a Kruskal-Wallis one-way analysis of variance on ranks, followed by a Dunn's method for pair-wise multiple comparison, or a Friedman repeated measures analysis of variance on ranks, followed by a Tukey test for pairwise multiple comparison, according to the nature of the data. The differences for $PA\text{-}aO_2$ values were tested between groups of similar FIO_2 for the effect of time or of recumbency. The differences for Pa/AO_2 and Pa/FIO_2 values were tested between groups of different FIO_2 for the effect of FIO_2 on pooled data or within each class of recumbency. All statistical tests were performed as two-tailed with standard computer statistical software (Sigmastat 3.5 for Windows, Systat software Inc., San Jose, California, USA). Values of $P < 0.05$ were considered significant.

Results

After exclusion of few horses due to repositioning during the surgical procedure, 19 horses were included in lateral recumbency and 21 in dorsal. Results for demographic and physiologic variables are presented in Table 1. The type of surgical intervention was significantly related to recumbency position. Castrations were more frequent in dorsal recumbency. Eye

Table 1 Demographic and physiologic variables of 40 horses under general anaesthesia receiving high (>0.95) or low (0.3) FIO_2.

	group HIGH		group LOW	
	L	D	L	D
Weight (kg BW)	562±17	572±16	562±16	488±16*
Age (years)	12 (9.5-14.2)*	4 (3-5.5)	5 (2.9-12.3)	3 (2-4)
	2 Orthop.	7 Castr.	6 Orthop.	7 Castr.
Type of intervention #	4 Eye	1 Eye	4 Eye	
	3 Soft	3 Soft		3 Soft
Duration of anaesthesia (min)	60(60-65)	60(60-68)	67(63-90)	60(60-63)
Recovery score	2(1-2.3)	2(1-2.8)	2.5(2-3)	2(1-2)
Number of score 1;2;3;4;5	4;3;2;0;0	5;3;3;0;0	0;5;4;1;0	4;5;1;0;0
Recovery time (min) §	52±14	48±9	44±9	39±7
End-tidal isoflurane (%)	1.17±0.12	1.16±0.12	1.19±0.10	1.16±0.11
Respiratory rate (breath/min)	8(6-8)	7(6-8)	6(6-8)	6(6-8)
Heart rate (beats/min)	32±2	31 3	31 3	31 3
Systolic arterial pressure (mmHg) #	101 13	103 15	97 12	106 14
Mean arterial pressure (mmHg) #	83±11	86±14	80±10	89±14
Diastolic arterial pressure (mmHg) #	71±12	76±15	67±10	76±15

Data are presented as mean±SD, median (IQR, 25%-75%) or number of horses. * indicates a significant difference from other groups. § indicates a significant difference between groups HIGH and LOW. # indicates a significant difference between groups L and D. D - Dorsal recumbency. L - Lateral recumbency.

surgeries and orthopedic interventions were more frequent in lateral recumbency.

Ventilator cycling rate was significantly decreased with time in all classes from 8 to 6 breaths per minute (in order to maintain target end-tidal partial pressure for CO_2). During general anesthesia, systolic, mean and diastolic arterial pressures significantly decreased progressively with time in all classes (from 98±17 to 79±9 mmHg for mean arterial pressures). Dobutamine was administered in 4 (36.4%), 3 (33%), 1 (10%) and 5 (50%) horses from classes HIGH-D, HIGH-L, LOW-D and LOW-L, respectively, for a mean duration of 20 minutes at a mean dosage of 0.2 μg/kg/minute. Results of the arterial blood gas analysis are presented in Tables 2 and 3. Overall, $PaCO_2$, pH and VD% values were never significantly different between groups.

The PaO_2 values were significantly higher ($P<0.001$) in group HIGH than in group LOW for pooled data at T1, T2 and T3, but not at T4, T5, nor T6. There was no significant effect of body positioning (D vs. L) on PaO_2. In 5 horses, an intraoperative PaO_2 was measured once below 70 mmHg (62, 61, 56, 69 mmHg in class LOW-D, 66 mmHg in class LOW-L). The horse showing the worst recovery score (4) was measured with $PaO_2>90$ mmHg at all time-points. There was no significant difference between the groups D and L on pooled data for $PA\text{-}aO_2$, Pa/AO_2, Pa/FIO_2, or FSHUNTe, but there was a significant effect of the recumbency on Pa/FIO_2 specifically within the treatment group LOW ($P=0.013$), and on FSHUNTe within the treatment group HIGH ($P=0.044$). The $PA\text{-}aO_2$ values significantly increased over time during general anesthesia in groups HIGH-L and LOW-D. There was a significant difference between the treatment groups HIGH and LOW on pooled data for Pa/AO_2 ($P=0.009$) and FSHUNTe ($P=0.003$). These differences were also significant within subgroup L, but not within D. Additionaly, in subgroup L, there was a significant difference in the Pa/FIO_2 between treatments ($P=0.019$).

At T4, T5, and T6, the indices of oxygenation were not analyzed because PaO_2 and FIO_2 were similar between groups and PAO_2 cannot be estimated. After the horses recovered standing position, all arterial blood gas values returned within normal range without any difference between groups.

Discussion

The present study found that the indicators of venous admixture (Pa/AO_2 and FSHUNTe) were better preserved when low FIO_2 (0.3) was used during general anesthesia with isoflurane in mechanically ventilated horses under clinical conditions. This suggests a lesser development of venous admixture with lower FIO_2 (0.3), probably via modulation of atelectasis for-

Table 2 Arterial blood gas values related to $PaCO_2$ and pH in 40 horses under general anaesthesia receiving high (>0.95) or low (0.3) FIO_2.

		group HIGH		group LOW	
		L	D	L	D
$PaCO_2$ (mmHg)	T1	39(36-41)	41(41-42)	40(39-43)	41(40-45)
	T2	43(42-45)	43(42-45)	46(43-47)	45(44-47)
	T3	48(45-50)	47(46-49)	48(46-49)	46(43-49)
	T4	48(43-56)	48(46-54)	55(49-58)	51(46-53)
	T5	49(47-50)	48(47-50)	47(42-50)	48(47-50)
	T6	49(45-50)	48(45-50)	46(43-51)	47(45-48)
	T7	43(43-45)	43(43-46)	43(38-44)	42(40-48)
V_D%	T1	8.4±3.9	10.3±2	10.1±3.2	8.5±4.2
	T2	8 ±3.9	8.9±4.6	9.1±5	9 ±3.1
	T3	9.4±4.4	8.8±3.1	9.1±3.3	6.3±4.9
pH	T1	7.45(7.41-7.47)	7.43(7.41-7.45)	7.42(7.41-7.44)	7.41(7.4 -7.44)
	T2	7.42(7.40-7.42)	7.43(7.40-7.45)	7.4 (7.38-7.42)	7.44(7.4 -7.47)
	T3	7.4 (7.35-7.44)	7.39(7.38-7.43)	7.38(7.36-7.4)	7.43(7.41-7.46)
	T4	7.37(7.35-7.43)	7.4 (7.39-7.43)	7.35(7.31-7.37)	7.41(7.36-7.44)
	T5	7.42(7.39-7.43)	7.4 (7.38-7.42)	7.4 (7.38-7.43)	7.43(7.4 -7.44)
	T6	7.42(7.4 -7.44)	7.42(7.41-7.45)	7.4 (7.39-7.42)	7.43(7.4 -7.44)
	T7	7.45(7.43-7.48)	7.43(7.43-7.46)	7.43(7.40-7.44)	7.46(7.44-7.49)

Data are presented as mean±SD or median (IQR, 25%-75%). Sample times are at 20 (T1), 40 (T2) and 60 (T3) minutes after beginning of anesthesia, at 5 (T4), 10 (T5) and 15 (T6) minutes after the end of anesthesia and 5 minutes after recovering standing position (T7). D - Dorsal recumbency, L – Lateral recumbency.

mation. The effect was mostly significant in the sub-group of horses positioned in lateral recumbency compared to dorsal. The FIO_2 of 0.3 led to clearly lower intra-operative PaO_2, below 70 mmHg in some horses. Maintaining a lower FIO_2 during the whole anesthesia did not provide any difference on PaO_2 during the recovery. The results presented here confirm that the absence of oxygen supplementation during the recovery from general anesthesia is consistent with low PaO_2 (50–60 mmHg) in all horses.

Overall, these findings corroborate the conclusion obtained for intra- and post-anesthetic indices of oxygenation in a previous crossover study exposing 5 spontaneously breathing horses to 0.3 FIO_2 (*Cuvelliez* et al. 1990). The oxygenation indices were better preserved with the use of lower FIO_2. Similar findings were reported in a retrospective study comparing 0.8 and 0.6 FIO_2 (*Schauvliege* et al. 2015). Another trial exposing 5 mechanically ventilated horses to 0.5 FIO_2 reported no effect of FIO_2 in mechanically ventilated horses placed in dorsal recumbency (*Hubbell* et al. 2011). In horses anesthetized with isoflurane (*Crumley* et al. 2013) or intravenous anesthetics (*Karrasch* et al. 2015) and breathing spontaneously in dorsal recumbency, the use of 0.5 FIO_2 did not improve the pulmonary gas exchange compared to maximal oxygen concentrations. It could be hypothesized that the potential impact of dorsal recumbency on atelectasis and venous admixture development minimizes the benefit of reducing FIO_2. Similar conclusions were obtained in horses undergoing laparotomy with mechanical ventilationand receiving 0.35, 0.55 or 0.9 FIO_2 (*Schulte-Bahrenberg* et al. 2011). In the present study, the number of horses was targeted at 20 horses per group to detect the effect of FIO_2. Therefore, the evaluation of the effect of recumbency within each group suffered a low statistical power (only 10 horses per subgroup).

Regarding the potential bias attributable to uneven group selection, class LOW-D weighed less than the other classes by approximately 80 kg as a result of body weight not having been included within the randomization process. Body weight has been reported as a possible predictor for low arterial oxygen tension (*Whitehair* and *Willits* 1999, *Mansel* and *Clutton* 2008, *Moens* et al. 1995). However, the correlation was significant when comparing groups of different morphology with large differences in height per unit body mass (H/kg) or thoracic circumference (*Mansel* and *Clutton* 2008). Large variations in body shape probably influence the risk for hypoxemia more largely than bodyweight, and it is unlikely that variations in body weight to the extent of 80 kg within a group of relatively similar morphology (adult warmblood) may have significantly influenced the study outcome. However, body shape was not recorded in the present study and a bias from this parameter cannot be excluded. The significantly higher age (12-year-old versus 3- to 5-year-old) of HIGH-L can potentially have influenced the longer recovery times found for this class. However, recovery times from HIGH-L were significantly different from group LOW-D (P = 0.022) but not from LOW-L neither HIGH-D, which tends to invalidate an effect of age on recovery time in the present study. Mean arterial pressures were 5 to 10 mmHg lower in horses placed in lateral compared to dorsal position. The authors do not consider that this result could have significantly influenced the values for PaO_2.

Table 3 Arterial blood gas values related to PaO_2 in 40 horses under general anaesthesia receiving high (>0.95) or low (0.3) FIO_2.

		group HIGH		group LOW	
		L	D	L	D
PaO_2 (mmHg)	T1 §	250(144-283)	259(122-410)	101(91-110)	89(87-101)
	T2 §	253(194-335)	337(200-511)	97(92-101)	84(76-100)
	T3 §	142(115-236)*	302(186-377)	92(86- 98)	78(66- 87)
	T4	55(50- 68)	62(57- 68)	66(60- 73)	56(50- 64)
	T5	56(50- 68)	60(56- 64)	66(56- 69)	55(50- 59)
	T6	56(46- 66)	58(53- 66)	66(61- 81)	57(49- 63)
	T7	96(81- 99)	93(88- 96)	96(90- 99)	95(88- 96)
$PA\text{-}aO_2$ (mmHg)	T1	325(298-434)	332(175-450)	60(54- 66)	73(61- 81)
	T2	361(275-430)	253(101-422)	65(57- 69)	70(59- 83)
	T3	474(380-506)*	318(237-434)	62(59- 67)	81(74- 89)*
Pa/AO_2	T1 §	0.43(0.25-0.49)	0.44(0.21-0.7)	0.63(0.59-0.67)	0.55(0.52-0.63)
	T2	0.41(0.31-0.55)	0.57(0.32-0.84)	0.6 (0.57-0.64)	0.54(0.47-0.63)
	T3 §	0.23(0.19-0.38)	0.49(0.3 -0.61)	0.6 (0.56-0.63)	0.49(0.43-0.54)
Pa/FiO_2 (mmHg)	T1	284(162-317)	285(136-453)	337(303-357)	292(284-337)
	T2	266(202-356)	370(209-539)	318(307-337)	278(250-327)
	T3	147(120-247)	315(194-394)	305(287-327) #	258(220-281)
$FSHUNT_e$ (%)	T1 §	30(21- 41)	27(15- 32)	15(12- 22)	12(10- 16)
	T2 §	27(20- 35) #	18(8- 29)	14(10- 22)	15(12- 19)
	T3 §	33(25- 36) #	22(17- 30)	17(9- 20)	17(16- 25)

Data are presented as mean±SD or median (IQR, 25%-75%). Sample times are at 20 (T1), 40 (T2) and 60 (T3) minutes after beginning of anesthesia, at 5 (T4), 10 (T5) and 15 (T6) minutes after the end of anesthesia and 5 minutes after recovering standing position (T7). * indicates a significant difference from other time points. § indicates a significant difference between groups HIGH and LOW. # indicates a significant difference between groups L and D.
D - Dorsal recumbency. L - Lateral recumbency

A potential weakness of the present study is the use of pressure controlled ventilation mode (peak inspiratory airway pressure of 25 cmH_2O) for intermittent positive pressure ventilation and subsequent VT variation. An insufficient VT in horses placed in dorsal recumbency may lead to passive pulmonary atelectasis from hypoventilation (*Woodring* and *Reed* 1996), particularly in the absence of positive end-expiratory pressure. Insufficient distribution of VT to dependent lung areas is particularly pronounced in horses (*Moens* et al. 1998), but the critical VT inducing areas of lung collapse is unknown. In the present study, the delivered volume could not be appropriately reported but it was not allowed to decrease below 10 mL/kg. This is in agreement with previous studies where VT close to 15 mL/kg were maintained with PIP between 22 (*Moens* et al. 1998) and 30 cmH_2O (*Hubbell* et al. 2011). In humans under general anesthesia, VT as low as 6 mL/kg did not induce more lung atelectasis than traditional VT (*Cai* et al. 2007), but high pressures and large volumes induced more lung injury (*Hong* et al. 2010). Still, the influence of PIP and VT on development of atelectasis in healthy lungs of horses during general anesthesia is not well characterized.

Anesthetized horses are particularly subjected to compression atelectasis and to develop low arterial oxygen tensions (*Moens* et al. 1998). In the present study an overall median PaO_2 of 90.5 mmHg (79.5–100.5) was measured during general anesthesia when 0.3 FIO_2 was applied. The PaO_2 decreased at few occasions between 60 and 70 mmHg in dorsal recumbency and can be caused by a reduced functional residual capacity and residual volume (*Gleed* and *Dobson* 1988, *Whitehair* and *Willits* 1999). Breathing ambient air without supplemental oxygen is common in field anesthesia and values for mean PaO_2 between 43 ± 3 mmHg and 65.5 ± 4 mmHg were reported in lateral recumbency (*Frias* et al. 2003, *Mama* et al. 2005), versus 50.9 ± 7 to 60.5 ± 6.5 mmHg in dorsal recumbency (*Yamashita* et al. 2007). When oxygen is administered by nasal insufflation at 15 L/min PaO_2 does not clearly improve (*Matthews* et al. 1999, *Wagner* et al. 2008) and the use of 0.3 FIO_2 in the present study provided a better oxygenation as well as compared to the use of 0.5 FIO_2 in spontaneously breathing horses under general anesthesia in dorsal recumbency (*Crumley* et al. 2013).

The main determinants of tissue oxygen delivery are tissue blood flow and CaO_2 (*Bigeleisen* 2001). The latter is likely to change during general anesthesia when SaO_2 decreases due to low PaO_2. It remains unclear which value of the oxygen status should be considered as a critical threshold. In a previous experimental setting, the use of air (FIO_2 of approximately 0.2) as the carrier gas during isoflurane anesthesia decreased skeletal muscle oxygenation (*Portier* et al. 2009). In the present study all the horses recovered uneventfully, and neither immediate nor delayed clinical signs of inadequate oxygenation were observed. In the small crossover study from *Hubbell* et al. (2011), the horses did not receive additional oxygen during the recovery phase and PaO_2 was measured around 44 mmHg with SaO_2 of 84 %, however recoveries were graded satisfactory and no complication was noted while CaO_2 was calculated over 14 mL O_2/dL. In both studies all the selected horses were healthy. In case of anemia or shift to the right of the hemoglobin dissociation curve, similar values for PaO_2 could lead to low arterial oxygen content and potentially severe hypoxia. To the author's knowledge, there is no consensus regarding a critical CaO_2 threshold to be considered unacceptable.

In the present study, several oxygen tension-based indices of oxygen were used, as well as the oxygen content-based parameter FSHUNTe were reported and compared in order to quantify the degree of venous admixture in the different groups. The limitations of these parameters to represent the true intrapulmonary shunt and the ventilation-perfusion mismatch have been largely discussed in the literature (*Bigeleisen* 2001, *Doyle* 1986). Here, the difference PA-aO_2 was used to compare groups under varying circumstances but at the same FIO_2 (ie D vs L), and the ratio Pa/AO_2 and PaO_2/FiO_2 to compare groups under similar circumstances at different FIO_2 (ie HIGH vs LOW) (*Doyle* 1986, *Torda* 1981). The oxygen content-based parameter FSHUNTe has been reported to be more reliable as it takes account for SaO_2 (*Araos* et al. 2012). This index had the best correlation to actual venous admixture in sheep over a large range of FIO_2 (*Araos* et al. 2012), as well as in horses (*Briganti* et al. 2015). Still, its use requires several assumptions like a constant oxygen carrying capacity for hemoglobin estimated in the present study at 3.5 mg/dL, as well as an estimated value for pulmonary end-capillary partial pressure and saturation of oxygen. Moreover, without co-oximetry or a specific calculation based on equine $P50O_2$, the SaO_2 is not fully reliable.

Another hypothesis was that improved pulmonary function with less pulmonary atelectasis could improve the oxygen status during the recovery period. Previous investigations reported PaO_2 values of 60 mmHg in horses recovering from general anesthesia without additional oxygen administration (*Mason* et al. 1987, *McMurphy* and *Cribb* 1989, *Johnson* et al. 1994). In the present study, the results from both groups were similar to previously published data, and the use of 0.3 FiO_2 during general anesthesia did not induce any difference on PaO_2 during awakening compared to $FIO_2 < 0.95$. The use of low intra-operative FIO^2 is not efficacious to improve arterial oxygenation during the recovery phase, but did not compromise the patients compared to high FIO^2. According to previous report, oxygen supplementation via nasal continuous insufflation at a high flow was found to provide only slight improvement in such situation (*Mason* et al. 1987). Therefore intermittent ventilation with high FIO_2 administered via the endotracheal tube (eg. via a Hudson valve) appears recommended if PaO_2 needs to be increased during the recovery phase (*Mason* et al. 1987, *Johnson* et al. 1994).

In conclusion, it appears from the present study that pulmonary function in horses positioned in lateral recumbency during general anesthesia can be positively influenced by the use of 0.3 FIO_2. On the other side, this did not provide any difference for post-operative PaO_2 values in horses breathing room air during recovery. Importantly, even if no adverse event occurred in the present study, the low PaO_2 values associated with the use of 0.3 FIO_2 requires routine individual arterial blood gas monitoring to monitor and treat adequately occurrence of hypoxemia. Overall and under the conditions of the present study, the use of 0.3 FIO_2, despite potentially reducing venous admixture, appeared to decrease safety margin during anesthesia without benefit during the recovery phase.

Animal Welfare Statement

The present study was approved by the local Ethic Committee of the Department for Veterinary Clinical Sciences at the Vetsuisse Faculty, University of Berne (2007/Nov).

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Erweiterte Zusammenfassung

Auswirkung eines niedrigen inspiratorischen Sauerstoffanteils auf die Oxygenierung bei klinischen Pferden unter Vollnarkose

In der tiermedizinischen Vollnarkose ist eine Zuführung einer hohen FIO_2 (Sauerstoff-Einatmungsfraktion) über 0.95 (z.B. 95%) üblich. Ziel dieser Studie war es, die Verwendung eines

hohen (> 0,95) oder niedrigen (0,3) Sauerstoffanteils im inspiratorischen Luftgemisch während der Narkose bei Pferden zu vergleichen. Bei Pferden wird oft ein hoher inspiratorischer Sauerstoffanteil gegeben, um das Risiko einer Hypoxämie während der Narkose zu reduzieren. Auf der anderen Seite birgt ein solch hoher Sauerstoffanteil das Risiko vermehrt Lungenatelektasen zu verursachen. Dies könnte sich in der Folge negativ auf die Lungenfunktion während der Aufwachphase auswirken. Trotz mehrerer experimenteller Forschungsarbeiten bleibt unklar, ob ein reduzierter Sauerstoffanteil für die Praxis tatsächlich Vorteile und mehr Sicherheit mit sich bringt. Diese Studie untersucht, ob eine Sauerstoffanteil von 0,3 in der inspiratorischen Atemluft die Lungenfunktion weniger beeinträchtigt als die Anwendung reines Sauerstoffs ($FiO_2 > 0,95$). Eine ausgeprägte Hypoxämie soll dabei vermieden werden, damit die Sicherheit während die Narkose nicht abnimmt. Ein spezielles Augenmerk wird dabei auch darauf gerichtet, ob die verbesserte Lungenfunktion eine positive Auswirkung auf den arteriellen Sauerstoffpartialdruck während der Aufwachphase hat. Vierzig ausgewachsene, für elektive Eingriffe vorgesehene Pferde wurden in Dorsal- oder in Seitenlage mit Isofluran anästhesiert. Sie erhielten einen inspiratorischen Sauerstoffanteil von entweder > 0,95 (Gruppe HIGH) oder 0,3 (Gruppe LOW). Alle Pferde wurden sofort mit einem druckgesteuertem Modus beatmet. An mehreren Zeitpunkten während und nach der Narkose wurde eine arterielle Blutgasanalyse durchgeführt, verschiedene Parameter der Lungenfunktion ausgewertet und zwischen den Gruppen verglichen. Die LOW Gruppe zeigte niedrigere intraoperative PaO_2-Werte. Allerdings zeigte sie bessere Werte für die venöse Beimischung als die HIGH Gruppe. Es gab einen signifikanten Unterschied für Pa/AO_2 ($P = 0.009$) and FSHUNTe ($P = 0.003$) zwischen Gruppe LOW und HIGH, wobei der Pa/FIO_2 nur innerhalb der Gruppe in der Seitenlage ($P = 0.019$) unterschiedlich war. Ansonsten zeigte die Lagerung keinen Einfluss bei diesen Parametern. Fünf Pferde erreichten einen PaO_2 unter 70 mmHg; alle aus der LOW Gruppe (62, 61, 56, 69 mmHg in der Gruppe LOW-Dorsal, 66 mmHg in der Gruppe LOW-Lateral). Für beide Gruppen sank der PaO_2 stark während der Aufwachphase, allerdings ohne signifikanten Unterschied zwischen den beiden Gruppen. Obwohl diese klinische Studie mehrere Einschränkungen zeigt, verbesserte sich die Lungenfunktion während der Narkose und unter den spezifischen Bedingungen durch die Verwendung einer niedrigeren inspiratorischen Fraktion von Sauerstoff (0,3). Während der Aufwachphase konnte dieses positive Ergebnis allerdings nicht aufrechterhalten werden. Die Gruppe mit der niedrigeren Sauerstoffkonzentration zeigte grenzwertig niedrige PaO_2. Unter Berücksichtigung der Bedingungen der hier präsentierten Studie, wurde die Sicherheit während der Narkose von der Anwendung 0,3 FIO_2 insgesamt eher negativ beeinflusst.

Schlüsselwörter: Anästhesie, Oxygenierung, Atelektase, venöse Beimischung, Hypoxämie, Narkose, Pferd