SHORT COMMUNICATION

Effect of different inspired fractions of oxygen on F-shunt and arterial partial pressure of oxygen in isoflurane-anaesthetized and mechanically ventilated Shetland ponies

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Abstract

Objective To determine the effect of fraction of inspired oxygen (FiO_2) on intrapulmonary shunt fraction as measured by F-shunt in ponies during isoflurane anaesthesia.

Study design Prospective, randomized clinical study.

Animals A group of 23 adult Shetland ponies undergoing a total of 32 anaesthetic procedures.

Methods Ponies were premedicated intravenously (IV) with detomidine (0.01 mg kg^{-1}) and either morphine (0.1 mg kg^{-1}) or butorphanol (0.02 mg kg^{-1}). Anaesthesia was induced with ketamine (2.2 mg kg^{-1}) and midazolam (0.07 mg kg^{-1}) administered IV. Ponies were randomly allocated to maintenance of anaesthesia with isoflurane in oxygen (group TH; $FiO_2 = 0.95$) or a mixture of oxygen and medical air (group TL; $FiO_2 = 0.65$); all ponies were given a constant rate of infusion of detomidine. Animals were mechanically ventilated to maintain $PaCO_2$ between 40 and 50 mmHg. Arterial blood gas analysis was performed every 30 minutes. The F-shunt equation was calculated for each time point T0, T30, T60 and T90. Data were analysed using linear mixed model analysis and presented as mean ± standard deviation ($p < 0.05$).

Results PaO_2 was greater in group TH than in group TL (TH: 406 ± 90, 438 ± 83, 441 ± 69 and 464 ± 53 mmHg *versus* TL: 202 ± 90, 186 ± 84, 172 ± 85 and 191 ± 98 mmHg at T0, T30, T60 and T90, respectively; $p < 0.0001$). In TH, F-shunt was < TL. Significant differences were found at T60 (TH: 13.2% ± 4.3 *versus* TL: 19.4% ± 8.3; $p = 0.016$) and T90 (TH: 11.7% ± 3.5 *versus* TL: 18.6% ± 9.5; $p = 0.036$).

Conclusions and clinical relevance Our findings do not support a beneficial effect of using a reduced FiO_2 to improve oxygenation in anaesthetized and mechanically ventilated Shetland ponies.

Keywords absorption, atelectasis, equine, inspired oxygen fraction, pony.

Introduction

A common complication during equine anaesthesia is impaired pulmonary gas exchange. The effects of possible hypoxaemia on the brain, skeletal muscle, cardiovascular, ventilatory and gastrointestinal systems may be partially responsible for the higher mortality risk associated with equine anaesthesia (Auckburally & Nyman 2017).

The change of body position to lateral and particularly dorsal recumbency tends to cause atelectasis in dependent lung regions. Atelectasis contributes to ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch within the lung parenchyma and therefore to impaired arterial oxygenation. The three main mechanisms of lung collapse have been described: compression atelectasis, absorption atelectasis and loss of surfactant action (Auckburally & Nyman 2017). Compression atelectasis, produced when external pressure causes the alveoli to collapse, is thought to occur in horses owing to the sloping diaphragm and overlying intestinal organs, particularly in dorsal recumbency (Moens et al. 1995). Absorption atelectasis can develop when less gas enters the alveoli by ventilation than is removed. Because oxygen is more soluble than nitrogen, the use of a high fraction of inspired oxygen (FiO_2) during anaesthesia may increase absorption atelectasis; however, in equine species, the evidence is equivocal. Some studies showed less atelectasis in

horses breathing a reduced F_IO_2 (Marntell et al. 2005; Staffieri et al. 2009; Schauvliege et al. 2015). Contrary to these findings, Hubbell et al. (2011) and Crumley et al. (2013) did not report an improvement in gas exchange using a reduced F_IO_2 in isoflurane-anaesthetized horses. There is little information about the effects of F_IO_2 on gas exchange in ponies.

The aim of this study was to evaluate the effect of two different F_IO_2 on the development of venous admixture as measured by F-shunt in dorsally recumbent and mechanically ventilated Shetland ponies during isoflurane anaesthesia. Our hypothesis was that reduced F_IO_2 would attenuate absorption atelectasis and V/Q mismatch and therefore reduce F-Shunt.

Materials and methods

A total of 23 adult female Shetland ponies anaesthetized for orthopaedic procedures over the course of three separate, unrelated research studies were included. Ethical approval was obtained (AVD108002015307) for a total of 32 anaesthetic procedures (nine ponies were anaesthetized twice). All the animals were considered healthy based on physical examination before anaesthesia. Food and water were provided until the morning of the study. The ARRIVE guidelines for treating experimental animals were followed.

Each anaesthetic procedure was randomly assigned to one of two groups: TH, targeting an F_IO_2 of 0.95 and TL, targeting an F_IO_2 of 0.65. Randomization was performed using an online random group generator (www.randomlist.com). Ponies were sedated with 0.01 mg kg^{-1} detomidine (Domosedan; Orion, Finland) administered intravenously (IV). A 14 gauge catheter (Intraflon 2; Vygon, France) was placed in a jugular vein. Then, depending on the orthopaedic procedure, an opioid was administered: either 0.1 mg kg^{-1} morphine IV (Morfine HCl; Centrafarma, the Netherlands) or 0.02 mg kg^{-1} butorphanol IV (Dolorex; MSD, the Netherlands). All animals were given 2.5 g ampicillin (Ampi-dry 5000; Dopharma, the Netherlands) and 0.6 mg kg^{-1} meloxicam IV (Metacam; Boehringer-Ingelheim, Germany). If the level of sedation was considered insufficient prior to anaesthetic induction, additional detomidine was administered IV (0.005−0.01 mg kg^{-1}). Induction of anaesthesia was performed with 2.2 mg kg^{-1} ketamine (Narketan; Vetoquinol, France) and 0.07 mg kg^{-1} midazolam (Midazolam Actavis; Actavis, Iceland), both administered IV. After induction, ponies were hoisted and positioned in dorsal recumbency on the surgical table, and then orotracheally intubated. Upon entering the surgical theatre, ponies were connected to a large or small animal circle system (Model 2800C; Mallard Medical, CA, USA) according to their body weight (<150 kg the small circle system was used). Anaesthesia was maintained with isoflurane (Iso-Vet; Piramal Healthcare, UK) in oxygen or a mix of medical air and oxygen to achieve the F_IO_2 according to the group allocation. Mechanical ventilation was started immediately at a respiratory rate (f_R) of 8 breaths $minute^{-1}$ and tidal volume (VT) of 10 mL kg^{-1}, and airway pressure was monitored. A constant-rate infusion (CRI) of detomidine (0.01 mg kg^{-1} $hour^{-1}$) was administered during surgery and a 21 gauge butterfly catheter (Surflo; Terumo, Belgium) was placed in the facial artery for invasive blood pressure monitoring and arterial blood gas sampling. Electrocardiogram, heart rate, f_R, haemoglobin oxygen saturation, end-tidal partial pressure of carbon dioxide, end-tidal fraction of isoflurane, F_IO_2, VT and peak inspiratory pressure (PIP) (measured by spirometry) and invasive blood pressure were recorded from a multiparameter monitor (Datex-Ohmeda S/5; GE Healthcare, IL, USA) every 10 minutes. The f_R and VT were adjusted to maintain arterial partial pressure of carbon dioxide ($PaCO_2$) between 40 and 50 mmHg (5.3−6.6 kPa). If mean arterial blood pressure was less than 70 mmHg, a CRI of dobutamine (Dobutamine-hameln; Hameln Pharma Plus, Germany) was administered to effect (0.5−4 μg kg^{-1} $minute^{-1}$). A forced warmed air blanket (Bairhugger; 3M Company, MN, USA) was used for thermal support. At the end of the surgical procedure, 20 mg kg^{-1} procaine penicillin (Procapen; ASTfarma, Germany) was administered intramuscularly, and the animals were moved to the recovery box. If at any point, the arterial partial pressure of O_2 (PaO_2) was less than 80 mmHg, the pony was removed from the study and appropriate measures were taken.

At 1 minute after arterial catheter placement, a 2 mL heparinized arterial blood sample (Rapidlyte; Siemens, Germany) was obtained and immediately analysed for PaO_2, $PaCO_2$ and arterial haemoglobin oxygen saturation using a blood gas analyser (Rapidlab 1260; Siemens, Germany) (T0). At the same time, 5 mL of jugular venous blood was collected into a tube containing ethylenediaminetetraacetic acid for haemoglobin concentration ([Hb]) measurement. Blood sampling was repeated every 30 minutes until the end of surgery. Arterial oxygen content, capillary oxygen content and F-shunt were calculated (Appendix A).

Statistics

An *a priori* sample size calculation was performed using reported F-shunt calculation previously reported in horses (Briganti et al. 2015). With a power of 80% and an alpha of 0.05, for a change of 25% in F-shunt between groups, 16 ponies were required per group. Since very few samples were collected 90 minutes after the first blood sample, calculations were restricted from T0 to T90. Data were assessed for normality using Kolmogorov−Smirnov test. For normally distributed data, mean ± standard deviation are shown. Mean and standard deviation were calculated for PaO_2 and F-shunt for each group at each time point (T0, T30, T60 and T90). Linear mixed model analysis was performed, with pony

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identification (ID) as a random factor, F_IO_2 as fixed factor and time as a repeated factor, to compare F-shunt and PaO_2 results of both groups. Student's *t* test was performed for comparison of VT, PIP, body weight and age. SPSS Statistics Version 25.0 (IBM, NY, USA) and Microsoft Office Excel 2007 (WA, USA) were used for statistical analysis and plots. Statistical significance was accepted at $p < 0.05$.

Results

Pony demographic, timing and spirometry data are shown in Tables S1 and S2. A pony in group TL was excluded from statistical analysis owing to PaO_2 less than 80 mmHg at the first measurement point.

Bodyweight and age were not significantly different between the two groups ($p = 0.83$ and $p = 0.53$, respectively). Likewise, there was no significant difference in time from induction to the first blood sample ($p = 0.78$), time to start of mechanical ventilation ($p = 0.48$), V_T ($p = 0.32$) and PIP ($p = 0.61$). The F_IO_2 administered was 0.64 ± 0.06 in group TL and 0.93 ± 0.03 in group TH.

PaO_2 was always greater in group TH than in group TL (TH: 406 ± 90, 438 ± 83, 441 ± 69 and 464 ± 53 mmHg *versus* TL: 202 ± 90, 186 ± 84, 172 ± 85 and 191 ± 98 mmHg at T0, T30, T60 and T90, respectively) and this difference was significant at all time points ($p < 0.0001$). F-shunt was greater in group TL than in group TH, and this difference was significant at T60 (TH: 13.2% ± 4.3 *versus* TL: 19.4% ± 8.3; $p = 0.016$) and T90 (TH: 11.7% ± 3.5 *versus* TL: 18.6% ± 9.5; $p = 0.036$) (Fig. 1). There was no significant difference intragroup for PaO_2 or F-shunt.

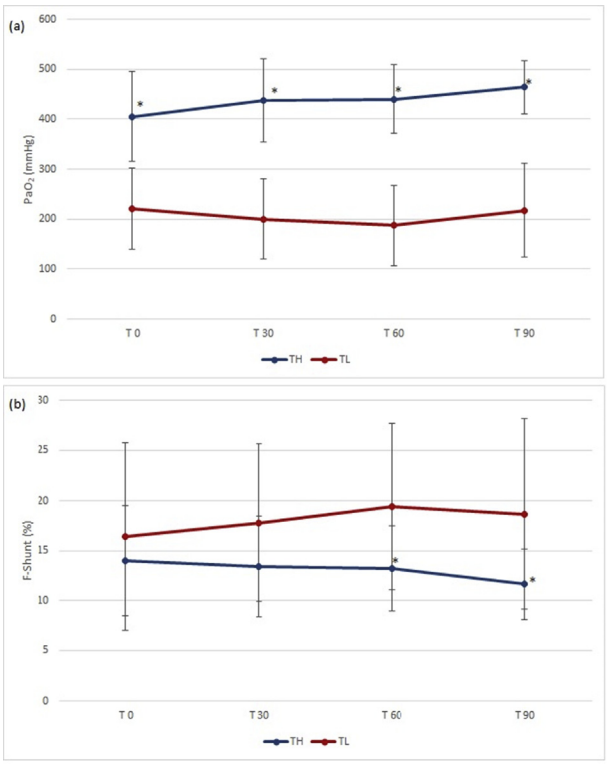

Figure 1 Graph (a) mean values (dots) and standard deviation (error bars) of arterial partial pressure of oxygen (PaO_2) measured in 23 isoflurane-anaesthetized mechanically ventilated Shetland ponies given either an inspired fraction of oxygen (F_IO_2) of 0.95 (TH) or 0.65 (TL) and graph (b) calculated F-shunt. There were 16 ponies per group, 32 anaesthetic procedures, and nine ponies were anaesthetized twice. T0—T90: time in minutes from first arterial blood sampling. * Significant difference between groups $p < 0.05$.

Discussion

The most clinically relevant finding of this study was a lack of improvement in oxygenation and no reduction in intrapulmonary shunt development when a reduced F_IO_2 (0.64) was delivered compared with an F_IO_2 of 0.93, in dorsally recumbent mechanically ventilated Shetland ponies during isoflurane anaesthesia.

Atelectasis formation during general anaesthesia contributes highly to the increase in intrapulmonary shunting (Auckburally & Nyman 2017). The gold standard formula to calculate venous admixture ($\dot{Q}s/\dot{Q}t$) is Berggren's shunt equation (Berggren 1942). For this, a blood sample from the pulmonary artery is required in order to calculate mixed venous oxygen content. However, pulmonary artery catheter placement is an invasive procedure and requires more sophisticated equipment. Therefore, alternative calculations and estimates have been developed, one of which is the F-shunt equation. It is an oxygen content—based index that assumes a fixed value of 3.5 mL dL^{-1} for the arterial-to-mixed venous oxygen content difference [$C(a\text{-}v)O_2$], so sampling of mixed venous blood can be avoided (Briganti et al. 2015). Assuming a fixed value for the arterial-to-mixed venous oxygen content difference may be incorrect since it ignores the possibility of changes in oxygen extraction as a result of changes in tissue perfusion and cellular metabolism. Despite this, F-shunt showed a good agreement with calculations using the Berggren's equation for venous admixture estimation in horses (Briganti et al. 2015). It should be noted that the F-shunt equation has not been formally validated in ponies.

As in the present study, other studies have found no advantage to the use of a reduced F_IO_2 in horses during mechanical ventilation (Hubbell et al. 2011; Taylor & Seymour 2016). In some studies that reported a positive effect of a reduced F_IO_2 (Marntell et al. 2005; Schauvliege et al. 2015), horses were allowed to breathe spontaneously. A possible explanation may be that early institution of mechanical ventilation can overcome any benefit of reduced F_IO_2. Early institution of mechanical ventilation may reduce the

impairment of gas exchange owing to a reduction in atelectasis or via better $\dot{V}/\dot{Q}$ matching or both (Wolff & Moens 2010). In our study, there was no significant difference between groups in time from induction to starting mechanical ventilation, V_T, PIP and body weight between groups; therefore, the results of this study may not be related to different mechanical ventilation strategies between groups.

Several studies have shown a positive effect of a lower F_IO_2 on pulmonary gas exchange in mechanically ventilated horses (Staffieri et al. 2009; Levionnois et al. 2016) when F_IO_2 of 0.21−0.3 was compared with F_IO_2 higher than 0.9. It should be noted that studies that showed no benefit of using a reduced F_IO_2 provided an F_IO_2 equal or higher than 0.5 in the 'reduced F_IO_2' group (Hubbell et al. 2011; Taylor & Seymour 2016). Also, differences in anaesthetic protocol could account for some of the discrepancies observed between studies.

An unexpected finding in our study was that the F-shunt decreased over time in group TH, although it was not significantly different from group TL. We cannot offer a straightforward explanation for this. A possible reason could be an increased respiratory minute volume over time due to progressive relaxation of intercostal muscles during anaesthesia, although there were no differences in V_T or PIP between groups. Different body conformation (and therefore degrees of diaphragmatic compression) between groups may play a role. In this study, we did not compare the body conformation of the ponies included in the study, which we consider a limitation of our study design. Also, some of the ponies were anaesthetized twice, potentially affecting the results. Although the reason for the reduction in F-shunt over time in group TH but not TL remains uncertain, it does stress the possibly reduced contribution of absorption atelectasis to total gas exchange impairment in these ponies.

In conclusion, no improvement in oxygenation and intrapulmonary shunt development was found when a reduced F_IO_2 was used during isoflurane anaesthesia in mechanically ventilated ponies. The lack of effect on shunt fraction may indicate that the atelectasis produced could result from compression rather than due to absorption.

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Authors' contributions

ACR: anaesthesia management, data collection, data management, statistical analysis, elaboration of drafted and final version of manuscript. JPAMvL: study design, critical review of manuscript. JdG: statistical analysis, critical review of manuscript.

Conflict of interest statement

The authors declare no conflict of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article: https://doi.org/10.1016/j.vaa.2021.05.005.

Appendix A. Calculations performed in each group and for each time point.

Arterial oxygen content (CaO_2) = ([Hb] * SaO_2 * 1.34) + (PaO_2 * 0.003)

Capillary oxygen content ($Cc'O_2$) = ([Hb] * 1.34) + (PaO_2 * 0.003)

F-Shunt = [($Cc'O_2$–CaO_2)/($Cc'O_2$–CaO_2 + 3.5)] * 100

Where:

[Hb]: haemoglobin concentration

1.34: amount of oxygen in mL carried by 1 g of haemoglobin

0.003: solubility coefficient of oxygen

PaO_2: partial pressure of oxygen in arterial blood.

SaO_2: haemoglobin saturation of oxygen in arterial blood