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Effect of low inspired oxygen fraction on respiratory indices in mechanically ventilated horses anaesthetised with isoflurane and medetomidine constant rate infusion

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ABSTRACT

Horses may become hypoxaemic during anaesthesia despite a high inspired oxygen fraction (FiO_2). A lower FiO_2 is used commonly in human beings to minimise atelectasis and to improve lung function, and previously has been shown to be of potential benefit in horses in experimental conditions. Other studies suggest no benefit to using a FiO_2 of 0.5 during clinically relevant conditions; however, low FiO_2 (0.65) is commonly used in practice and in a large number of studies. The present study was performed to compare the effect of a commonly used FiO_2 of 0.65 versus 0.90 on calculated respiratory indices in anaesthetised mechanically ventilated horses in a clinical setting. Eighteen healthy Thoroughbred horses anaesthetised for experimental laryngeal surgery were recruited into a prospective, non-blinded, randomised clinical study. Before anaesthesia, the horses were randomly allocated into either low (0.65) or high (0.90) FiO_2 groups and arterial blood gas (ABG) analysis was performed every 30 min during anaesthesia to allow for statistical analysis of respiratory indices. As expected, PaO_2 was significantly lower in horses anaesthetised with a low FiO_2, but was sufficient to fully saturate haemoglobin. There were no significant improvements in any of the other respiratory indices. There is no obvious benefit to be gained from the use of a FiO_2 of 0.65 compared to 0.90 for mechanically ventilated Thoroughbred horses anaesthetised in lateral recumbency with isoflurane and a medetomidine constant rate infusion.

Introduction

General anaesthesia in horses may lead to hypoxaemia, hypercapnia and a large alveolar (A) arterial (a) difference in the partial pressure of oxygen ($P(A\text{-}a)O_2$), even with maximal fractional inspired oxygen (FiO_2) (Hall et al., 1968). The main causes of hypoxaemia during anaesthesia, which can be difficult to treat, are intrapulmonary shunt and ventilation-perfusion (V_A:Q) mismatch (Rees et al., 2010). Other potential causes of hypoxaemia include (1) hypoventilation, which can be corrected by mechanical ventilation; and (2) diffusion limitation, which although unlikely to be encountered in healthy horses, occurs at high intensity exercise (Wagner et al., 1989).

Atelectasis is caused by compression of the thorax by the abdominal contents (Sorenson and Robinson, 1980; Moens et al., 1995), absorption of alveolar gas (Nyman and Hedenstierna, 1989; Rothen et al., 1995b, 1995c) and reduced surfactant function, as seen in human beings (Magnusson and Spahn, 2003). Atelectasis develops early in the anaesthetic period and gas exchange impairment is semi-quantitatively related to the area of atelectatic lung (Nyman et al., 1990).

During anaesthesia, functional residual capacity (FRC) is reduced (Sorenson and Robinson, 1980), potentially below closing capacity, leading to small airway closure (Hedenstierna and Edmark, 2010). Normal alveolar gas exchange results in oxygen absorption and CO_2 expulsion from the blood, with minimal nitrogen exchange; however, in trapped alveoli, there is no net inspired ventilation and so gas absorption occurs, leading to atelectasis (Briscoe et al., 1960; Dantzker et al., 1975; Joyce et al., 1993). The rate of collapse of a closed gas pocket or lung area is greater when it contains a high concentration of oxygen (Piiper et al., 1962; Joyce et al., 1993). This may be reduced using a low FiO_2; one study using helium and oxygen suggests that pulmonary gas exchange is better preserved with a low FiO_2 (Staffieri et al., 2009). Horses anaesthetised with isoflurane in low FiO_2 (0.6) had significantly lower PaO_2 and lower $P(A\text{-}a)O_2$, but similar PaO_2:FiO_2 ratios and similar numbers of hypoxaemic animals, when compared to horses anaesthetised with isoflurane in a higher FiO_2 (0.78) (Schauvliege et al., 2015). In two additional studies using oxygen/air mixtures, there was no benefit in using a FiO_2 of 0.5, with no improvement in oxygen delivery and significant hypoxaemia (Hubbell et al., 2011; Crumley et al., 2013).

Medetomidine is a selective and potent α_2 adrenoceptor agonist used for sedation and analgesia in veterinary anaesthesia (Virtanen

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et al., 1988; Pertovaara, 1993). When administered as a constant rate intravenous infusion (CRI) as a component of partial intravenous anaesthesia (PIVA), it reduces the minimum alveolar concentration (MAC) of isoflurane in horses (Neges et al., 2003) and improves the quality of recovery (Ringer et al., 2007). Medetomidine, like other α_2 agonists, causes cardiopulmonary effects, including reduction in cardiac output (*Qt*), biphasic changes in arterial blood pressure (ABP), bradycardia and arrhythmias (England and Clarke, 1996). With the exception of changes in ABP, these effects of bolus administration are not substantially different from pre-sedation values when steady state CRI values are reached (Bettschart-Wolfensberger et al., 1999). Other effects of medetomidine include a decrease in respiratory rate (f_R) and changes in $PaCO_2$ and PaO_2, although these are not always statistically or clinically significant (Wagner et al., 1991; Bettschart-Wolfensberger et al., 1999).

In view of the continued clinical use of low FiO_2 in practice and other clinical studies, the aim of this study was to compare calculated non-invasive respiratory indices in mechanically ventilated horses anaesthetised with isoflurane and a medetomidine CRI, using a FiO_2 of either 0.65 or 0.90. It was hypothesised that a low FiO_2 would improve calculated respiratory indices compared to a high FiO_2 but lower overall PaO_2.

Materials and methods

Animals

Eighteen Thoroughbred racehorses, retired due to laryngeal problems but otherwise healthy, were randomly assigned to receive either a low (0.65; ML) or a high (0.90; MH) FiO_2 during an experimental surgical procedure. All horses were included in the final results and all horses recovered uneventfully from anaesthesia. This prospective, randomised clinical study was approved by the Ethics and Welfare committee of the Royal Veterinary College (approval number RVC PURN: 2012 1179; date of approval 18 October 2012). The research horses were recruited from another study being performed under Home Office Licence regulations.

Anaesthesia

Horses were fasted for 10–12 h before anaesthesia for elective laryngeal surgery; access to water was not restricted. Flunixin meglumine (1.1 mg/kg IV; Flunixin Injection, Norbrook Laboratories) was infused through a 14 g × 13 cm jugular catheter (Milacath Extended Use, Mila). Gentamicin (6.6 mg/kg IV; Genta-kel, Kela; or GentaEquine, Dechra) was administered 30 min before anaesthesia. Procaine penicillin (20,000 IU/kg IM; Norocillin, Norbrook Laboratories) was administered 60–90 min prior to anaesthesia. Acepromazine (0.04 mg/kg IM; Calmivet, Vetoquinol) was administered 60 min before anaesthesia.

Medetomidine (0.007 mg/kg IV; Sedastart, Animalcare) and morphine (0.2 mg/kg IV; Morphine Sulphate, Martindale Pharmaceuticals) were administered for sedation and analgesia. Anaesthesia was induced with ketamine (2.2 mg/kg; Ketaset, Zoetis) and midazolam (0.04 mg/kg; Hypnovel, Roche Products) given simultaneously IV. After induction of anaesthesia and endotracheal (ET) intubation, each horse was positioned in right lateral recumbency on the operating table and the ET tube connected to a large animal anaesthetic machine (Mallard Medical 2800C, AB Medical Technologies). Isoflurane (Isoflo, Abbott Laboratories) was delivered at an initial concentration of 3% V/V in a fresh gas flow of 5 L/min, with either 3.5 L/min oxygen plus 1.5 L/min medical air (ML) to provide a FiO_2 of 0.65, as commonly used in practice, or 100% oxygen (MH). All horses were mechanically ventilated with a tidal volume (V_T) of 12 mL/kg and at an f_R to maintain an end-tidal CO_2 tension ($P_{ET}CO_2$) between 35 and 55 mmHg. All horses received compound sodium lactate (CSL) solution (Vetivex 11, Dechra Veterinary Products) at a rate of approximately 7 mL/kg/h during anaesthesia. A surgical plane of anaesthesia was maintained using isoflurane and a CRI of medetomidine at a dose of 3.5 μg/kg/h. Ketamine boluses (0.1–0.2 mg/kg IV) were used if the horse was deemed to be lightly anaesthetised. Dobutamine (Dobutamine, Hameln Pharmaceuticals) was infused at a dose of up to 5 μg/kg/min, if required, to maintain mean arterial blood pressure (MAP) > 70 mmHg.

Monitoring and data collection

ABP was measured using a multiparameter monitor (Datex-Ohmeda S/5, GE Healthcare) using a catheter placed in the left dorsal metatarsal artery. This catheter was also used to collect samples for arterial blood gas analysis (ABG), which was started as soon as practicable after induction of anaesthesia and thereafter at 30 min intervals. Each sample was analysed immediately using an IRMA TruPoint (QCR) blood gas analyser. Parameters recorded were isoflurane vaporiser setting (%), inspired (FiIso) and end-tidal (F_{ET}Iso) isoflurane concentrations, heart rate (HR), f_R, FiO_2, expired percentage of oxygen ($F_{ET}O_2$), saturation of haemoglobin with oxygen (SpO_2), $P_{ET}CO_2$, V_T, peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP). A rescue protocol for PaO_2 < 80 mmHg, an accepted level for hypoxaemia in equines (Haskins, 2007), was prepared but not used. All data were recorded manually every 5 min and study parameters collated between first and last ABG, so that the mean ± standard deviation for each parameter measured was within ABG measurements.

Table 1
Respiratory calculations.

Unit or index calculated	Calculation
Alveolar partial pressure of oxygen: PAO_2 (mmHg)	$PAO_2 = ([PB^a - PH_2O^b] \times FiO_2) - (PaCO_2/0.8)$
Pulmonary end-capillary oxygen content: $Cc'O_2$ (mL/dL)	$Cc'O_2 = ([Hb]^c \times$ Hüfner's Constant$^d \times Sc'O_2^e) + (0.0031 \times Pc'O_2^f)$
Arterial oxygen content: CaO_2 (mL/dL)	$CaO_2 = ([Hb] \times$ Hüfner's Constant $\times SaO_2^g) + (0.0031 \times PaO_2)$
Alveolar-to-arterial oxygen difference: $P(A\text{-}a)O_2$ (mmHg)	$P(A\text{-}a)O_2 = PAO_2 - PaO_2$
Arterial-to-inspired oxygen ratio (mmHg)	$PaO_2{:}FiO_2$
F-shunt (%)	$([Cc'O_2\text{-}CaO_2]/[Cc'O_2\text{-}CaO_2] + 3.5^h$ mL/dL) × 100

[a] Barometric pressure (mmHg).
[b] Vapour pressure of water = 47 mmHg.
[c] Haemoglobin concentration.
[d] Oxygen carrying capacity of haemoglobin (1.36 mL/g).
[e] Pulmonary end capillary oxygen saturation (for PAO_2 > 100 mm Hg assumed = 1).
[f] Pulmonary end-capillary partial pressure of oxygen (mmHg), assumed to be PAO_2.
[g] Arterial haemoglobin oxygen saturation (%).
[h] Arterial-venous oxygen content difference [$C(a\text{-}\bar{v})O_2$] in mechanically ventilated humans.

Data collation and analysis

Data were entered into a spreadsheet (Excel 2011 for Mac, Microsoft) before importation into a statistical programme (SPSS Statistics 21 for Mac, IBM) for analysis. After testing each sub-group for normality (Kolmogorov–Smirnov test), independent sample *t* tests were used to compare means of continuous data between low and high FiO_2 sub-groups. The means tested were age, weight, duration of procedure, average dobutamine infusion rate, HR, V_T, V_T/weight, f_R, V_M, PIP, PEEP, SpO_2, MAP, F_{ET}Iso, FiO_2, PaO_2, barometric pressure (PB), PAO_2, oxygen partial pressure ($P(A\text{-}a)O_2$), arterial oxygen pressure ratio ($PaO_2{:}FiO_2$), respiratory index ($P(A\text{-}a)O_2/PaO_2$), ratio of dead space to V_T ($V_D{:}V_T$) and the calculated ratio of the oxygen partial pressure differences between alveolar-arterial and arterio-venous values (F-shunt) (Table 1).

Independent samples Mann–Whitney *U* tests were used for analysis of American Society of Anesthesiologists (ASA) health status[1], body condition score (BCS) and quality of recovery; the χ^2 test was used for analysis of sex. Statistically significant results ($P < 0.05$) were taken forward into multivariate analysis, using a general linear model (GLM), along with risk factors from any test in which $P \leq 0.1$, or which had been shown previously to affect PaO_2 in other studies, including age, BCS and weight, and refined until only independent predictors with a $P < 0.05$ remained in the final model. A linear mixed effects (LME) model was then performed on the data to examine the effect of group and time on PaO_2.

Results

Demographic and clinical data are shown in Table 2. Cardiorespiratory data are shown in Table 3. There were no significant differences in age, weight, BCS or ASA category between the eight males and one female in the ML group, or the seven males and two females in the MH group. Duration of anaesthesia, haemoglobin concentration, additional analgesic drug usage, dobutamine usage, duration of anaesthesia, and length and quality of recovery were not significantly different between groups (Table 3).

There were no significant differences in SpO_2, Pa, F_{ET}, P(A-a), HR, f_R, V_T, V_M, MAP, PIP, PEEP, $V_D{:}V_T$, CaO_2 or CcO_2 during anaesthesia.

[1] See: https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system (accessed 12 March 2016).