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

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Highlights

- Poor oxygenation can be a major problem in horses during anaesthesia.
- Low FiO_2 is used to minimise atelectasis to improve respiratory function and oxygenation.
- Determination of invasive respiratory indices are difficult clinically, so non-invasive respiratory indices were substituted.
- Use of low FiO_2 did not result in significant improvement in respiratory indices.
- The calculated F-shunt was not lower in the low FiO_2 group.

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.

Keywords: Equine; Anaesthesia; Atelectasis; FiO_2 ; PaO_2 ; Respiratory indices

47 Introduction

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

55
56 Atelectasis is caused by compression of the thorax by the abdominal contents (Moens et al.,
57 1995; Sorenson and Robinson, 1980), absorption of alveolar gas (Nyman and Hedenstierna, 1989;
58 Rothen et al., 1995b, c;) and reduced surfactant function, as seen in human beings (Magnusson and
59 Spahn, 2003). Atelectasis develops early in the anaesthetic period and gas exchange impairment is
60 semi-quantitatively related to the area of atelectatic lung (Nyman et al., 1990).

61
62 During anaesthesia, functional residual capacity (FRC) is reduced (Sorenson and Robinson,
63 1980), potentially below closing capacity, leading to small airway closure (Hedenstierna and
64 Edmark, 2010). Normal alveolar gas exchange results in oxygen absorption and CO_2 expulsion
65 from the blood, with minimal nitrogen exchange; however, in trapped alveoli, there is no net
66 inspired ventilation and so gas absorption occurs, leading to atelectasis (Briscoe et al., 1960;
67 Dantzker et al., 1975; Joyce et al., 1993). The rate of collapse of a closed gas pocket or lung area is
68 greater when it contains a high concentration of oxygen (Piiper et al., 1962; Joyce et al., 1993). This
69 may be reduced using a low FiO_2 ; one study using helium and oxygen suggests that pulmonary gas
70 exchange is better preserved with a low FiO_2 (Staffieri et al., 2009). Horses anaesthetised with
71 isoflurane in low FiO_2 (0.6) had significantly lower PaO_2 and lower $P(A-a)O_2$, but similar
72 $PaO_2:FiO_2$ ratios and similar numbers of hypoxaemic animals, when compared to horses

73 anaesthetised with isoflurane in a higher FiO_2 (0.78) (Schauvliege et al., 2015). In two additional
74 studies using oxygen/air mixtures, there was no benefit in using a FiO_2 of 0.5, with no improvement
75 in oxygen delivery and significant hypoxaemia (Hubbell et al., 2011; Crumley et al., 2013).

76

77 Medetomidine is a selective and potent α_2 adrenoceptor agonist used for sedation and
78 analgesia in veterinary anaesthesia (Virtanen et al., 1988; Pertovaara, 1993). When administered as
79 a constant rate intravenous infusion (CRI) as a component of partial intravenous anaesthesia
80 (PIVA), it reduces the minimum alveolar concentration (MAC) of isoflurane in horses (Neges et al.,
81 2003) and improves the quality of recovery (Ringer et al., 2007). Medetomidine, like other α_2
82 agonists, causes cardiopulmonary effects, including reduction in cardiac output (Q_t), biphasic
83 changes in arterial blood pressure (ABP), bradycardia and arrhythmias (England and Clarke, 1996).
84 With the exception of changes in ABP, these effects of bolus administration are not substantially
85 different from pre-sedation values when steady state CRI values are reached (Bettschart-
86 Wolfensberger et al., 1999). Other effects of medetomidine include a decrease in respiratory rate
87 (f_R) and changes in PaCO_2 and PaO_2 , although these are not always statistically or clinically
88 significant (Wagner et al., 1991; Bettschart-Wolfensberger et al., 1999).

89

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

95

96 **Materials and methods**

97 *Animals*

98 Eighteen Thoroughbred racehorses, retired due to laryngeal problems but otherwise healthy,
99 were randomly assigned to receive either a low (0.65; ML) or a high (0.90; MH) FiO₂ during an
100 experimental surgical procedure. All horses were included in the final results and all horses
101 recovered uneventfully from anaesthesia. This prospective, randomised clinical study was approved
102 by the Ethics and Welfare committee of the Royal Veterinary College (approval number RVC
103 PURN: 2012 1179; date of approval 18 October 2012). The research horses were recruited from
104 another study being performed under Home Office Licence regulations.

105

106 *Anaesthesia*

107 Horses were fasted for 10-12 h before anaesthesia for elective laryngeal surgery; access to
108 water was not restricted. Flunixin meglumine (1.1 mg/kg IV; Flunixin Injection, Norbrook
109 Laboratories) was infused through a 14 G x 13 cm jugular catheter (Milacath Extended Use, Mila).
110 Gentamicin (6.6 mg/kg IV; Genta-kel, Kela; or GentaEquine, Dechra) was administered 30 min
111 before anaesthesia. Procaine penicillin (20000 IU/kg IM; Norocillin, Norbrook Laboratories) was
112 administered 60-90 min prior to anaesthesia. Acepromazine (0.04 mg/kg IM; Calmivet, Vetoquinol)
113 was administered 60 min before anaesthesia.

114

115 Medetomidine (0.007 mg/kg IV; Sedastart, Animalcare) and morphine (0.2 mg/kg IV;
116 Morphine Sulphate, Martindale Pharmaceuticals) were administered for sedation and analgesia.
117 Anaesthesia was induced with ketamine (2.2 mg/kg; Ketaset, Zoetis) and midazolam (0.04 mg/kg;
118 Hypnovel, Roche Products) given simultaneously IV. After induction of anaesthesia and
119 endotracheal (ET) intubation, each horse was positioned in right lateral recumbency on the
120 operating table and the ET tube connected to a large animal anaesthetic machine (Mallard Medical
121 2800C, AB Medical Technologies). Isoflurane (Isoflo, Abbott Laboratories) was delivered at an
122 initial concentration of 3% V/V in a fresh gas flow of 5 L/min, with either 3.5 L/min oxygen plus
123 1.5 L/min medical air (ML) to provide a FiO₂ of 0.65, as commonly used in practice, or 100%

124 oxygen (MH). All horses were mechanically ventilated with a tidal volume (V_T) of 12 mL/kg and at
125 an f_R to maintain an end-tidal CO_2 tension ($P_{ET}CO_2$) between 35 and 55 mmHg. All horses received
126 compound sodium lactate (CSL) solution (Vetivex 11, Dechra Veterinary Products) at a rate of
127 approximately 7 mL/kg/h during anaesthesia. A surgical plane of anaesthesia was maintained using
128 isoflurane and a CRI of medetomidine at a dose of 3.5 μ g/kg/h. Ketamine boluses (0.1-0.2 mg/kg
129 IV) were used if the horse was deemed to be lightly anaesthetised. Dobutamine (Dobutamine,
130 Hameln Pharmaceuticals) was infused at a dose of up to 5 μ g/kg/min, if required, to maintain mean
131 arterial blood pressure (MAP) > 70 mmHg.

132

133 *Monitoring and data collection*

134 ABP was measured using a multiparameter monitor (Datex-Ohmeda S/5, GE Healthcare)
135 using a catheter placed in the left dorsal metatarsal artery. This catheter was also used to collect
136 samples for arterial blood gas analysis (ABG), which was started as soon as practicable after
137 induction of anaesthesia and thereafter at 30 min intervals. Each sample was analysed immediately
138 using an IRMA TruPoint (QCR) blood gas analyser. Parameters recorded were isoflurane vaporiser
139 setting (%), inspired ($F_{I}Iso$) and end-tidal ($F_{ET}Iso$) isoflurane concentrations, heart rate (HR), f_R ,
140 $F_{i}O_2$, expired percentage of oxygen ($F_{ET}O_2$), saturation of haemoglobin with oxygen (SpO_2),
141 $P_{ET}CO_2$, V_T , peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP). A rescue
142 protocol for $PaO_2 < 80$ mmHg, an accepted level for hypoxaemia in equines (Haskins, 2007), was
143 prepared but not used. All data were recorded manually every 5 min and study parameters collated
144 between first and last ABG, so that the mean \pm standard deviation for each parameter measured was
145 within ABG measurements.

146

147 *Data collation and analysis*

148 Data were entered into a spreadsheet (Excel 2011 for Mac, Microsoft) before importation
149 into a statistical programme (SPSS Statistics 21 for Mac, IBM) for analysis. After testing each sub-

150 group for normality (Kolmogorov-Smirnov test), independent sample *t* tests were used to compare
151 means of continuous data between low and high FiO₂ sub-groups. The means tested were age,
152 weight, duration of procedure, average dobutamine infusion rate, HR, V_T, V_T/weight, f_R, V_M, PIP,
153 PEEP, SpO₂, MAP, F_{ET}Iso, FiO₂, PaO₂, barometric pressure (PB), PAO₂, oxygen partial pressure
154 (P(A-a)O₂), arterial oxygen pressure ratio (PaO₂:FiO₂), respiratory index (P(A-a)O₂/PaO₂), ratio of
155 dead space to V_T (V_D:V_T) and the calculated ratio of the oxygen partial pressure differences
156 between alveolar-arterial and arterio-venous values (F-shunt) (Table 1).

157

158 Independent samples Mann-Whitney *U* tests were used for analysis of American Society of
159 Anesthesiologists (ASA) health status¹, body condition score (BCS) and quality of recovery; the χ^2
160 test was used for analysis of sex. Statistically significant results ($P < 0.05$) were taken forward into
161 multivariate analysis, using a general linear model (GLM), along with risk factors from any test in
162 which $P \leq 0.1$, or which had been shown previously to affect PaO₂ in other studies, including age,
163 BCS and weight, and refined until only independent predictors with a $P < 0.05$ remained in the final
164 model. A linear mixed effects (LME) model was then performed on the data to examine the effect
165 of group and time on PaO₂.

166

167 **Results**

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

174

¹ See: <http://www.asahq.org/For-Members/Clinical-Information/ASA-Physical-Classification-System.aspx>.

175 There were no significant differences in SpO₂, Pa, F_{ET}, P(A-a), HR, *f*_R, V_T, V_M, MAP, PIP,
176 PEEP, V_D:V_T, CaO₂ or CcO₂ during anaesthesia. There were no significant differences in P(A-a)O₂
177 (*P* = 0.106), PaO₂:FiO₂ (*P* = 0.112) or F-shunt (*P* = 0.396) between the ML group and the MH
178 group. Horses in the ML group had significantly lower PaO₂ (337.7 ± 56.4 mmHg) and PAO₂
179 (396.1 ± 19.1 mmHg) than those in the MH group (496.8 ± 52.5 and 581.9 ± 21.3) (*P* < 0.001 for
180 both parameters). When taken into the GLM, only the FiO₂ sub-group was a significant independent
181 predictor of PaO₂ (*P* < 0.001). In the LME model, time was not a significant factor (*P* = 0.285),
182 while group (ML versus MH) again was significant for PaO₂ and PAO₂ (*P* < 0.001).

183

184 Discussion

185 The main finding of this study is that reducing FiO₂ to 0.65 in isoflurane and medetomidine
186 anaesthetised horses does not result in a statistically significant improvement in pulmonary indices,
187 compared to a FiO₂ of 0.90. Therefore, the hypothesis that pulmonary function, as measured by
188 pulmonary indices, would be improved by the use of a low FiO₂ of 0.65 is not supported.

189

190 Using low FiO₂ in an attempt to improve pulmonary function in horses is related to attempts
191 to improve overall anaesthetic risk in this species. Significant proportions of peri-anaesthetic deaths
192 in horses are caused by cardiac arrest or cardiovascular collapse (33%), myopathy (7%) and limb
193 fractures (25%) (Johnston et al., 2002). Hypoxaemia may play a part in some or all of these deaths
194 by contributing to inadequate myocardial oxygenation or poor peripheral oxygen delivery
195 (Schatzmann, 1995).

196

197 High FiO₂ administered to human beings in the peri-anaesthetic period has detrimental
198 effects, such as atelectasis and reformation after alveolar recruitment manoeuvres (Hedenstierna,
199 1990; Rothen et al., 1995a, b; Akca et al., 1999; Benoit et al., 2002; Hedenstierna and Edmark,
200 2010), increased intrapulmonary shunts in horses (Steffey et al., 1987; Marntell et al., 2005) and

201 increased systemic vascular resistance and reductions in cardiac index and heart rate in human
202 beings (Anderson et al., 2005). In addition, hyperoxia may lead to tissue damage through oxygen
203 toxicity in many species (Davis et al., 1983; Clutton et al., 2011). However, high FiO_2 ensures a
204 higher PaO_2 during anaesthesia, which may be beneficial for wound healing (Greif et al., 2000).
205 Oxygenation in the recovery period also improves the PaO_2 in horses (De Moor et al., 1974).

206

207 Use of a lower FiO_2 improves lung aeration and lowers atelectasis formation in dogs, cats
208 and human beings, as well as decreasing pulmonary shunting and improving gas exchange
209 (Hedenstierna, 1990; Rothen et al., 1995b; Staffieri et al., 2007, 2010). Improved P(A-a)O_2 in
210 horses was demonstrated using a FiO_2 of 0.3 compared to 0.8 (Cuvelliez et al., 1990) and decreased
211 pulmonary shunting observed with FiO_2 of 0.21 versus > 0.8 (Marntell et al., 2005). Use of a
212 helium-oxygen (Heliox) mixture allowed adequate oxygenation in horses with an FiO_2 of 0.4
213 (Driessen et al., 2003), whilst a low FiO_2 of 0.25 and then stepwise increases in FiO_2 to > 0.9 , again
214 using Heliox, better preserved pulmonary gas exchange than in horses breathing $\text{FiO}_2 > 0.9$
215 (Staffieri et al., 2009). In the current study, there were no significant improvements noted for any of
216 the respiratory indices and, whilst no pulmonary index improved with low FiO_2 , the horses in both
217 groups had more than adequate SpO_2 and PaO_2 throughout, with no horse becoming hypoxaemic.

218

219 Hubbell et al. (2011) and Crumley et al. (2013) demonstrated an improved P(A-a)O_2 with a
220 FiO_2 of 0.5; furthermore, Staffieri et al. (2009) showed that a step-wise increase in $\text{FiO}_2 > 0.5$
221 significantly worsened P(A-a)O_2 , indicating oxygen absorption in areas of low $\text{V}_A:\text{Q}$, without
222 replenishment, and a progressive collapse of alveoli. The critical inspired ventilation:perfusion ratio
223 ($\text{V}_{\text{AI}}:\text{Q}$) describes lung areas where $\text{V}_A:\text{Q}$ is so low that net absorption of alveolar gas occurs,
224 despite airways remaining open, leading to significant alveolar collapse (Dantzker et al., 1975) and
225 increased shunt formation.

226

227 In the present study, there were no significant differences in F-shunt values between the ML
228 and MH groups, similar to the findings of Hubbell et al. (2011). In contrast, Marntell et al. (2005)
229 found that a FiO_2 of 0.21 significantly reduced F-shunt values. These results suggest that a FiO_2 of
230 0.90 does not lead to greater shunt formation than a FiO_2 of 0.65 or 0.5. The lack of a reduction in
231 shunt formation with a lower FiO_2 , in comparison with maximal, also suggests that absorption
232 atelectasis as described is minimal and unlikely to be a major component of the relatively poorer
233 PaO_2 in the ML group (Nyman and Hedenstierna, 1989; Hubbell et al., 2011).

234

235 No horses in this study or the Heliox studies, all of which were positioned in lateral
236 recumbency, were hypoxaemic ($PaO_2 < 60$ mmHg). However, hypoxaemia has been observed in
237 some horses in other studies using air or an oxygen-air mixture; in the studies performed by Hubbell
238 et al. (2011) and Crumley et al. (2013), horses were positioned in dorsal recumbency, whilst in the
239 study by Marntell et al. (2005), horses were positioned in lateral recumbency. Horses in dorsal
240 recumbency and spontaneously breathing horses in lateral recumbency breathing a FiO_2 of 0.21
241 were at risk of hypoxaemia. Posture, especially dorsal recumbency, affects pulmonary function by
242 reducing effective lung area and FRC (Sorenson and Robinson, 1980; Day et al., 1995; Whitehair
243 and Willits, 1999), leading to PaO_2 values significantly below those in standing, sternal or laterally
244 recumbent horses, and contributing to large $P(A-a)O_2$ differences (Nyman and Hedenstierna, 1989;
245 Day et al., 1995). Mechanical ventilation instituted immediately after induction of anaesthesia
246 results in higher PaO_2 than when mechanical ventilation is delayed (Day et al., 1995; Wolff and
247 Moens, 2010). In the present study, mechanical ventilation was instituted immediately in all horses
248 to achieve similar values for $P_{ET}CO_2$.

249

250 Medetomidine CRI was used in this study in addition to morphine for analgesia, since the
251 analgesia provided by other protocols (PIVA with romifidine CRI or ketamine CRI plus morphine)
252 was inadequate to prevent movement in other research horses undergoing the same procedure,

253 despite liberal use of ketamine and morphine boluses. In this study, only two horses per group
254 required additional ketamine doses, and none of the horses moved, indicating that the PIVA
255 combination of isoflurane and medetomidine, with morphine, was sufficient to provide adequate
256 anaesthesia with $F_{ET}Iso$ of 1.1-1.2%.

257

258 Morphine and medetomidine have cardiopulmonary effects, but these are likely to be similar
259 in both groups and thus would not be expected to alter the results overall. Morphine has different
260 reported effects on the cardiopulmonary system of horses anaesthetised with isoflurane, including
261 none (Nolan et al., 1991), reduced PaO_2 (Love et al., 2006) and increased $PaCO_2$ with serious
262 respiratory depression (Steffey et al., 2003), depending on dose of morphine given. Medetomidine
263 CRI reduces the MAC of isoflurane (Bettschart-Wolfensberger et al., 2001; Neges et al., 2003) and
264 is a potent analgesic. In addition to cardiovascular effects, α_2 adrenergic agonists cause respiratory
265 depression, leading to lower f_R , reduced or minimally changed PaO_2 (Wagner et al., 1991;
266 Bettschart-Wolfensberger et al., 1999; Neges et al., 2003) and increased $PaCO_2$ (Bryant et al.,
267 1996).

268

269 There were no statistically significant differences between ML and MH groups in time to
270 recover to standing or in unassisted recovery quality. Although there were significant differences in
271 PaO_2 , this did not significantly influence the recovery to standing of horses in our study. In previous
272 studies, oxygen delivery (DO_2) was either not significantly different between groups (Hubbell et al.,
273 2011) or was significantly lower at one time point in the FiO_2 0.21 group (Marntell et al., 2005).

274

275 The IRMA TruPoint ABG analyser has not been validated for measuring equine
276 haemoglobin (Hb) concentrations, so this may have introduced some errors into our F-shunt
277 calculations, but these errors would occur in both ML and MH groups and thus would have minimal
278 effects on results. A further limitation of this study is that we used the human value of 3.5 mL/dL

279 for the arterial-mixed venous oxygen content difference ($C(a-\bar{v})O_2$). In contrast, values of 4-7
280 mL/dL have been measured by Marntell et al. (2005), who reported mean shunt values of $5-13 \pm$
281 5% in spontaneously breathing anaesthetised horses in left lateral recumbency. The F-shunt values
282 of $16-18 \pm 7\%$ calculated in the present study are broadly equivalent, given that they are likely to
283 have been overestimated.

284

285 An additional and important limitation of this study is that the combination of immediate
286 mechanical ventilation and lateral recumbency in lean ('flat-bellied') horses is likely to have
287 reduced the risk of small airway closure and significant absorption atelectasis. Dorsal recumbency
288 induces the greatest impairment to ventilation in the horse (McDonell and Hall, 1974; Sorensen and
289 Robinson, 1980); furthermore, in all positions, anaesthetised 'round-bellied' horses also had a lower
290 PaO_2 and larger $P(A-a)O_2$ than anaesthetised 'flat-bellied' horses (Moens et al., 1995). In dorsal
291 recumbency, 'round' and 'flat-bellied' horses have similar distribution of air flow to each lung. In
292 lateral recumbency, 'round-bellied' horses develop an uneven distribution of air flow, whilst 'flat-
293 bellied' horses retain equal airflow distribution (Moens et al., 1995). Moreover, tall, lightweight,
294 lean horses with a large thoracic circumference have a better PaO_2 when anaesthetised compared to
295 'round-bellied' horses (Mansel and Clutton, 2008). These studies support the general hypothesis
296 that body shape and the pressure exerted by abdominal contents is a major contributor to poor
297 respiratory function in horses during anaesthesia. The results of this study, in lean flat-bellied
298 Thoroughbred horses, therefore cannot be related to all horses in all recumbencies or indeed those
299 horses spontaneously ventilating.

300

301 Detrimental changes in the respiratory system in horses during anaesthesia usually occur
302 early in the anaesthetic process and worsen with time (Nyman et al., 1988). This was not seen in
303 this study in respect of PaO_2 , which remained relatively high in both groups, with little upward or
304 downward variation over the duration of each anaesthetic procedure. It may be that the combination

305 of anaesthetic protocol, young healthy Thoroughbred horses, immediate mechanical ventilation and
306 positioning in lateral recumbency prevented any time effect from becoming evident. Furthermore,
307 the low number of horses in the study may have reduced the power of the study.

308

309 **Conclusions**

310 Horses anaesthetised with a FiO_2 of 0.65 had a lower arterial oxygenation, but no significant
311 improvement in pulmonary indices, compared to horses in which a higher FiO_2 was used.
312 Hypoxaemia did not occur and low FiO_2 did not affect recovery quality and time to recovery;
313 therefore, this combination may be acceptable for mechanically ventilated horses, anaesthetised
314 with isoflurane and medetomidine CRI, positioned in lateral recumbency. The optimum overall
315 anaesthetic strategy to maintain high PaO_2 and excellent pulmonary function in horses is still to be
316 elucidated.

317

318 **Conflict of interest statement**

319 Neither of the authors has any financial or personal relationships that could inappropriately
320 influence or bias the content of the paper.

321

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326

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537 **Table 1**
 538 Respiratory calculations.
 539

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)	$Cc'O_2 = ([Hb]^c \times \text{Hüfner's Constant}^d \times Sc'O_2^e) + (0.0031 \times Pc'O_2^f)$
Arterial oxygen content: CaO_2 (mL/dL)	$CaO_2 = ([Hb] \times \text{Hüfner's Constant} \times SaO_2^g) + (0.0031 \times PaO_2)$
Alveolar-to-arterial oxygen difference: $P(A-a)O_2$ (mmHg)	$P(A-a)O_2 = PAO_2 - PaO_2$
Arterial-to-inspired oxygen ratio (mmHg)	$PaO_2:FiO_2$
F-shunt (%)	$([Cc'O_2 - CaO_2] / [Cc'O_2 - PaO_2] + 3.5^h \text{ mL/dL}) \times 100$

- 540
- 541 ^a Barometric pressure (mmHg).
- 542 ^b Vapour pressure of water = 47 mmHg.
- 543 ^c Haemoglobin concentration.
- 544 ^d Oxygen carrying capacity of haemoglobin (1.36 mL/g).
- 545 ^e Pulmonary end capillary oxygen saturation (for $PAO_2 > 100$ mm Hg assumed = 1).
- 546 ^f Pulmonary end-capillary partial pressure of oxygen (mmHg), assumed to be PAO_2 .
- 547 ^g Arterial haemoglobin oxygen saturation (%).
- 548 ^h Arterial-venous oxygen content difference $[C(a-v)O_2]$ in mechanically ventilated humans.

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549 **Table 2**

550 Demographic and other data of 18 horses anaesthetised with isoflurane and medetomidine and mechanically ventilated
 551 using either a low (0.65) or high (0.90) FiO₂.
 552

	Low FiO ₂ (n = 9)	High FiO ₂ (n = 9)
Age (years) ^a	6.1 ± 1.2	5.8 ± 1.6
Sex (number of males:number of females)	8:1	7:2
Weight (kg) ^a	558.8 ± 34.5	550.4 ± 58.2
Body condition score (0-9)	4	3.9 (range 3-4)
ASA ^b category	1 (range 1-2)	1
Haemoglobin (g/dL) ^a	11.4 ± 1.24	10.9 ± 1.1
Duration of anaesthesia (min) ^a	200 ± 36.1	178.9 ± 30.4
Number of horses receiving additional ketamine (dose range in mg)	2 (200-400)	2 (200-600)
Number of horses receiving additional morphine (dose range in mg)	7 (60-90)	6 (60-90)
Number of horses receiving dobutamine	9	9
Dose of dobutamine (µg/kg/min) ^a	0.61 ± 0.4	0.54 ± 0.3
Time to recovery (min) ^a	50.1 ± 22.7	45.1 ± 12.5
Recovery quality (median)	2 (range 1-3)	2 (range 1-3)

553

554 ^a Mean ± standard deviation.555 ^b American Society of Anesthesiologists health status.

556 **Table 3**

557 Measured and calculated cardiovascular and respiratory variables (mean \pm standard deviation) of 18 horses
 558 anaesthetised with isoflurane and medetomidine CRI and mechanically ventilated using either a low (0.65) or high
 559 (0.90) FiO₂.

560

	Low FiO ₂	High FiO ₂
FiO ₂ ^{a, b}	66.5 \pm 2.9	92.4 \pm 2.2
PaO ₂ (mmHg) ^a	337.7 \pm 56.4	496.8 \pm 52.5
PAO ₂ (mmHg) ^a	396.1 \pm 19.1	581.9 \pm 21.3
P(A-a)O ₂ (mmHg)	58.42 \pm 41.7	85.07 \pm 49.6
PaO ₂ :FiO ₂	505.6 \pm 66.3	537.6 \pm 53.2
F-shunt (%)	18.2 \pm 7.2	16.5 \pm 5.8
CaO ₂ (mL O ₂ /dL)	15.3 \pm 1.5	15.4 \pm 1.4
CcO ₂ (mL O ₂ /dL)	16.1 \pm 1.6	16.1 \pm 1.5
SpO ₂ (%)	95.8 \pm 1.9	96.9 \pm 1.6
PaCO ₂ (mmHg)	57.0 \pm 5.6	57.7 \pm 6.3
F _{ET} CO ₂ (mmHg)	44.5 \pm 3.6	45.2 \pm 3.7
P(A-a)CO ₂ (mmHg)	12.5 \pm 3.6	12.5 \pm 5.0
HR (beats/min)	30.0 \pm 3.3	27.6 \pm 2.9
fR (breaths/min)	7.8 \pm 0.9	7.1 \pm 0.6
V _T (L/breath)	6.9 \pm 1.0	6.4 \pm 0.8
V _T /weight (mL/kg)	12.3 \pm 1.2	11.6 \pm 1.4
V _M (L/min)	53.5 \pm 7.9	45.5 \pm 7.8
MAP (mmHg)	75.0 \pm 8.9	75.7 \pm 9.6
PIP (cmH ₂ O)	21.5 \pm 2.3	20.6 \pm 3.3
PEEP (cmH ₂ O)	3.7 \pm 0.8	3.6 \pm 0.6

561

562 ^a Significantly different between ML and MH groups ($P < 0.05$)563 ^b Independent predictor of PaO₂ from general linear model ($P < 0.05$).