The effect of two different intra-operative end-tidal carbon dioxide tensions on apnoeic duration in the recovery period in horses.

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Running head: *$PÉCO_2$ and spontaneous ventilation*

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Abstract

Objective To compare the effect of two different intra-operative end-tidal carbon dioxide tensions on apnoeic duration in the recovery period in horses.

Study Design Prospective randomised clinical study.

Animals Eighteen healthy client-owned adult horses (ASA I-II) admitted for elective surgery. Horses were of median body mass 595 (238-706) kg and mean age 9 ± 5 years.

Methods A standardised anaesthetic protocol was used. Horses were positioned in dorsal recumbency and randomly allocated to one of two groups. Controlled mechanical ventilation (CMV) was adjusted to maintain end tidal carbon dioxide tension ($PE´CO_2$) at 40 ± 5 mmHg (5.3 ± 0.7 kPa) (group40) or 60 ± 5 mmHg (8.0 ± 0.7 kPa) (group60). Arterial blood gas analysis was performed at the start of the anaesthetic period (T0), at one point during the anaesthetic (T1), immediately prior to disconnection from the breathing system (T2) and at the first spontaneous breath in the recovery box (T3).The time from disconnection from the breathing system to return of spontaneous ventilation (RSV) was recorded. Data were analysed using a two sample t-test or Mann-Whitney U test and significance assigned when $p < 0.05$.

Results Horses in group60 resumed spontaneous breathing significantly earlier than those in group40, (52 (14-151) and 210 (103-542) seconds respectively) ($p < 0.001$). Arterial oxygen tension (PaO_2), pH, base excess (BE) and plasma bicarbonate (HCO_3^-) were not different between the groups at RSV, however PaO_2 was significantly lower in group60 during (T0, T1) and at the end of anaesthesia (T2).

Conclusions and clinical relevance Aiming to maintain intra-operative $PE´CO_2$ at 60 ± 5 mmHg (8.0 ± 0.7 kPa) in mechanically ventilated horses resulted in more rapid RSV compared to when $PE´CO_2$ was maintained at 40 ± 5mmHg (5.3 ± 0.7 kPa).

Keywords: horse, mechanical ventilation, recovery from anaesthesia, hypercapnia.

Introduction

In anaesthetised horses, the dose-dependent respiratory depression produced by isoflurane (Steffey et al. 1987) and effect of recumbency may necessitate controlled mechanical ventilation (CMV) to improve pulmonary function (Day et al. 1995). Cessation of CMV may result in an apnoeic period of variable duration before spontaneous ventilation resumes (Wright & Hildebrand 2001). The impact of this apnoeic period and strategies to facilitate the transition from mechanical to spontaneous ventilation have been investigated (Wright & Hildebrand 2001; Brosnan et al. 2012; Ida et al. 2013). Horses may be 'weaned-off' mechanical ventilation to ensure return to spontaneous ventilation (RSV) prior to transfer to recovery by reducing minute ventilation towards the end of surgery.

In comparison to abrupt discontinuation of CMV however, this weaning process may result in a greater incidence of horses moving on the hoist during transfer to the recovery box (Wright & Hildebrand 2001). Weaning has been associated with hypoxaemia even with the use of oxygen-rich inspired gas (Wright & Hildebrand 2001; Santos et al. 2003). Apnoeic horses may remain normoxaemic due to apnoeic mass movement oxygenation (AMMO) (Wright & Hildebrand 2001) but the effect of prolonged apnoea on this mechanism is not known.

Isoflurane elimination during recovery may also be affected by hypoventilation since the partial pressure of volatile anaesthetic agent in the alveolar gas decreases as a function of alveolar ventilation (Eger 1974). It has been demonstrated that insufflation of 5-10% carbon dioxide (CO_2) in oxygen (O_2) in the immediate recovery period increases alveolar ventilation by inducing hypercapnic hyperpnoea, resulting in faster times to standing without affecting recovery quality (Brosnan et al. 2012). Normocapnia

has been defined as arterial carbon dioxide tension ($PaCO_2$) 40mmHg (5.33 kPa) (Wagner 1993) and mechanical ventilation should aim to maintain $PaCO_2$ between 35 and 50 mmHg (4.67- 6.67 kPa) (Hartsfield 2007). However, considering the detrimental effects of CMV on cardiac output (Hodgson et al. 1986; Steffey et al. 1992; Mizuno et al. 1994), there may be cardiovascular benefits of mild hypoventilation, with some studies advocating maintaining $PaCO_2$ between 50-70 mmHg (6.67-9.33 kPa) (Kerr & McDonell 2009) or below 70-75 mmHg (9.33-10 kPa) (Taylor &Young 1993; Blissitt et al. 2008). Permitting mild to moderate hypercapnia may also facilitate the transition from CMV to spontaneous breathing. This study was designed to investigate the effect of two different intra-operative end-tidal carbon dioxide tension ($PE´CO_2$) values on the duration of apnoea in the immediate recovery period. We hypothesised that maintaining intra-operative $PE´CO_2$ values at 60 ± 5mmHg (8.0 ± 0.7 kPa) (group60) would result in a faster RSV compared to maintaining $PE´CO_2$ values at 40 ± 5 mmHg (5.3 ± 0.7 kPa).

Materials and Methods

Study Design

Prospective, randomised, controlled clinical study approved by the University of Liverpool Ethics Committee (VREC94). Systemically healthy (ASAI-II) adult horses (>3 years of age) presenting to The Philip Leverhulme Equine Hospital for elective orthopaedic or soft tissue surgery were eligible for inclusion if they were to be positioned in dorsal recumbency, showed no evidence of respiratory disease based on physical examination and informed owner consent was granted.

Anaesthetic Protocol

Food but not water was withheld for at least eight hours prior to induction of general anaesthesia. Pre-anaesthetic medication consisted of acepromazine maleate 0.03 mg kg^{-1}

intramuscularly (IM) (Vetranquil; Ceva, France) 45 minutes prior to aseptic placement of a 12 Gauge intravenous cannula (Intraflo 2; Vygon, France). Romifidine 50-80 µg kg^{-1} intravenously (IV) (Sedivet; Boehringer Ingelheim, UK) and morphine 0.2mg kg^{-1} IV (Morphine Sulphate; Wockhardt, UK) were administered within 15 minutes of intravenous cannula placement. Induction of general anaesthesia using ketamine 2.2 mg kg^{-1} IV (Ketaset; Pfizer, UK) and diazepam 0.05 mg kg^{-1} IV (Diazepam; Hameln Pharmaceuticals, UK) was followed by orotracheal intubation. General anaesthesia was maintained using isoflurane (Isoflo; Abbott, UK) in 100% oxygen delivered via a large animal circle breathing system (LAVC 2000; Eickemeyer, Germany). The circle system was not prefilled with oxygen and isoflurane. Fresh gas flow was 10 L min^{-1} for the first 5 minutes, reduced to 10 mL kg^{-1} for the anaesthesia duration. Mechanical ventilation was delivered via pressure-limited flow-controlled ventilator (Mark 7 Bird Servo; Medical Dist Co Inc., USA) and adjusted to maintain $PE´CO_2$ at either 40 ± 5 mmHg (5.3 ± 0.7 kPa) (group40) or 60 ± 5 mmHg (8.0 ± 0.7 kPa) (group60). Both tidal volume and respiratory rate adjustments were carried out in a step wise manner to adjust minute ventilation and achieve the target $PE´CO_2$. A 20 Gauge (Intraflon; Vygon, France) cannula was placed in the mandibular artery to permit invasive arterial blood pressure measurement and acquisition of samples for blood gas analysis. Arterial blood gas analysis was performed using two blood gas analysers (Radiometer ABL77; Radiometer Medical, Denmark, RapidPoint 500; Siemens, UK) for which statistical agreement was confirmed prior to utilisation of data. Other instrumentation included electrocardiography, pulse oximetry, respiratory gases and volatile anaesthetic agent monitoring (Datex-Ohmeda S/5; GE Healthcare, UK). Intravenous fluids (Vetivex 11; Dechra, UK) were administered (3-4 mL kg^{-1} hr^{-1}) throughout the duration of general

anaesthesia. Dobutamine (Dobutamine; Wockhardt, UK) was administered intravenously as required to ensure mean arterial pressure remained above 70 mmHg.

Sample collection

Arterial blood gas analysis was performed on four occasions for each horse. The first sample (T0) was withdrawn immediately after an arterial cannula was secured. A second sample (T1) was taken approximately 20-30 minutes later to ensure that ventilator settings were appropriate and to assess the difference between $PaCO_2$ and $PE´CO_2$. A third sample (T2) was withdrawn at the end of anaesthesia immediately prior to disconnection from the breathing system and the final sample was drawn at the moment spontaneous breathing resumed in the recovery box whilst the orotracheal tube was still in place (T3). Samples were drawn over three consecutive breaths for T0, T1 and T2. Sampling at T3 was drawn at the moment of RSV via an arterial cannula which was then either immediately removed or secured for recovery and removed when the horse was standing. All samples were analysed immediately after collection but temperature correction was not performed. The time from breathing system disconnection to RSV was recorded. After sampling was completed at RSV, oxygen was supplemented via a demand valve and nasal insufflation.

Pilot study and sample size calculations

Sample size calculations were based on a pilot study involving ten horses randomly allocated to two groups. Pilot data demonstrated RSV in group60 of 68 ± 50 seconds compared to 327 ± 176 seconds in group40. A 50% reduction in apnoeic time was considered clinically important and in order to demonstrate statistical differences in time to RSV between the two groups (alpha error 0.05, beta error 0.15), it was estimated that nine horses would be required in each group (Eng, 2003).

Animals The study population included 18 horses comprising a mixed population of males and females (11 geldings, 3 mares and 4 stallions) of median body mass 595 (238-706) kg and mean age 9 ± 5 years.

Statistical Analysis

All continuous study data were assessed for normal distribution using the Anderson-Darling test. Parametric data is displayed as mean ± standard deviation and analysed using a two-sample Student's t-test. Non-parametric data is displayed as median (range) and analysed using the Mann-Whitney U test. Computer software (Minitab 17 Statistical Software; Minitab Ltd, UK) was used to analyse the data and statistical significance was assigned when $p < 0.05$. No statistical differences in parameters and baseline data were found between pilot and study data for each group so the data was pooled.

Results

Eighteen horses completed the study and no adverse events were recorded. There was no difference between the groups in body mass**,** age, anaesthetic duration, time to standing, end-tidal isoflurane concentration or rate of dobutamine infused over the anaesthetic period (Table 1). Loco-regional analgesia techniques were carried out where applicable to the surgical procedure undertaken and non-steroidal anti-inflammatory drugs were administered to all horses (Table 2).

Time to RSV was significantly shorter in group60, with a median time of 52 (14-151) seconds compared to 210 (103-542) seconds in group40 ($p < 0.001$) (Figure 1).

At the end of anaesthesia (T2), pH was significantly lower in group 60 but at the time of RSV (T3) there was no difference in pH between groups (Table 3). At RSV, there was no difference between the groups in $PE´CO_2$ or $PaCO_2$ (Table 3). Using data pooled

from both groups, the overall mean $PaCO_2$ at RSV was 66 ± 11 mmHg (8.8 ± 1.4 kPa). The $PaCO_2$- $PE´CO_2$ difference at the end of anaesthesia (T2) was significantly lower in group40 but there was no difference between groups at RSV (T3) (Table 3). Arterial oxygen tension (PaO_2) was significantly lower in group60 during (T1) at the end of anaesthesia (T2) but at the time of RSV (T3) there was no difference between the groups (Table 3). At RSV, PaO_2 was less than 60 mmHg (8.0 kPa) in three horses in each group. Base Excess (BE) and plasma bicarbonate (HCO_3^-) concentrations were not different between the groups at any time point (Table 3).

During anaesthesia, two horses in group60 took occasional spontaneous breaths resulting in slightly lower than target $PE´CO_2$ values while one horse breathed spontaneously throughout general anaesthesia leading to exclusion from the study (Fig 2). One horse in group40 was severely hypotensive soon after the onset of general anaesthesia leading to the withdrawal of CMV and the exclusion of the horse from the study (Fig 2). Data for $PE´CO_2$ at RSV was lost for two horses in group60 and one horse in group40 due to equipment failure but the study remained adequately powered for the primary objective.

Discussion

Our results show that maintaining intra-operative $PE´CO_2$ at 60 ± 5 mmHg (8.0 ± 0.7 kPa) shortens the time to RSV compared to maintaining intra-operative $PE´CO_2$ at 40 ± 5 mmHg (5.3 ± 0.7 kPa). During volatile agent anaesthesia, the ventilatory response to $PaCO_2$ is reduced in a dose dependent manner compared to the conscious state (Lumb 2010a). This was reflected in the current study by the elevated overall $PaCO_2$ in both groups at RSV and is consistent with a previous study where $PaCO_2$ was 66 ± 9 mmHg (8.8 ± 1.2 kPa) at the time spontaneous breathing resumed after cessation of CMV in

isoflurane-anaesthetised horses (Wright & Hildebrand 2001). Since $PaCO_2$ was significantly higher in group60 at the end of anaesthesia, apnoeic threshold was reached faster resulting in an earlier onset of spontaneous breathing. During a period of apnoea after CMV in halothane-anaesthetised horses, the rate of rise in $PaCO_2$ in horses is reported to be 12 mmHg (1.6 kPa) in the first minute and 6 mmHg (0.8 kPa) in subsequent minutes (Hubbell & Muir 1985). In comparison to this finding, horses in our study in group40 demonstrated a slightly slower mean rate of rise in $PaCO_2$ which is in agreement with previous reports in isoflurane-anaesthetised horses (Wright & Hildebrand 2001).

Aiming to maintain $PE´CO_2$ at 60 ± 5 mmHg (8.0 ± 0.7 kPa) may influence delivered minute volume and in our study, delivered minute volume was significantly lower in group60 which may have contributed to lower PaO_2 values seen during general anaesthesia. Although these values did not approach hypoxaemia, this finding should be considered when managing clinical cases.

Hypoxaemia may also influence ventilatory response and potential sources of hypoxaemia in the recovery period include decreased alveolar ventilation, diffusion impairment, increased shunt fraction and ventilation-perfusion mismatching (Richards 1982; Lumb 2010b). In conscious standing horses, hypoxaemic ventilatory drive occurs when PaO_2 reaches 38 mmHg (5.1 kPa) (Pelletier & Leith 1995). In our study, at the end of anaesthesia, PaO_2 values in group60 were significantly lower than in group40 and whilst hypoxic drive cannot be ruled out as a contributory factor in RSV there was no difference in PaO_2 between groups at RSV. These findings are in agreement with a previous study which showed that there was no advantage in terms of PaO_2 in horses which were weaned from ventilation compared to those which demonstrated apnoea

after disconnection from CMV (Wright & Hildebrand 2001). In our study, nasal insufflation of oxygen (15L/min) and an oxygen demand valve were utilised after RSV which have been shown to improve arterial oxygenation (Waterman et al. 1982; Mason et al. 1987).

The negative impact of CMV on the equine cardiovascular system has been documented (Hodgson et al. 1986; Steffey et al. 1992; Mizuno et al. 1994). In circumstances where CMV is necessary, mild hypoventilation (reduced minute ventilation with associated increase in $PaCO_2$ (Hubbell & Muir 2014)), may have beneficial cardiovascular effects. In halothane-anaesthetised horses, a reduction in ventilation frequency during CMV resulted in increased $PaCO_2$ which stimulated spontaneous breathing. This was associated with an improvement in cardiac output (Nyman & Hedenstierna 1988). In our study, although cardiovascular function was not investigated, there was no difference in dobutamine infusion rates between groups intra-operatively.

Faster recovery times have followed a shorter apnoeic phase in recovery after weaning from ventilation compared to horses which were not weaned and demonstrated an apnoeic pause (Wright & Hildebrand 2001). However, in our study, time to standing was similar between groups and since recovery quality was not analysed, it is not known whether a shorter apnoeic phase influenced recovery quality. In the current study, no movement of horses occurred during hoisting to the recovery box which contrasts with an earlier study where horses weaned from ventilation moved during transport to the recovery box which is considered undesirable (Wright & Hildebrand 2001).

Limitations of the study relate to its clinical nature. Standardisation of the anaesthetic protocol was adhered to where possible but different surgical procedures necessitated

varying analgesic techniques. The use of loco-regional analgesic techniques may have afforded a reduction in isoflurane requirement facilitating a shorter time to RSV, however there was no difference in end-tidal isoflurane requirements between groups. Adjustments made to tidal volume and respiratory rate to achieve the $PE´CO_2$ target for each group were not standardised but were carried out in a stepwise manner and the resulting normal distribution of data in each group indicate that a fairly systematic approach was employed. During anaesthesia, two horses in group60 took occasional spontaneous breaths resulting in slightly lower than target $PE´CO_2$ values. This may have been due to the effect of $PaCO_2$ on ventilatory drive which may be dampened during general anaesthesia but remained present in group60 where higher $PE´CO_2$ values were aimed for. Furthermore, the study was not blinded which may allow a source of bias to be present.

The **results** of our study show that maintaining intra-operative $PE´CO_2$ at 60 ± 5mmHg (8.0 ± 0.7 kPa) results in a significantly shorter apnoeic phase in recovery compared to maintaining intra-operative $PE´CO_2$ at 40 ± 5mmHg (5.3 ± 0.7 kPa). Although the apnoeic phase was shorter in group60, PaO_2 values were lower in this group during and at the end of anaesthesia. However, at the time of RSV, PaO_2 values were not different between groups. In **conclusion**, the two different intra-operative $PE´CO_2$ values investigated in this study influenced the time to RSV, however, to gain further information pertaining to a wider range of $PE´CO_2$ values and potential clinical advantages of a shorter apnoeic phase, further investigation is required.

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345

346 **Table .** Data for 18 anaesthetised horses where mechanical ventilation was adjusted to
347 maintain end-tidal carbon dioxide ($P_E´CO_2$) at 40 ± 5 mmHg (5.3 ± 0.7 kPa) (Group40)
348 or 60 mmHg ± 5 mmHg (8 ± 0.7 kPa) (Group60).
349

Group	Anaesthetic duration (minutes)	Time to standing (minutes)	End-tidal isoflurane concentration (%)	Tidal volume delivered (mL kg^{-1})	Respiratory rate (breaths per minute)	Dobutamine infusion rate (μg kg^{-1} min^{-1})
Group40	109 ± 42	22 (16-60)	1.1 ± 0.1	10.5 ± 2.0*	6 ± 1*	0.8 ± 0 .3
Group60	87 ± 36	23 (14-75)	1.2 ± 0.1	8.4 ± 1.4*	5 ± 1*	1.0 ± 0.4
p-value	0.26	0.9	0.14	0.02	0.03	0.51

350 * Statistical difference between the groups ($p < 0.05$). Data is displayed as mean ±
351 standard deviation (SD) or median (range).
352

353 **Table 2.** Surgical procedures, loco-regional anaesthesia techniques and non-steroisal

354 anti-inflammatory drug (NSAID) administration in 18 horses. For group details see

355 Table 1.

		Group40	Group60
Surgical procedure	Orthopaedic procedures	4	5
	Soft tissue procedures	5	4
Local technique	Caudal epidural (Co1-Co2) morphine [a] (0.1mg kg^{-1}) and methadone[b] (0.1 mg kg^{-1})	2	1
	Intra-testicular mepivacaine[c] (100 mg total).	1	1
	Pudendal perineural levobupivacaine[d] (50mg).	0	1
	Perineural anaesthesia of the medial and lateral palmar and palmar metacarpal nerves using levobupivacaine[d] (50mg).	1	0
NSAID	Flunixin[e] 1.1mg kg^{-1} IV	5	3
	Phenylbutazone[f] 4.4mg kg^{-1} IV	4	6

356 [a]Morphine Sulphate (Martindale Pharmaceuticals, UK), [b]Physeptone (Martindale

357 Pharmaceuticals, UK), [c]Intra-epicaine (Dechra, UK), [d] Chirocaine (Abbott, UK), [e]

358 Meflosyl (Pfizer, UK), [f] Equipalazone (Dechra, UK).

359

360 **Table 3.** Time to resume spontaneous ventilation (RSV) and arterial blood gas data for
361 18 anaesthetised horses where mechanical ventilation was adjusted to maintain the end-
362 tidal carbon dioxide ($P_E´CO_2$) at 40 ± 5 mmHg (5.3 ± 0.7 kPa) (Group40) or 60 ± 5
363 mmHg (8 ± 0.7 kPa) (Group60).
364

Parameter	**Group**	**T0**	**T1**	**T2**	**T3 (RSV)**
Time to RSV	40				210 (103-542)*
(seconds)	60				52 (14-151)
					p<0.001
pH	40	7.42 ± 0.03*	7.41 ± 0.03*	7.42 ± 0.02*	7.33 ± 0.06
	60	7.33 ± 0.02	7.32 ± 0.03	7.31 ± 0.03	7.35 ± 0.04
		p < 0.001	p < 0.001	p < 0.001	p = 0.44
$P_E´CO_2$	40	40 (39-48)*	40 (40-42)*	40 (38-42)*	51 (42-62)
(mmHg)	60	52 (38-62)	53 (44-63)	54 (44-60)	44 (40-56)
$P_E´CO_2$	40	5.3 (5.1-6.4)	6.9 (5.1-8.3)	5.3 (5.1-5.6)	6.8 (5.6-8.3)
(kPa)	60	6.9 (5.1-8.3)	7.1 (5.9-8.4)	7.2 (5.9-8)	5.9 (5.3-7.5)
		p = 0.006)	p < 0.001	p < 0.001	p = 0.2
$PaCO_2$ (mmHg)	40	49 ± 5*	49 ± 4*	53 ± 4*	68 ± 13
	60	61 ± 11	66 ± 7	67 ± 8	64 ± 9
$PaCO_2$ (kPa)	40	6.5 ± 0.6	6.5 ± 0.6	7.1 ± 0.5	9.1 ± 1.7
	60	8.2 ± 1.4	8.8 ± 0.9	8.9 ± 1	8.6 ± 1.2
		p = 0.009	p < 0.001	p = 0.001	p = 0.46
$PaCO_2$- $P_ÉCO_2$	40	8 (2-12)	10 (1-14)	11 (6-15)*	16 (7-35)

(mmHg)	60	12 (1-16)	13 (2-20)	18 (8-20)	17 (0-28)
$PaCO_2$- $P_{É}CO_2$	40	1.1 (0.3-1.6)	1.3 (0.1-1.9)	1.5 (0.8-2)	2.1 (0.9-4.7)
(kPa)	60	1.6 (0.1-2.1)	1.7 (0.3-2.7)	2.4 (1.1-2.7)	2.3 (0-3.7)
		$p = 0.35$	$p = 0.1$	$p < 0.001$	$p = 0.92$
PaO_2 (mmHg)	40	285 ± 164	408 ± 121*	377 ± 133*	65 (51-250)
	60	166 ± 79	242 ± 108	148 ± 60	73 (45-102)
PaO_2 (kPa)	40	38 ± 21.9	54.4 ± 16.1	50.3 ± 17.7	8.7 (6.8-33.3)
	60	22.1 ± 10.5	32.3 ± 14.4	19.7 ± 8	9.7 (6.0-13.6)
		$p = 0.08$	$p = 0.008$	$p = 0.001$	$p = 0.40$
HCO_3^- (mmol L^-	40	29.5 ± 0.9	29.4 ± 1.2	30.9 ± 1.6	31.4 ± 2.1
^{1})	60	28.7 ± 3.5	29.5 ± 1.8	31.0 ± 1.9	30.5 ± 1.4
		$p = 0.5$	$p = 0.9$	p = 0.92	$p = 0.27$
BE (mmol/L)	40	6.1 ± 1.1	6.2 ± 1.5	7.2 ± 1.4	8.5 ± 1.6
	60	5.5 ± 4.3	7.1 ± 2	8.7 ± 1.6	7.9 ± 1.4
		$p = 0.71$	$p = 0.3$	$p = 0.06$	$p = 0.47$

* Statistical difference between the groups ($p < 0.05$). Blood gas analysis was performed at the onset of general anaesthesia (T0), 20-30 minutes later (T1), at the end of anaesthesia (T2) and at RSV (T3). Data are displayed as mean ± standard deviation (SD) or median (range).

Figure 1. Box plot of the time taken to resume spontaneous ventilation in 18 anaesthetised horses where mechanical ventilation was adjusted to maintain $PE´CO_2$ at 40 ± 5mmHg (5.3 ± 0.7 kPa) (Group40) or 60 ± 5 mmHg (8.0 ± 0.7 kPa) (Group60).