RESEARCH PAPER

Comparison of single-breath continuous positive airway pressure manoeuvre with inhaled salbutamol to improve oxygenation in horses anaesthetized for laparotomy

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Abstract

Objective To compare the efficacy of single-breath continuous positive airway pressure manoeuvre (CPAP-M) with inhaled salbutamol, and a combination of both.

Study design Randomized, clinical study.

Animals A total of 62 client-owned horses (American Society of Anesthesiologists status III–V) anaesthetized for laparotomy.

Methods Horses were premedicated with intravenous (IV) xylazine (0.4–0.6 mg kg^{-1}), anaesthesia was induced with midazolam (0.06 mg kg^{-1} IV) and ketamine (2.2 mg kg^{-1} IV) and maintained with isoflurane in oxygen using volume-controlled ventilation without positive end-expiratory pressure. If PaO_2 was < 100 mmHg (13.3 kPa), either a CPAP-M (50 cmH_2O for 45 seconds) or salbutamol (0.002 mg kg^{-1}) was administered. The intervention was considered successful if PaO_2 reached 100 mmHg (13.3 kPa). If PaO_2 remained < 100 mmHg (13.3 kPa), treatments were switched. PaO_2/FiO_2 ratio and estimated shunt fraction (F-shunt) were derived from data obtained from arterial blood gas measurements. Dynamic compliance (C_{dyn}) was calculated from variables recorded at the moment of arterial blood analysis. Fisher's exact tests compared success rates between treatments, and linear models were performed to test whether the treatment modified the values of the measurements; $p < 0.05$.

Results Salbutamol was the first intervention in 28 horses and was effective in 22 horses. CPAP-M was the first intervention in 34 horses and was effective in 26 horses. CPAP-M after salbutamol was performed in six horses, with four responders, and salbutamol after CPAP-M was administered to eight horses, with one responder. Salbutamol, but not CPAP-M, significantly decreased F-shunt. Both salbutamol and CPAP-M significantly increased C_{dyn}.

Conclusions and clinical relevance Salbutamol and CPAP-M were comparably effective in improving oxygenation and C_{dyn} in anaesthetized horses with PaO_2 < 100 mmHg (13.3 kPa). Whether combining both treatments might be beneficial needs to be confirmed on a larger number of horses.

Keywords alveolar recruitment manoeuvre, continuous positive airway pressure, dynamic compliance, estimated shunt fraction, horses, salbutamol.

Introduction

Horses are prone to develop large areas of lung atelectasis during general anaesthesia. The subsequent pulmonary shunt causes significant impairment of oxygenation (Nyman & Hedenstierna 1989; Nyman et al. 1990). Treating hypoxaemia remains a challenge in equine anaesthesia, its outcome being largely unpredictable (Auckburally & Nyman 2017). Different strategies have been attempted to improve oxygenation.

Increasing the inspired oxygen fraction (FiO_2) has a low success rate given that impairment of oxygenation is caused predominantly by pulmonary shunt (Benator et al. 1973). Latest advances in equine mechanical ventilation rely on the open lung concept which aims to open the alveoli and keep them open. This is achieved by applying a high peak inspiratory pressure (PIP) to re-inflate atelectatic areas initially,

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which is also referred as an alveolar recruitment manoeuvre (ARM). In addition, a positive end-expiratory pressure (PEEP) is maintained to prevent recollapse (Lachmann 1992). In horses, PIP of up to 80 cmH_2O and PEEP of up to 30 cmH_2O have been required (Bringewatt et al. 2010; Hopster et al. 2011, 2017). There are only two studies, with conflicting results, reporting the use of single-breath continuous positive airway pressure manoeuvre (CPAP-M) in horses. Santos et al. (2013) used 50 cmH_2O applied for 50 seconds, not followed by PEEP, with only a partial and transient improvement of oxygenation. Nevertheless, Araos et al. (2019) showed that 50 cmH_2O applied for 20 seconds, followed by a 10 cmH_2O PEEP, was responsible for improved lung mechanics and better oxygenation.

Among drugs administered to improve oxygenation, the aerosolized β_2-adrenergic agonist salbutamol (albuterol) has commonly been used at the dose of 0.002 mg kg^{-1} with satisfactory results (Robertson & Bailey 2002; Patschova et al. 2010; Casoni et al. 2014).

There is no consensus on the best way to treat hypoxaemia in anaesthetized horses, so the present study aimed to compare the efficacy of inhaled salbutamol with a CPAP-M followed by PEEP, in horses with an arterial partial pressure of oxygen (PaO_2) < 100 mmHg (13.3 kPa) at any time during general anaesthesia. A second aim was to investigate the impact of combining both interventions by immediately switching treatment options when the first attempt was unsuccessful in restoring PaO_2 to > 100 mmHg (13.3 kPa). The results obtained with PaO_2 were compared with those based on PaO_2/FiO_2 ratio and estimated shunt fraction (F-shunt) with exactly the same standard settings.

We hypothesized that salbutamol would be more effective than CPAP-M in restoring $PaO_2 \geq 100$ mmHg (13.3 kPa), whether it was administered as first intervention or even after CPAP-M failed to do so.

Material and methods

This study was conducted after obtaining institutional approval for animal experimentation (Committee for the Ethical Use of Animals, University of Liege, number 1474).

Cases were selected from client-owned horses anaesthetized for laparotomy at the Equine Hospital of the Faculty of Veterinary Medicine of the University of Liege between March 2014 and January 2019. By signing the admission form, owners gave written informed consent for the collection of data from, and treatment of their horses included in the study and its publication in an anonymized format. The inclusion criteria were: 1) 1 year of age or greater; 2) body weight > 200 kg; and 3) mechanical ventilation within 10 minutes of anaesthetic induction with PaO_2 < 100 mmHg (13.3 kPa) at any time during the anaesthetic period.

The anaesthesia protocol was standardized. Xylazine (0.4−0.6 mg kg^{-1}) injected intravenously (IV; Proxylaz; Prodivet Pharmaceuticals, Belgium) and flunixin meglumine (1.1 mg kg^{-1} IV; Emdofluxin; Emdoka, Belgium) were administered for premedication and anaesthesia was induced with midazolam (0.06 mg kg^{-1} IV; Midazolam Mylan; Mylan, Belgium) and ketamine (2.2 mg kg^{-1} IV; Ketamidor; Ecuphar, Belgium). Isoflurane (IsoFlo; Zoetis, Belgium) was delivered in 100% oxygen and end-tidal percentage was adjusted to maintain adequate anaesthetic plane. No other drugs were used to maintain anaesthesia apart from ketamine boli (0.2−0.4 mg kg^{-1} IV). Volume-controlled ventilation (VCV) was provided from the beginning of anaesthesia (Tafonius; Vetronics, UK) using the following ventilator settings: tidal volume (V_T) 10 mL kg^{-1}, respiratory rate (f_R) 8 breaths $minute^{-1}$, inspiratory-to-expiratory time ratio 1:2, no PEEP. f_R was adjusted to maintain expired carbon dioxide partial pressure ($P_{E'}CO_2$) between 35 and 50 mmHg (4.7 and 6.7 kPa), and inspiratory time was consequently adapted to maintain inspiratory-to-expiratory time ratio 1:2. Adjustment of V_T was left at the discretion of the anaesthetist, but without exceeding 15 mL kg^{-1}. Lactated Ringer's solution was infused (10−20 mL kg^{-1} $hour^{-1}$) and hypotension was treated as follows: dobutamine (Dobutrexmylan; Mylan) was initiated at a rate of 0.5 μg kg^{-1} $minute^{-1}$ and increased by 0.5 μg kg^{-1} $minute^{-1}$ every 5 minutes until mean arterial pressure (MAP) reached 60 mmHg, or until infusion rate reached 3 μg kg^{-1} $minute^{-1}$. Norepinephrine (Levophed; Hospira, Belgium) was added when MAP remained under 60 mmHg and dobutamine reached 3 μg kg^{-1} $minute^{-1}$. Infusion was initiated at 0.1 μg kg^{-1} $minute^{-1}$ and increased by 0.1 μg kg^{-1} $minute^{-1}$ every 3 minutes until MAP reached 60 mmHg or until the infusion rate reached 1 μg kg^{-1} $minute^{-1}$. Atropine (5 μg kg^{-1}; Atropine; Sterop, Belgium) was administered when low heart rate (HR) was deemed to significantly contribute to hypotension, but not following α_2-adrenergic agonist.

A catheter was placed in the facial artery or the transverse facial artery for continuous direct arterial pressure measurement and repeated arterial blood sampling. The first arterial blood gas measurement was performed immediately after the catheter had been placed and, at intervals of 30 minutes thereafter. Invasive arterial blood pressure, pulse oximetry, electrocardiogram, inspired and expired percentages of oxygen and isoflurane, inspired carbon dioxide partial pressure and $P_{E'}CO_2$, airway pressure and flow-volume loops were continuously recorded using a multiparameter monitor (Solomon; Vetronics, UK). Arterial partial pressure of carbon dioxide ($PaCO_2$), PaO_2, pH, packed cell volume, plasma electrolytes, arterial saturation of haemoglobin and total haemoglobin were measured with co-oximetry (Cobas b 123; Roche, Belgium;

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GEM 5000; Werfen, Belgium; GEM 3500, Werfen) immediately after sampling. Different co-oximeters were successively used throughout the study for reasons beyond our control but unrelated to their performances (contractual obligation). Samples from the same horse were consistently analysed with the same co-oximeter.

If any arterial blood gas measurement revealed a PaO_2 < 100 mmHg (13.3 kPa), the action to improve oxygenation was randomly assigned by flipping a coin and either a CPAP-M followed by a predetermined PEEP was performed, or salbutamol was administered.

Practically, the CPAP-M consisted of interrupting VCV during the inspiratory phase and, using the ventilator, applying a CPAP of 50 cmH_2O for 45 seconds. Immediately after VCV was resumed, 10 cmH_2O PEEP was maintained until the end of the procedure.

Salbutamol (Salbutamol; Sandoz, Belgium) was supplied in a metered-dose inhaler. It was administered through a specifically designed pore in the Y-piece of the breathing system, close to the endotracheal tube. Each depression of the nozzle through the pore at the onset of inspiration delivered 0.1 mg of active substance to the animal. A dose of 0.002 mg kg^{-1} was administered to the horses rounded to the nearest 50 kg.

Arterial blood gas measurement was repeated 5 minutes after treatment and PaO_2 was used to assess the efficacy of the treatment. The intervention was considered successful if PaO_2 reached 100 mmHg (13.3 kPa). However, if PaO_2 was still < 100 mmHg (13.3 kPa), treatment options were switched without delay to evaluate the potential benefit of combining both interventions: a CPAP-M followed by PEEP was performed in horses that were given salbutamol first and, conversely, salbutamol was aerosolized in horses treated with a CPAP-M first. Again, arterial blood gas measurement was repeated 5 minutes after the second treatment.

From a mechanistic perspective, PaO_2/FIO_2 ratio and F-shunt were calculated for each arterial blood gas measurement, whenever all the required data were available, using the following formula:

$$\text{F} - \text{shunt} = \frac{1.36*Hba*(1 - SaO_2) + 0.0031*(PAO_2 - PaO_2)}{[1.36*Hba*(1 - SaO_2) + 0.0031*(PAO_2 - PaO_2)] + 3.5}*100$$

where Hba, arterial haemoglobin concentration (g dL^{-1}); PAO_2, alveolar partial pressure of oxygen (mmHg); PaO_2, arterial partial pressure of oxygen (mmHg); SaO_2, arterial haemoglobin oxygen saturation (%).

Haemodynamic variables (HR, diastolic, mean, and systolic arterial pressure), dobutamine requirement and actual ventilatory variables (PIP, level of PEEP, V_T and f_R) were recorded and analysed thereafter. Furthermore, every time arterial blood gas measurement was performed, and whenever all the required data were available, dynamic compliance (C_{dyn}) was manually calculated from variables obtained over a single breath, using the following formula:

$$C_{dyn} = V_T / (PIP - PEEP)$$

where C_{dyn}, dynamic compliance (mL cmH_2O^{-1}); PEEP, positive end-expiratory pressure (cmH_2O); PIP, peak inspiratory pressure (cmH_2O); V_T, tidal volume (mL).

Statistical analysis

All analyses were performed using the SAS system (SAS Institute Inc., NC, USA). Sample size was calculated based on mean and standard deviation values assumed from previous clinical use of both treatments (Proc GLMPOWER). An *a priori* power analysis revealed that 62 horses would be needed to detect a 20% difference in PaO_2 between salbutamol and CPAP-M, with a power of 80% and $\alpha = 0.05$.

First, *t* tests were used to determine whether mean variables (V_T, body mass, age, time from induction of anaesthesia, PaO_2) were equal in first treatment application (SAL, CPAP-M). Chi-square tests were used to determine whether sex, f_R, American Society of Anesthesiologists (ASA) status, PIP, PEEP and FIO_2 were independent of treatment application (SAL, CPAP-M).

Next, the null hypothesis of no linear dependence (Pearson correlation coefficients) between initial values of ventilatory variables was tested with a *t* test (Proc CORR).

Then, two-sided Fisher's exact tests were used to compare success rates, based on PaO_2, between treatment options (SAL *versus* CPAP-M, CPAP-M-SAL *versus* SAL-CPAP-M, SAL *versus* CPAP-M-SAL, CPAP-M *versus* SAL-CPAP-M).

In addition, four linear models were used to test whether the difference in measurements (PaO_2/FIO_2 ratio, C_{dyn} or F-shunt) before and after the first treatment application (SAL, CPAP-M) was significantly different from null ($n = 48$ horses). These models were adjusted for the following fixed effects: PIP, PEEP, V_T and f_R at the time blood gas measurement first revealed PaO_2 < 100 mmHg (13.3 kPa); time at which the treatment was applied; ASA; sex; age; and body mass (Proc GLM).

Furthermore, two linear models were performed for the second treatment application (SAL-CPAP-M or CPAP-M-SAL) of 14 horses with the same fixed effects in the models as

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described above with the exception of the time at which the treatment was applied that was not included.

In all six models, Q-Q plots and Shapiro-Wilk test showed that observed residuals were independent and normally distributed. Orthogonal least square means of each measurement were compared across treatments (SAL, CPAP-M, SAL-CPAP-M and CPAP-M-SAL).

Results

Study population

Of the 62 horses included in the study, 53 horses were anaesthetized as emergencies (22 ASA III E, 25 ASA IV E and six ASA V E), whereas nine horses underwent elective procedures (nine ASA III). There were seven stallions, 27 geldings and 28 mares. Their body mass ranged from 230 to 731 kg (median 550 kg) and their age from 24 to 311 months (median 137.5 months). Horses were subjectively categorized into five body conformation types: 27 warmblood types, one thoroughbred type, three draft types, six pony types and 25 miscellaneous. Of the 62 horses, 50 horses recovered from anaesthesia while 12 horses were euthanized with owner's consent during surgery.

Initial variables

The time from induction of general anaesthesia to the first arterial blood gas measurement that revealed PaO_2 < 100 mmHg (13.3 kPa) ranged from 12 to 231 minutes. Ventilatory variables immediately prior to this initial arterial blood gas measurement were as follows: F_IO_2 ranged from 28% to 96% (median 80%), V_T from 7.0 to 14.0 mL kg^{-1} (median 10.7 mL kg^{-1}), f_R from 4 to 15 breaths $minute^{-1}$ (median 8 breaths $minute^{-1}$), PIP from 10 to 45 cmH_2O (median 28 cmH_2O), no PEEP was used in 56 horses, a PEEP of 5 cmH_2O was applied in five horses and a PEEP of 10 cmH_2O in one horse, and manually calculated C_{dyn} ranged from 75 to 602 mL cmH_2O^{-1} (median 223 mL cmH_2O^{-1}). At that time, the PaO_2 ranged from 36 to 95 mmHg (4.8−12.7 kPa) (median 66 mmHg, 8.8 kPa), the PaO_2/F_IO_2 ratio from 0.4 to 2.0 (median 0.9) and the F-shunt (calculated for 53 horses) from 22% to 69% (median 40%).

A significant positive correlation coefficient was found between initial PaO_2 and initial V_T ($r = 0.36$), between initial PaO_2 and time from induction ($r = 0.35$), and between initial V_T and time from induction ($r = 0.28$). Significant negative correlations were found between initial PaO_2 and initial PIP ($r = -0.30$), between initial C_{dyn} and initial PIP ($r = -0.73$), and between initial C_{dyn} and initial f_R ($r = -0.35$). No other significant correlation was found between initial values of ventilatory variables.

Treatment allocation

Salbutamol was performed as first intervention in 28 horses and increased PaO_2 to > 100 mmHg (13.3 kPa) in 22 horses (SAL), whereas it was ineffective in six horses. A CPAP-M was performed as first intervention in 34 horses and was effective in 26 horses (CPAP-M), whereas it was not effective in eight horses. When the first attempt to restore PaO_2 to > 100 mmHg (13.3 kPa) was unsuccessful, treatment options were switched: a CPAP-M was performed in six horses (SAL-CPAP-M) and salbutamol was administered to eight horses (CPAP-M-SAL). CPAP-M proved to be efficacious in four out of six horses when it was performed as second intervention. Salbutamol effectively increased PaO_2 to > 100 mmHg (13.3 kPa) in one out of eight horses when it was administered as second treatment option (Fig. 1). Of the horses that did not respond to either intervention or to a combination of both, body conformation types were distributed in the same proportions as in the overall study population.

ASA status, sex, body mass, age, time from induction, PaO_2 and ventilatory variables immediately prior to the arterial blood gas measurement were comparable in SAL and CPAP-M horses. The time interval between treatment administration and blood gas measurement ranged between 5 and 10 minutes.

Effect of a single intervention

Least square mean of the change in F-shunt was significantly greater after salbutamol was administered as the sole intervention in SAL horses (difference of −8.8%) (Fig. 2). Least square means of the change in PaO_2/F_IO_2 ratio were not significantly altered by the treatment in SAL horses (Fig. 3). Least square means of the change in F-shunt and PaO_2/F_IO_2 ratio were not significantly affected by performing a CPAP-M as a unique intervention in CPAP-M horses (Figs 2 & 3). Least square mean of the change in F-shunt was significantly higher for SAL than for CPAP-M horses. Changes in F-shunt in SAL horses were significantly influenced by initial V_T.

Least square means of the change in C_{dyn} significantly increased after either salbutamol or CPAP-M was performed as the sole intervention in SAL (difference of 130.2 mL cmH_2O^{-1}) and in CPAP-M (difference of 147.5 mL cmH_2O^{-1}) horses (Fig. 4). Moreover, least square means of the change in C_{dyn} were not significantly different between SAL and CPAP-M horses (Table 1). Changes in C_{dyn} in SAL and CPAP-M horses were significantly affected by initial PIP and initial V_T.

Haemodynamic variables and dobutamine requirement are presented in Table 2. Infusion rate of dobutamine was sometimes approximated but was always recorded, which allowed *a posteriori* calculation.

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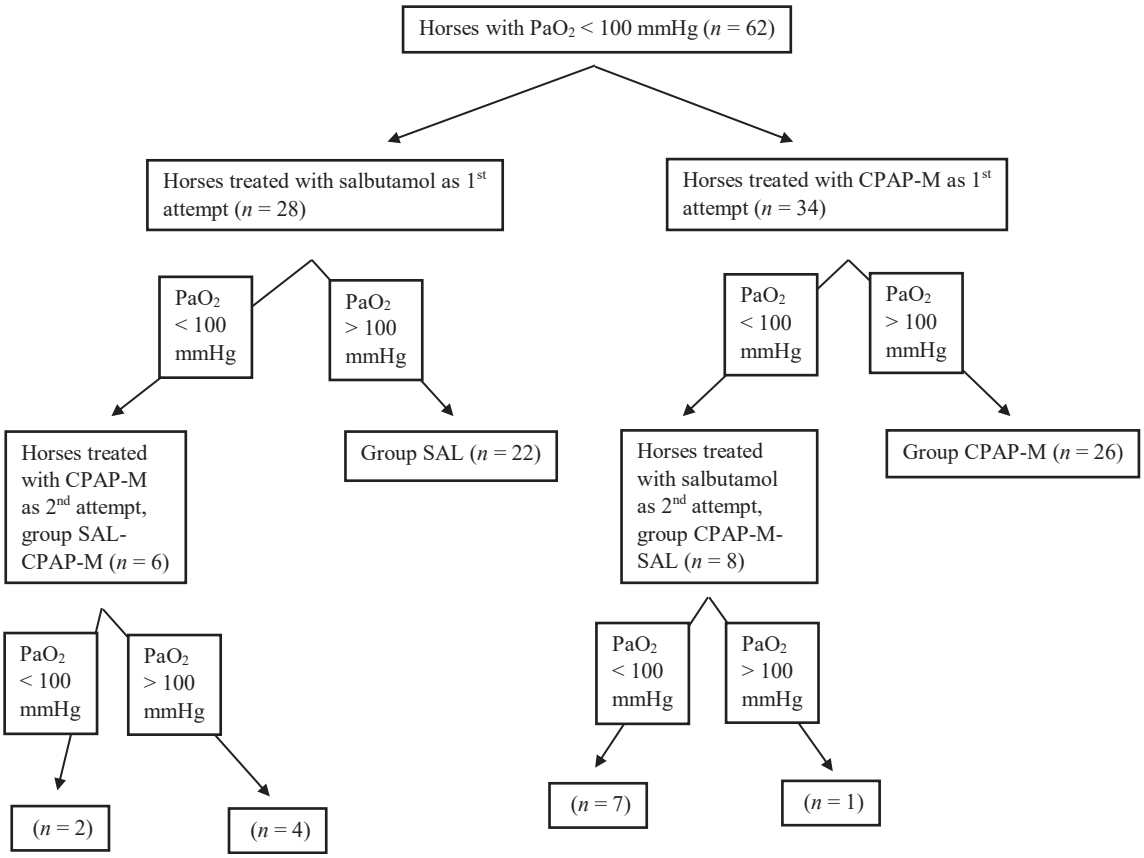

Figure 1 Distribution of the 62 horses included in the study. CPAP-M, single-breath continuous positive airway pressure manoeuvre; PaO_2, arterial partial pressure of oxygen.

Effect of combining interventions

Least square means of the change in PaO_2/FIO_2 ratio, F-shunt or C_{dyn} were not significantly affected after a second attempt to increase PaO_2 above 100 mmHg (13.3 kPa) in SAL-CPAP-M or CPAP-M-SAL horses (Table 1).

Comparison of success rates

The success rates, based on PaO_2, and compared by two-sided Fisher's exact test, were statistically equivalent between SAL and CPAP-M, between CPAP-M-SAL and SAL-CPAP-M, and between CPAP-M and SAL-CPAP-M. However, SAL and CPAP-M-SAL had significantly different success rates.

Discussion

This study showed that salbutamol and CPAP-M were comparably effective in improving oxygenation when administered to horses with PaO_2 < 100 mmHg (13.3 kPa) at any time during general anaesthesia. Moreover, when the first attempt failed, combining both interventions had variable outcomes, depending on the order. Indeed, using salbutamol after unsuccessful CPAP-M only provided a very marginal benefit in improving oxygenation. However, when PaO_2 did not reach 100 mmHg (13.3 kPa) after salbutamol administration, performing a CPAP-M was effective in two thirds of cases. Therefore, this study suggests that horses presenting with hypoxaemia despite the administration of salbutamol might benefit from the application of a CPAP-M. This way, only two (7%) of the 28 horses treated with salbutamol remained hypoxaemic.

Both salbutamol and CPAP-M have the advantages of being easy to learn, simple to use and achievable in a short period of time when the need becomes apparent during anaesthesia. The potential favourable effects are readily observable. The short duration of CPAP-M (45 seconds in duration) eases its implementation in a clinical setting, whereas completion of an ARM conducted using a stepwise PIP and PEEP titration takes at least 36 minutes (Wettstein et al. 2006; Moens et al. 2014). Furthermore, salbutamol is inexpensive and its administration by inhalation is noninvasive. Beyond the very few reports of cardiovascular side effects assumed to result from systemic absorption (Casoni et al. 2014), salbutamol has been

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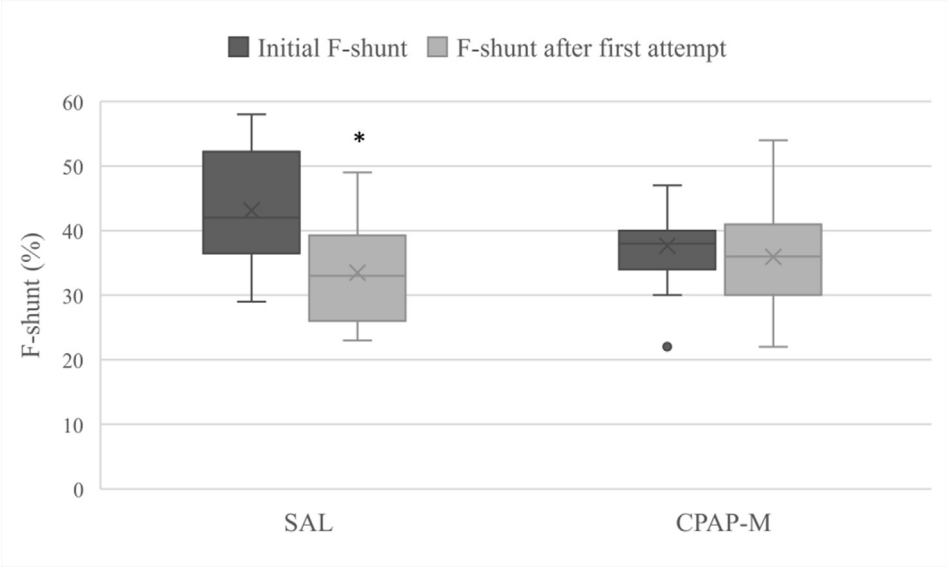

Figure 2 Box and whisker plots presenting the changes in the estimated shunt fraction (F-shunt) in horses responsive to salbutamol (SAL) or to a single-breath continuous positive airway pressure manoeuvre (CPAP-M) administered as the first attempt to improve oxygenation. The box represents the interquartile range, the upper bar represents the maximum value, the lower bar represents the minimum value, the bar within the box represents the median, the cross within the box represents the mean and the solid circle represents an outlier. *Significant difference ($p < 0.05$) between initial F-shunt and F-shunt 5−10 minutes after the first attempt to improve oxygenation.

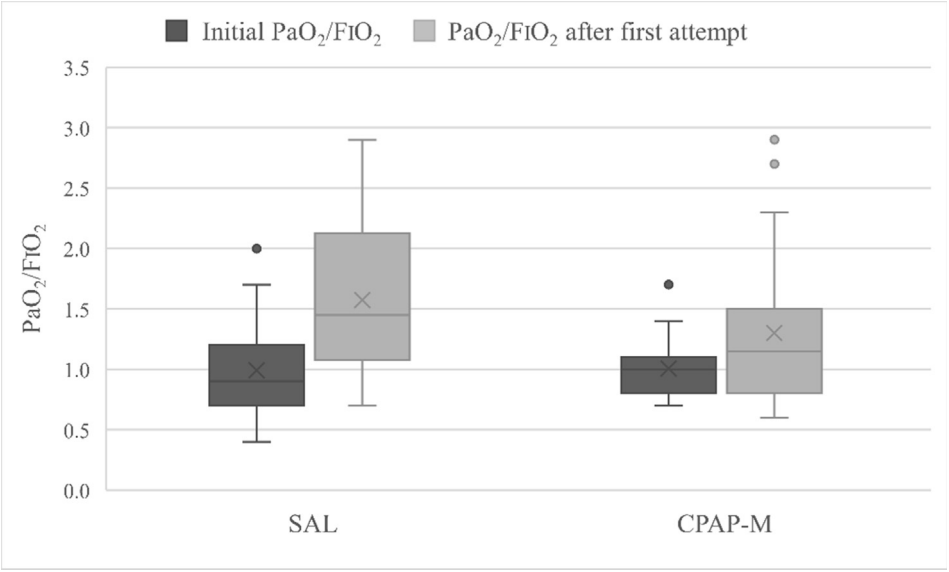

Figure 3 Box and whisker plots presenting the change in the PaO_2/FIO_2 ratio in horses responsive to salbutamol (SAL) or to a single-breath continuous positive airway pressure manoeuvre (CPAP-M) administered as the first attempt to improve oxygenation. FIO_2, inspired oxygen fraction; PaO_2, arterial partial pressure of oxygen. The box represents the interquartile range, the upper bar represents the maximum value, the lower bar represents the minimum value, the bar within the box represents the median, the cross within the box represents the mean and solid circles represent outliers.

administered to a wide variety of veterinary patients. CPAP-M does not cost anything but requires a large animal ventilator to be applied properly. Moreover, application of an ARM is responsible for increased expression of markers indicative of the early signs of ventilator-induced lung injury (Hopster et al. 2016b). In addition, although the open lung concept has

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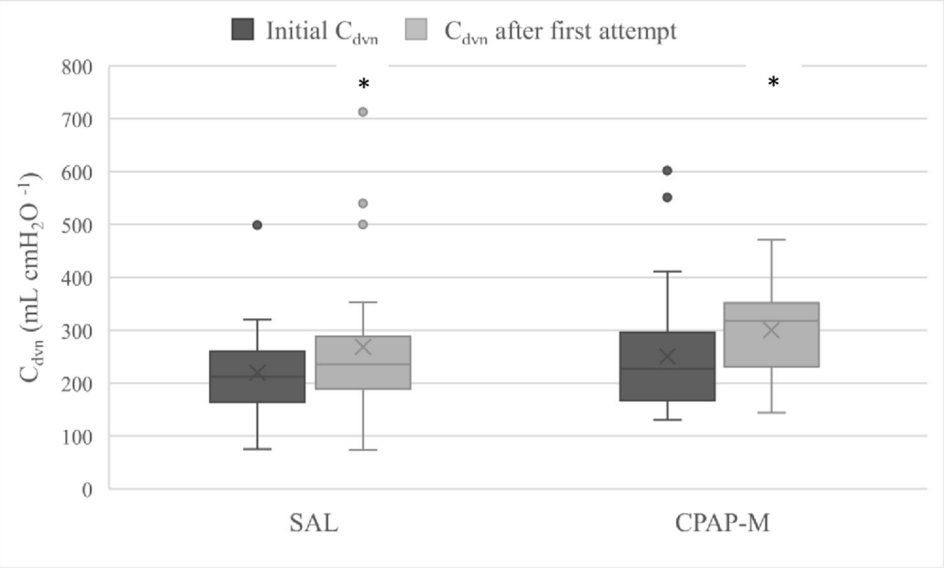

Figure 4 Box and whisker plots presenting the change in the dynamic compliance (C_{dyn}) in horses responsive to salbutamol (SAL) or to a single-breath continuous positive airway pressure manoeuvre (CPAP-M) administered as the first attempt to improve oxygenation. The box represents the interquartile range, the upper bar represents the maximum value, the lower bar represents the minimum value, the bar within the box represents the median, the cross within the box represents the mean and solid circles represent outliers. *Significant difference ($p < 0.05$) between initial C_{dyn} and C_{dyn} 5−10 minutes after the first attempt to improve oxygenation.

Table 1 Changes in arterial partial pressure of oxygen (Δ PaO_2, in mmHg), PaO_2/FIO_2 ratio (Δ PaO_2/FIO_2 ratio), estimated shunt fraction (Δ F-shunt, in %) and dynamic compliance (Δ C_{dyn}, in mL cmH_2O^{-1}) obtained by least squares means in the four groups compared in this study. Data were measured in 62 horses during isoflurane anaesthesia. Horses with a PaO_2 < 100 mmHg were randomly allocated to have either salbutamol SAL ($n = 22$) or a single-breath continuous positive airway pressure manoeuvre (CPAP-M, $n = 26$) to improve oxygenation. If treatment was ineffective, the opposite treatment was applied SAL-CPAP-M ($n = 6$) or CPAP-M-SAL ($n = 8$)

	Δ PaO_2	Δ PaO_2/FIO_2 ratio	Δ F-shunt	Δ C_{dyn}
SAL	54.0	0.50	−8.8*	130.2*
CPAP-M	27.6	0.11	−1.1	147.5*
SAL-CPAP-M	−48.4	−0.50	−2.0	261.5
CPAP-M-SAL	−72.3	−0.67	−8.0	406.9

*Significant difference ($p < 0.05$) between initial variable and the same variable after the first attempt to improve oxygenation.

been applied to equine anaesthesia with encouraging results, increased airway pressures associated with ARM might potentially impair cardiac output (CO). Despite improvements in oxygenation, Hopster et al. (2016a) showed that ARM is detrimental to intestinal perfusion and results in decreased oxygen delivery when PIP and PEEP exceed 40 cmH_2O and 20 cmH_2O, respectively.

The severity of lung atelectasis in some of the horses in our study (F-shunt up to 69%) might have prevented the CPAP-M from recruiting the lung extensively. Indeed, because of great variation in time constants between lung regions, CPAP-M might result in over-inflation of functional areas rather than recruitment of collapsed alveoli (Soni & Williams 2008). Moreover, our study relied on the overall lung compliance, which does not give any insight into how distinct lung regions respond to the CPAP-M. Nonetheless, the improvement in C_{dyn} and the absence of change in F-shunt and PaO_2/FIO_2 ratio might actually suggest over-distension of previously opened alveoli and at least partial failure in recruiting atelectatic areas. Indeed, effective recruitment should have improved ventilation-to-perfusion ratio and, consequently, reduced F-shunt and increased PaO_2/FIO_2 ratio.

The exact mechanism underlying the potential benefit of inhaled salbutamol in treating hypoxaemia in anaesthetized horses remains elusive. Robertson & Bailey (2002) showed that salbutamol nebulized at a dose of 0.002 mg kg^{-1} administered to hypoxaemic horses almost doubled PaO_2. PaO_2 may have increased as a result of bronchodilation and/or increased CO. Patschova et al. (2010) studied the effect of inhaled salbutamol (0.002 mg kg^{-1}). They observed an increase in CO and oxygen delivery, without a change in lung ventilation, C_{dyn}, or in the amount of pulmonary shunt. Arroyo et al. (2016) studied the effect of aerosolized salbutamol in

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Table 2 Haemodynamic variables and dobutamine requirements (mean ± standard deviation) obtained from the three recordings before and after the first attempt to improve oxygenation. The first attempt to improve oxygenation consisted of either the inhalation of salbutamol ($n = 28$) or the application of a single-breath continuous positive airway pressure manoeuvre ($n = 34$). All the horses were included, independent of the effect of this first intervention on their arterial partial pressure of oxygen. The three closest measurements before the intervention were recorded within 5, 10 and 15 minutes preceding the intervention. The three closest measurements after the intervention were recorded within 5, 10 and 15 minutes following the intervention. DAP, diastolic arterial pressure (in mmHg); HR, heart rate; MAP, mean arterial pressure (in mmHg); SAP, systolic arterial pressure (in mmHg)

	Salbutamol		**Continuous positive airway pressure-manoeuvre**	
	Before	**After**	**Before**	**After**
HR (beats minute^{-1})	48 ± 16	50 ± 15	41 ± 10	43 ± 13
DAP (mmHg)	68 ± 19	70 ± 15	66 ± 18	74 ± 15
MAP (mmHg)	81 ± 17	84 ± 14	82 ± 20	89 ± 17
SAP (mmHg)	99 ± 18	103 ± 17	102 ± 20	110 ± 22
Dobutamine (μg kg^{-1} minute$^{-1)}$	1.0 ± 0.6	0.7 ± 0.6	0.6 ± 0.7	0.6 ± 0.7

standing horses with recurrent airway obstruction and observed an increase in C_{dyn}. To the best of the authors' knowledge, this is the first study to demonstrate the benefit of inhaled salbutamol on both C_{dyn} (manually calculated, for one breath per measurement period) and indicators of oxygenation (PaO_2, F-shunt) in anaesthetized horses. Treatment failure might be attributed to individual differences in β_2-adrenergic receptors distribution (Törneke 1999).

Pulmonary shunt is mainly responsible for impairment of oxygenation during equine anaesthesia, and this was probably the case in the present study given that F-shunt largely exceeded the expected value of 33% in some horses (Nyman & Hedenstierna 1989; Nyman et al. 1990). F-shunt is a content-based index that is proven to be a better estimate of venous admixture compared with tension-based indices (PaO_2/FIO_2 ratio and PaO_2) (Wandrup 1995; Araos et al. 2012; Briganti et al. 2015). The improvement in F-shunt, but not in PaO_2/FIO_2 ratio, probably demonstrates the efficacy of inhaled salbutamol in reducing venous admixture.

Neither salbutamol nor CPAP-M had any clinically relevant effects on haemodynamic variables or dobutamine requirement. Although a very transient decrease in arterial blood pressure was observed in most horses submitted to CPAP-M, it resolved as soon as VCV was resumed and did not prompt any intervention. Whereas Patschova et al. (2010) proposed that salbutamol increased HR and, consequently, CO, no clinically relevant change in HR was observed in our study.

Despite the absence of an association between initial PaO_2 and body mass, body conformation type might have played a role in the development of low PaO_2 values. Indeed, horses included in the study mostly belonged to the warmblood body type which exhibits the less favourable morphometric characteristics in terms of maintaining oxygenation (Mansel & Clutton 2008). However, warmblood horses are also the most heavily represented in our overall caseload. Nonetheless, body conformation did not appear to affect treatment response. No body type was over-represented among horses that did not respond to either intervention or the combination when compared to their distribution in the general study population.

The time interval between treatment administration and blood gas measurement was initially set at 5 minutes, as it is equal to the onset and time-to-peak effect of salbutamol (Derksen et al. 1999). Nevertheless, the actual time interval ranged between 5 and 10 minutes. As the effects of salbutamol should be maximal at 10 minutes and last for 30 minutes to 3 hours (Derksen et al. 1999), this small delay should not have affected our results. However, blood gas measurement was only repeated once after treatment, which might preclude us from concluding the longer-term effects.

In additional to the outcome variables, the study revealed several correlations between ventilatory variables, oxygenation and time from induction. However, this study was not specifically designed to look at these variables, which precludes us from drawing any conclusion from these observations.

This study has several limitations. First, although initial ventilator settings were standardized, the clinician was allowed to adjust them to best fit the needs of the animal. Furthermore, several anaesthetists participated in the study. Although recommendations were given to adjust f_R, inspiratory-to-expiratory time ratio and V_T, other variables were left at the discretion of the anaesthetist, which might have affected our results. Second, C_{dyn} relies on PIP, which was measured in the presence of gas flow (no end-inspiratory hold) and is therefore dependent on the resistive components of the respiratory system and, consequently, subject to variation. Mean PIP values obtained over several breaths should have been used. However, as VCV was applied, lung conditions are expected to be stable between breaths and C_{dyn} calculated over one breath is an acceptable alternative. Future studies should specifically compare the effect of salbutamol and CPAP-M on C_{dyn}. Third,

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different co-oximeters were used without confirming their accuracy prior to the study. This may have influenced the measurement of PaO_2. Nonetheless, each horse was analysed with the same co-oximeter. Fourth, block randomization should have been used to ensure that an equal number of horses were assigned to each treatment option. Finally, this study is underpowered. Indeed, the actual power, calculated using $\alpha = 0.05$ and a total sample size of 62 horses, was 50%. The minimum sample size required to obtain an 80% chance (at $\alpha = 0.05$) of detecting a non-zero difference for PaO_2 between groups, based on the standard errors obtained from our actual sample, should be 98 horses. A larger sample size should be used in the future. Nevertheless, this study found a significant difference for F-shunt, which is more relevant than PaO_2 alone in terms of venous admixture. Further investigations combining interventions to improve oxygenation in hypoxaemic anaesthetized horses are warranted.

Conclusions

This study showed that inhaled salbutamol and CPAP-M had comparable success rates in improving oxygenation and C_{dyn} when administered to horses with $PaO_2 < 100$ mmHg (13.3 kPa) at any time during general anaesthesia for laparotomy. Moreover, salbutamol, but not CPAP-M, significantly decreased F-shunt. Whereas nebulizing salbutamol after unsuccessful CPAP-M only provided a very marginal benefit in terms of oxygenation, performing a CPAP-M after salbutamol was effective in two thirds of the refractory cases.

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Authors' contributions

JDupont: study design and execution, data analysis and manuscript writing. AG and AS: study execution. JDetilleux: statistical analyses and manuscript review. CS: study design, study execution and manuscript review. DS: study design and manuscript review.

Conflict of interest statement

The authors declare no conflict of interest.

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