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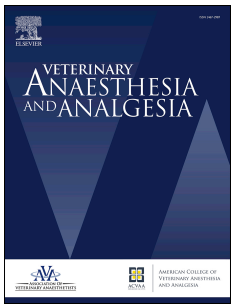

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FULL RESEARCH STUDY

Retrospective study of the changes in dynamic compliance and ventilation/perfusion mismatch following salbutamol inhalation in hypoxaemic mechanically ventilated anaesthetized horses

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Authors' contributions

JD: study design, data analysis and writing of the manuscript. BRD: data analysis and writing of the manuscript. AS: review of the manuscript. DS and CS: study design and review of the manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

Abstract

Objective To study the changes in dynamic compliance (C_{dyn}), ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch and haemodynamic variables in hypoxaemic anaesthetized horses whose PaO_2 increased following salbutamol inhalation.

Study design Retrospective, clinical, cohort study.

Animals A group of 73 client-owned horses treated with salbutamol when PaO_2 < 100 mmHg (13.3 kPa) during anaesthesia.

Methods Horses were divided into two groups: responders (R), where PaO_2 after salbutamol ≥ 1.2 PaO_2 before treatment (i.e. ≥ 20% increase), and non-responders (NR), where PaO_2 after salbutamol < 1.2 PaO_2 before treatment. Demographic data and intraoperative variables before treatment were compared between R and NR. C_{dyn}, arterial to end-tidal carbon dioxide difference [$P(a\text{-}E´)CO_2$], estimated ratio of dead space to tidal volume ($est.V_D/V_T$), estimated shunt fraction (F-shunt), heart rate, systolic, mean and diastolic arterial pressure, and dobutamine requirements were compared before and after treatment within R and NR. For each variable, the difference (Δ) between values pre- and posttreatment was calculated and compared between groups R and NR. Numerical data were compared using univariate or bivariate analysis and categorical data were compared using Chi-square test; $p < 0.05$.

Results Of the 73 horses 50 were classified as R while 23 horses were classified as NR. There was no statistical difference between R and NR for demographic data or initial intraoperative variables except for body weight [R: 531 (170-715) kg, NR: 540 (420-914) kg]. While salbutamol did not alter C_{dyn} in either group, it significantly decreased $P(a\text{-}E´)CO_2$, $est.V_D/V_T$ and F-shunt in R only. $\Delta P(a\text{-}E´)CO_2$, $\Delta est.V_D/V_T$ and ΔF-shunt

were significantly greater in R (-17.8%, -19.0% and -24.1%, respectively) than in NR (11.5%, 6.6% and -0.3%, respectively).

Conclusions and clinical relevance In hypoxaemic anaesthetized horses responding to inhaled salbutamol by an ≥ 1.2 increase in PaO_2 no change in C_{dyn} was detected , but indicators of $\dot{V}/\dot{Q}$ mismatch improved.

Keywords dynamic compliance, horse, hypoxaemia, salbutamol, venous admixture, ventilation/perfusion mismatch

Introduction

General anaesthesia is associated with the rapid development of lung atelectasis and pulmonary shunt in horses (Nyman & Hedenstierna 1989; Nyman et al. 1990). Hypoxaemia has been a long-standing problem in equine anaesthesia, but no consensus exists regarding the best treatment option (Auckburally & Nyman 2017).

Increasing the inspired oxygen fraction (FIO_2) has a limited efficacy given that pulmonary shunt is mainly responsible for impairment of oxygenation (Benator et al. 1973). The open lung concept, which aims to open the alveoli and keep them open, has been promisingly implemented in equine mechanical ventilation using stepwise alveolar recruitment manoeuvres (ARM) (Levionnois et al. 2006; Wettstein et al. 2006; Ambrosio et al. 2013; Hopster et al. 2016; Ambrisko et al. 2017; Andrade et al. 2019; Andrade et al. 2022).

Inhaled salbutamol (albuterol) (2 μg kg^{-1}) has most commonly been used with satisfactory results in anaesthetized horses (Robertson & Bailey 2002; Patschova et al. 2010; Casoni et al. 2014; Clark-Price et al. 2022; Dupont et al. 2022). The exact mechanism of action remains elusive, but it has been hypothesized that salbutamol can increase arterial partial pressure of oxygen (PaO_2) by affecting respiratory mechanics and/or haemodynamics. β_2-Adrenergic agonists have well-known bronchodilatory properties, and as such salbutamol has been reported to improve dynamic compliance (C_{dyn}) (Robertson & Bailey 2002; Dupont et al. 2022). In addition, the positive effect of salbutamol on oxygenation has been attributed to an increase in cardiac output (CO) and lung perfusion, and therefore a favourable impact on ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch (Patschova et al. 2010; Clark-Price et al. 2022).

The present study explored the underlying changes in respiratory mechanics and haemodynamics in hypoxaemic horses whose PaO_2 increased following salbutamol inhalation. Moreover, the potential impact of demographic data and intraoperative variables on the response to salbutamol was investigated. We hypothesized that aerosolized salbutamol would affect C_{dyn}, $\dot{V}/\dot{Q}$ mismatch or both in horses that responded positively.

Material and methods

All the anaesthetic records of horses anaesthetized at the Equine Hospital of the Faculty of Veterinary Medicine of the University of Liege between March 2014 and October 2020 were reviewed. By signing the admission form, owners gave written informed consent for the collection of data from their horses and its publication in an anonymized format.

Data recorded included demographic data; preanaesthetic assessment and blood work; concurrent diseases and medication; American Society of Anesthesiologists (ASA) status; procedure performed; identity of the anaesthetist and surgeon; duration of anaesthesia and surgery; details about intubation and vascular accesses; drugs, fluids and gases administered; recumbency and details about recovery and postoperative care. Continuous intraoperative monitoring consisted of invasive arterial blood pressure, pulse oximetry, electrocardiogram, capnography, inspired and expired percentages of oxygen and isoflurane, airway pressure and flow-volume loops (Solomon; Vetronics, UK). For invasive arterial blood pressure measurement, the transducer was zeroed to atmospheric pressure at the level of the shoulder joint in dorsal recumbency, and at the level of the sternum in lateral recumbency. Intraoperative variables [peripheral oxygen

saturation, heart rate (HR), systolic, mean and diastolic arterial pressure (SAP, MAP, DAP), end-tidal partial pressure of carbon dioxide ($P_{E'}CO_2$), respiratory rate (f_R), tidal volume (V_T), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), pulse quality, mucous membrane colour, capillary refill time, ocular reflexes, body temperature] were manually recorded every 5 minutes. Intraoperative 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; GEM 5000; Werfen, Belgium; GEM 3500; Werfen, Belgium). Arterial blood was collected on calcium-balanced heparin lithium (Monovette 2 mL; Sarstedt, Germany) through the arterial catheter, after discarding 1 mL of blood. Air bubbles were quickly removed, the sample was gently mixed by rolling the syringe between palms, and the analysis was performed within 5 minutes after sampling. Different co-oximeters were used for reasons unrelated to their performances (contractual obligation). Samples from the same horse were consistently analysed with the same co-oximeter.

Cases that met the following criteria were included: (1) 6 months of age or greater, (2) body weight (BW) > 100 kg, (3) to be mechanically ventilated within 10 minutes of anaesthetic induction and (4) to be treated with salbutamol when PaO_2 < 100 mmHg (13.3 kPa) at any time during the anaesthetic period. Horses that received an ARM before salbutamol administration, were treated with atropine, norepinephrine or an infusion of an α_2-adrenoceptor agonist before salbutamol administration or before a blood gas measurement following salbutamol administration were excluded from analysis.

Every time arterial blood gas measurement was performed, and whenever all the required data were available, C_{dyn} relative to BW [C_{dyn}(BW)], the estimated ratio of dead space to tidal volume (est.V_D/V_T) and estimated shunt fraction (F-shunt) were manually calculated from variables obtained over a single breath, using the following formulae:

$C_{dyn}\ (BW) = \frac{[VT/(PIP-PEEP)]}{BW}$ (Dupont et al. 2022)

Where BW, body weight (kg); C_{dyn}(BW), dynamic compliance relative to BW (mL $cmH_2O^{-1}\,kg^{-1}$); PEEP, positive end-expiratory pressure (cmH_2O); PIP, peak inspiratory pressure (cmH_2O); V_T, tidal volume (mL).

$st.V_D/V_T = (PaCO2 - PE'\,CO2)/PaCO2$ (Mosing et al. 2018)

where $PaCO_2$, arterial partial pressure of carbon dioxide (mmHg); $P_E{\acute{}}CO_2$, end-tidal partial pressure of carbon dioxide (mmHg); est.V_D/V_T, estimated ratio of dead space to tidal volume.

$\text{F-shunt} = \frac{1.36*Hba*(1-SaO2)+0.0031*(PAO2-PaO2)}{[1.36*Hba*(1-SaO2)+0.0031*(PAO2-PaO2)]+3.5} * 100$ (Araos et al. 2012)

where F-shunt, estimated shunt fraction (%); Hba, arterial haemoglobin concentration (g dL^{-1}); P_AO_2, alveolar partial pressure of oxygen (mmHg) and PaO_2, arterial partial pressure of oxygen (mmHg); SaO_2, arterial haemoglobin oxygen saturation (%).

Statistical analysis

All analyses were performed using MedCalc for Windows, version 20.027 (MedCalc Software, Belgium). Variables were summarized as frequency for categorical variables; the mean ± standard deviation (SD) for continuous, normally distributed variables; or the median (range) for skewed data. Horses were divided between responders (R),

where PaO_2 after nebulizing salbutamol ≥ 1.2 PaO_2 before treatment (i.e. ≥20% increase), and non-responders (NR), where PaO_2 after nebulizing salbutamol < 1.2 PaO_2 before treatment.

First, ASA status, type of surgical procedure (colic or caesarean section surgeries *versus* all the other procedures), recumbency, sex, body conformation, BW, age, time from induction to the first arterial blood gas measurement that revealed PaO_2 < 100 mmHg (13.3 kPa), intraoperative variables (f_R, V_T, PIP, PEEP, HR, SAP, MAP, DAP, PaO_2), C_{dyn}(BW), arterial to end-tidal carbon dioxide difference [$P(a\text{-}E')CO_2$], est.V_D/V_T, F-shunt and dobutamine requirements were compared between R and NR to determine whether they were equal before salbutamol administration.

Next, the effect of aerosolized salbutamol on C_{dyn}(BW) was evaluated by comparing C_{dyn}(BW) before and after treatment within R and NR. The difference between C_{dyn}(BW) after and C_{dyn}(BW) before ([Δ C_{dyn}(BW)] was calculated. Δ C_{dyn}(BW) were compared between R and NR.

Then, the same analyses were repeated for $P(a\text{-}E')CO_2$, est.V_D/V_T, F-shunt, HR, SAP, MAP, DAP and infusion rates of dobutamine.

Finally, the distribution of boli and infusions of anaesthetics administered on top of isoflurane during maintenance was compared between R and NR.

The normality of data distribution was evaluated using Shapiro-Wilk test. Chi-square test was used to compare categorical data. Skewed independent data were compared using Mann-Whitney U test. For normally distributed independent data, homogeneity of variance was tested using Fisher's F-test and data were subsequently compared using Student's t-test or Welch test as appropriate. Skewed dependent data

were compared using Wilcoxon signed-rank test. Normally distributed dependent data were compared using paired Student's t-test. *p*-values of < 0.05 were considered statistically significant.

Results

Study population

A total of 102 horses treated with salbutamol during general anaesthesia were identified, 73 animals met the inclusion criteria, while 29 cases were excluded. Of the 73 horses included in the study, 34 horses underwent elective procedures (10 ASA I, 21 ASA II and three ASA III) and 39 horses were anaesthetized for emergency procedures (one ASA II E, 11 ASA III E, 20 ASA IV E and seven ASA V E). Details of the procedures are shown in Fig. 1. Recumbency, sex and body conformation type (Mansel & Clutton 2008) are presented in Table 1. Their median (range) BW was 536 (170-914) kg and their mean ± SD age was 149 ± 81 months.

Anaesthetic management

Premedication consisted of a combination of acepromazine [administered intramuscularly (IM) (0.1 mg kg^{-1}) or intravenously (IV) (0.05 mg kg^{-1}); Placivet; Kela, Belgium] and xylazine (0.6 mg kg^{-1} IV; Proxylaz; Prodivet Pharmaceuticals, Belgium), except for horses anaesthetized for colic and caesarean section surgeries that only received xylazine (0.4 to 0.6 mg kg^{-1} IV). Flunixin meglumine (1.1 mg kg^{-1} IV; Emdofluxin; Emdoka, Belgium) was administered before each procedure, except for orthopaedic cases that received phenylbutazone (2.2 mg kg^{-1} IV; Fenylbutazon; VMD, Belgium). 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).

Maintenance of anaesthesia consisted of isoflurane (IsoFlo; Zoetis, Belgium) delivered either in 100% oxygen or in a mixture of oxygen and medical air (F_IO_2 38 to 97%). Apart from isoflurane, ketamine boli (0.14 to 0.89 mg kg^{-1} IV) were administered in 40 horses, xylazine boli (0.06 to 0.38 mg kg^{-1} IV) in 32 horses, morphine (Morphine HCl Sterop; Sterop, Belgium) boli (0.09 to 0.15 mg kg^{-1} IV) in 17 horses, midazolam boli (0.03 to 0.04 mg kg^{-1} IV) in two horses, detomidine (Domidine; Dechra, Netherlands) boli (3.5 to 6.2 µg kg^{-1} IV) in two horses, lidocaine (Xylocaine; AstraZeneca, Belgium) boli (0.76 to 1.3 mg kg^{-1} IV) in two horses, ketamine infusions (0.6 to 1 mg kg^{-1} $hour^{-1}$ IV) in 15 horses, midazolam infusions (0.02 mg kg^{-1} $hour^{-1}$ IV) in 13 horses and lidocaine infusions (2.8 to 3 mg kg^{-1} $hour^{-1}$ IV) in 2 horses (Table 2). The distribution of boli and infusions administered on top of isoflurane during maintenance was similar between R and NR. Lactated Ringer's solution was infused (5 to 20 mL kg^{-1} $hour^{-1}$) and hypotension was treated with dobutamine (Dobutrexmylan; Mylan, Belgium) (0.1-2 µg kg^{-1} $minute^{-1}$) to maintain MAP > 60 mmHg.

Volume-controlled ventilation (VCV) was provided from the beginning of anaesthesia (Tafonius; Vetronics, UK). Ventilator settings (f_R, V_T, PEEP, inspiratory-to-expiratory time ratio) were adjusted to best match each horse's needs.

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 2 µg kg^{-1} was administered to the horses rounded to the nearest 50 kg.

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) was 40 (8-192) minutes. Ventilatory and haemodynamic variables immediately prior to this initial arterial blood gas measurement were as follows: f_R 8 (6-16) breaths minute^{-1}, V_T 10.1 (7.4-16.0) mL kg^{-1}, PIP 24 (12-55) cmH_2O, PEEP 0 (0-11) cmH_2O, C_{dyn}(BW) 0.44 (0.17-1.02) mL cmH_2O^{-1} kg^{-1}, F_IO_2 77 (38-97) %, HR 42 (20-98) beats minute^{-1}, SAP 101 ± 22 mmHg, MAP 78 ± 19 mmHg, DAP 65 ± 19 mmHg and dobutamine requirements 0.2 (0-2.0) µg kg^{-1} minute^{-1}. Initial blood gas revealed PaO_2 71 ± 15 mmHg and allowed for calculation of F-shunt 41 ± 10 %, $P(a\text{-}E')CO_2$ 14 (-3-47) mmHg and est.V_D/V_T 0.26 ± 0.10.

Treatment success

A total of 50 horses were classified as R while 23 horses were classified as NR. Demographic data and initial intraoperative variables were not statistically different between R and NR before salbutamol administration except for body weight [R: 531 (170-715) kg, NR: 540 (420-914) kg] (p = 0.0453) (Tables 3 & 4).

Effect of salbutamol inhalation

Aerosolized salbutamol did not significantly affect C_{dyn}(BW) in R (p = 0.6481) or in NR horses (p = 0.7406) [Fig. 2(a) & Table 3]. In addition, Δ C_{dyn}(BW) was not significantly different in R than in NR.

Nebulized salbutamol significantly altered P(a-E´)CO_2 (p = 0.0034), est.V_D/V_T (p = 0.0005) and F-shunt (p < 0.0001) in R only [Fig. 2(b, c, d) & Table 3]. ΔP(a-E´)CO_2 was significantly larger in R (difference of -17.8%) than in NR (difference of 11.5%) (p = 0.0142). Furthermore, ΔV_D/V_T was significantly larger in R (difference of -19.0%) than in NR (difference of 6.6%) (p = 0.0182). Moreover, ΔF-shunt was significantly larger in R (difference of -24.1%) than in NR (difference of -0.3%) (p < 0.0001).

Inhaled salbutamol did not significantly affect HR, SAP or dobutamine requirements in either group. MAP significantly increased in R (difference of 10.4%) only (p = 0.0227) while DAP significantly increased in both R (difference of 12.4%) (p = 0.0177) and NR (difference of 12.1%) (p = 0.0359) (Table 3). However, there was no significant difference in ΔHR, Δ SAP, ΔMAP, Δ DAP or Δ dobutamine between groups R and NR.

Discussion

This study showed that salbutamol was successful in increasing PaO_2 by at least 20% (PaO_2 after treatment ≥ 1.2 PaO_2 before treatment) in 68% (50/73) of the horses with PaO_2 < 100 mmHg (13.3 kPa) at any time during the anaesthetic period. Out of these, P(a-E´)CO_2, est.V_D/V_T and F-shunt decreased while C_{dyn}(BW) remained unchanged.

Pulmonary shunt is mainly responsible for impaired oxygenation during equine anaesthesia, and this was probably the case in the present study as F-shunt was 41 ± 10 %, which exceeded the expected value of 19 and 33% for laterally and dorsally recumbent horses, respectively (Nyman & Hedenstierna 1989; Nyman et al. 1990). F-shunt is a content-based index which is a better estimate of venous admixture than

238 tension-based indices (Wandrup 1995; Araos et al. 2012; Briganti et al. 2015). The
239 improvement of F-shunt following salbutamol administration in R only suggests its
240 efficacy in improving oxygenation by reducing venous admixture, as already proposed
241 by Dupont et al. (2022).

242 The rationale behind using both $P(a\text{-}E')CO_2$ and $est.V_D/V_T$ to assess dead space
243 in our study was the assumption that those indices do not encompass exactly the same
244 components. Indeed, while $P(a\text{-}E')CO_2$ is supposed to approximate physiological
245 Enghoff's dead space (V_D Enghoff), $est.V_D/V_T$ only estimates alveolar V_D Enghoff.
246 Comparing $P(a\text{-}E')CO_2$ and $est.V_D/V_T$ might have highlighted changes in anatomical
247 dead space secondary to bronchodilation caused by salbutamol (Derksen et al. 1999;
248 Robertson & Bailey 2002; Dupont et al. 2022). $est.V_D/V_T$ is obtained by substituting
249 mixed-expired partial pressure of carbon dioxide ($P\bar{E}CO_2$) by $PE'CO_2$ in V_D Enghoff's
250 equation $[(PaCO2 - P\bar{E}CO2)/PaCO2]$. Enghoff's approach is used as a surrogate of the
251 true physiological dead space measurement proposed by Bohr (V_D Bohr), replacing
252 alveolar partial pressure of carbon dioxide ($PACO_2$) by $PaCO_2$ in Bohr's V_D equation
253 $[(PACO2 - P\bar{E}CO2)/PACO2]$. By doing so, V_D Enghoff integrates lung atelectasis and
254 venous admixture, and, consequently, overestimates V_D Bohr in the case of pulmonary
255 perfusion abnormalities. Moreover, Mosing et al. (2018) showed that both $P(a\text{-}E')CO_2$
256 and $est.V_D/V_T$ are closely associated with the alveolar part of Enghoff's V_D and are
257 therefore influenced by venous admixture and factors affecting lung perfusion, such as
258 CO and pulmonary pressure. They concluded that neither $P(a\text{-}E')CO_2$ nor $est.V_D/V_T$
259 should be regarded as indicators of V_D Bohr but rather as global indices of $\dot{V}/\dot{Q}$
260 mismatch. In our study, the highest values for $P(a\text{-}E')CO_2$ and $est.V_D/V_T$ were observed
261 in the horse with the highest value for F-shunt. In light of these results, the authors

probably failed to assess dead space, and changes in $P(a\text{-}E')CO_2$ and est.V_D/V_T observed after salbutamol inhalation in R only are most likely the consequence of changes in F-shunt.

The β_2-adrenergic agonists constitute the cornerstone of asthma and chronic obstructive pulmonary disease therapy in humans (Billington et al. 2017). Salbutamol is a relatively selective β_2-adrenergic agonist (27 times more selective for β_2 subtype than for β_1 subtype) that has demonstrated potent bronchodilatory activity (Price & Clissold 1989; Billington et al. 2017). The β_2-adrenergic receptor is the predominantly subtype of β-adrenergic receptors present in the equine upper airway (Törneke et al. 1999) and aerosolized salbutamol has proven to effectively relieve bronchospasm in horses suffering from recurrent airway obstruction (Derksen et al. 1999).

In accordance with results published by Patschova et al. (2010), no change in C_{dyn} was observed after salbutamol aerosolization. This in contrast with Dupont et al. (2022) who reported a significant change in C_{dyn} following salbutamol nebulization. Both studies used absolute C_{dyn} while we calculated C_{dyn}(BW). Patschova et al. (2010) used a small number of experimental horses with similar BW while Dupont et al. (2022) included a larger number of horses with a wider range of BW. Because Olsson & Lindahl (1985) showed that C_{dyn} is directly proportional to BW, and because BW was significantly different between R and NR, the authors felt that it would be more appropriate to calculate C_{dyn}(BW). The absence of any change in C_{dyn}(BW) might have been due to the near maximal bronchodilation already achieved with isoflurane (Watney et al. 1987), making additional bronchial muscle relaxation from salbutamol unnoticeable. C_{dyn}(BW) is influenced by body condition score and thoracic shape in dogs (Asorey et al. 2020; García-Sanz et al 2020). Nevertheless, the retrospective nature

of the study prevented the authors from evaluating the potential impact of these variables on the response to salbutamol.

Increasing BW represents a risk for developing severe hypoxaemia (Marchese et al. 2022). As the difference in BW between R and NR reached significance, heavier horses might be less likely to increase their PaO_2 after salbutamol nebulization based on these results.

Though the number of horses anaesthetized at our institution is approximately evenly divided between lateral and dorsal recumbency, most of the horses included in this study were positioned in dorsal recumbency. This observation is inherently related to the inclusion criteria [i.e. PaO_2 < 100 mmHg (13.3 kPa)] as lower PaO_2 is a more frequent occurrence in horses anaesthetized in dorsal recumbency (Whitehair & Willits 1999).

Following systemic uptake, inhaled salbutamol has been shown to shift the autonomic nervous system balance towards sympathetic activation by acting on β-adrenergic receptors located extrabronchially, therefore causing an increase in CO (Cekici et al. 2009; Snyder et al 2011). While the favourable impact of aerosolized salbutamol on oxygenation has been attributed to an increase in CO and pulmonary perfusion by some authors (Patschova et al. 2010; Clark-Price et al. 2022), no change in HR, in blood pressure or in dobutamine requirements were noticed in other studies (Robertson & Bailey 2002; Dupont et al. 2022). Although MAP and DAP increased after salbutamol administration in our study, the magnitude of change was similar between R and NR. Moreover, no change in HR, SAP or dobutamine requirements

were observed. Yet, our sample size might have been too small to detect subtle changes in haemodynamic variables.

Large individual variations of the density of β_2-adrenergic receptors exist both in the heart and in the airway among the equine population (Törneke et al. 1999), which may be responsible for treatment failure.

Treatment success has been arbitrarily defined and is not supported by scientific evidence but rather based on clinical impression and experience. To the best of the authors' knowledge, there are very few studies that quantify the effectiveness of the treatment of hypoxaemia in terms of success rate. A recent study comparing salbutamol and continuous positive airway pressure (Dupont et al. 2022) recruited horses with PaO_2 < 100 mmHg (13.3 kPa) and considered the treatment as successful if $PaO_2 \geq 100$ mmHg (13.3 kPa). However, this was judged inappropriate by the authors because going from 99 (13.2) to 100 (13.3) mmHg (kPa) would have been rated as successful but going from 60 (8.0) to 72 (9.6) mmHg (kPa) (ratio of 1.2) would not. Moreover, classifying a horse with a PaO_2 < 100 mmHg (13.3 kPa) after treatment as a NR might have been too severe. Indeed, using the threshold of 100 mmHg would have led to categorize a horse with PaO_2 going from 40 (5.3) to 99 (13.2) mmHg (kPa) (ratio of 2.5) as a NR despite the tremendous increase.

This study has several limitations. First, the anaesthetic management was not standardized among horses and anaesthetists, which is inherent in its retrospective nature. Although ventilatory variables immediately prior to the initial arterial blood gas revealed that PaO_2 < 100 mmHg (13.3 kPa) were similar between R and NR, the wide range of FIO_2, and to a lesser extent of V_T, might have affected PaO_2 and, consequently,

the results of this study. While there were no significant differences in the distribution of boli and infusions of anaesthetics administered in addition to isoflurane between R and NR, the variation in anaesthetic protocols further complicates the ability to isolate the effect of salbutamol on PaO_2. Second, using the cut-off value of 1.2 led to some horses being classified as R while still hypoxaemic. However, treating severe hypoxaemia rarely relies on a single intervention, and combining salbutamol with continuous positive airway pressure manoeuvres might be beneficial (Dupont et al. 2022). Third, in a prospective study, static compliance (C_{st}) could have been used instead of C_{dyn}(BW). C_{st} relies on plateau pressure, which is obtained in the absence of gas flow, by applying an inspiratory hold. C_{st} is only affected by lung and chest wall compliance. Conversely, C_{dyn}(BW) relies on PIP, which is measured in the presence of gas flow and is therefore also dependent on the resistive components of the respiratory system and, consequently, subject to variation. Mean PIP values obtained over several breaths should have been preferred. Nevertheless, VCV was applied, and lung conditions were expected to be stable between breaths. Hence, C_{dyn}(BW) calculated over one breath is an acceptable alternative. At our institution annual servicing and the automatic leak and compliance testing are routinely performed before using the Tafonius. In addition to those tests equipment calibration prior to compliance calculations should have been performed to guarantee the reliability of the results in the context of a prospective ventilatory mechanic's study. Fourth, though different co-oximeters were used, the same device was used throughout anaesthesia of an individual horse. Lastly, CO measurement was not performed. Indeed, the beneficial effect of salbutamol on oxygenation is, at least partially, related to its favourable impact on haemodynamics and lung perfusion (Patschova et al. 2010), and changes in CO are

known to affect $P(a\text{-}E')CO_2$ (Whaba et al. 1996). Because CO is a product of HR and stroke volume, and because no change in HR was observed, further studies should be conducted to measure CO following inhalation of salbutamol in clinical cases suffering from impaired oxygenation.

Conclusions

This retrospective study showed that inhaled salbutamol was effective in improving PaO_2 but not C_{dyn}(BW) in 68% of these cases when administered to anaesthetized horses with a PaO_2 < 100 mmHg (13.3 kPa).

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Table 1. Recumbency, sex and body conformation type of the 73 horses included in the study.

	Emergency procedures		Elective procedures	
	Colic or C-section	Other surgery	Colic or C-section	Other surgery
Recumbency				
- Dorsal	38	1	3	22
- Left lateral	0	0	0	5
- Right lateral	0	0	0	4
Sex				
- Stallions	6	0	0	14
- Geldings	15	0	1	10
- Mares	17	1	2	7
Body conformation				
- Warmblood	15	0	3	11
- Thoroughbred	1	0	0	0
- Draft	3	0	0	4
- Pony	3	0	0	2
- Miscellaneous	16	1	0	14

C-section, caesarean section.

Table 2. Distribution of boli and infusions of drugs administered to 73 horses during anaesthesia maintained with isoflurane in oxygen, no significant differences were observed between groups. Salbutamol was administered to all horses during anaesthesia and 50 horses were responders (R) and 23 were non-responders (NR) based on an increase in PaO_2 of 20%.

	R (*n* = 50)	NR (*n* = 23)
Ketamine bolus	29	11
Xylazine bolus	22	10
Morphine bolus	11	6
Midazolam bolus	2	0
Detomidine bolus	1	1
Lidocaine bolus	2	0
Ketamine infusion	11	4
Midazolam infusion	9	4
Lidocaine infusion	2	0

Table 3. Physiological variables measured before and after salbutamol administration to 73 horses, 50 responders (R) and 23 non-responders (NR). Data are shown as median (range) or mean ± standard deviation.

	R (n = 50)		NR (n = 23)	
	Before	After	Before	After
f_R (breaths minute^{-1})	8 (6-16)	8 (5-12)	8 (6-12)	8 (6-12)
VT (mL kg^{-1})	10.1 (7.4-16.0)	10.4 (8.6-16.0)	10 (8.5-13.8)	10 (8.5-15.2)
PIP (cmH_2O)	24 (12-55)	24 (14-57)	24 (17-42)	25 (19-41)
PEEP (cmH_2O)	0 (0-11)	0 (0-9)	0 (0-2)	0 (0-3)
C_{dyn}(BW) (mL cmH_2O^{-1} kg^{-1})	0.50 ± 0.18	0.48 (0.18-1.43)	0.44 ± 0.13	0.43 ± 0.10
FIO_2 (%)	81 (38-97)	83 (63-97)	75 ± 9	74 ± 10
HR (beats minute^{-1})	43 (20-98)	42 (25-127)	42 (29-73)	40 (29-73)
SAP (mmHg)	100 ± 23	105 (85-173)	105 ± 20	110 ± 15
MAP (mmHg)	76 ± 19	84 ± 10	83 ± 19	89 ± 12
DAP (mmHg)	62 ± 19	68 ± 11	70 ± 18	77 ± 12
Dobutamine requirements (µg kg^{-1} minute^{-1})	0.25 (0-1.2)	0.4 (0-1.8)	0 (0-2)	0 (0-0.5)
PaO_2 (mmHg)	71 ± 16	117 (40-307)	72 ± 14	72 ± 13
PaO_2 (kPa)	9.5 ± 2.1	15.6 (5.3-40.9)	9.6 ± 1.9	9 .6 ± 1.7
F-shunt (%)	39 (26-86)	29 (19-77)	38 ± 5	38 ± 6

$P(a\text{-}E')CO_2$ (mmHg)	15 (1-47)	12 (-1-47)	13 ± 6	14 ± 4
est.V_D/V_T	0.27 ± 0.10	0.22 ± 0.10	0.24 ± 0.11	0.26 ± 0.07

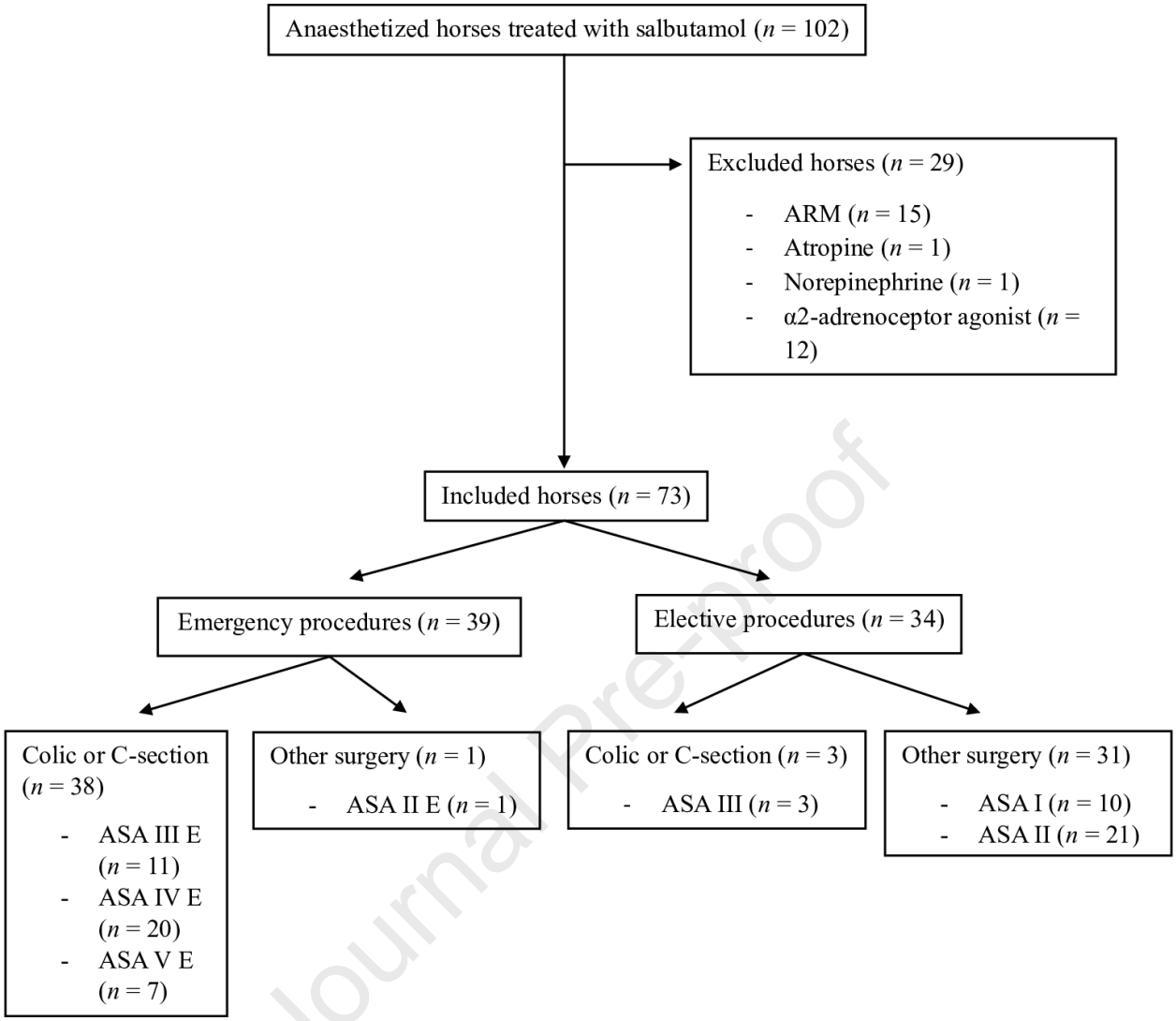
C_{dyn}(BW), dynamic compliance relative to body weight; DAP, diastolic arterial pressure; est.V_D/V_T, estimated ratio of dead space to tidal volume; FIO_2, inspired oxygen fraction; f_R, respiratory rate; F-shunt, estimated shunt fraction; HR, heart rate; MAP, mean arterial pressure; PaO_2, arterial partial pressure of oxygen; $P(a\text{-}E')CO_2$, arterial to end-tidal carbon dioxide difference; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; SAP, systolic arterial pressure; tidal volume (V_T).

Table 4. American Society of Anesthesiologists (ASA) status, type of surgical procedure, recumbency, sex, body conformation type, age, body weight and time from induction of anaesthesia of 73 horses, 50 responders (R) and 23 non-responders (NR), to inhaled salbutamol during isoflurane general anaesthesia. Data are shown as median (range) or mean ± standard deviation.

	R (*n* = 50)	NR (*n* = 23)
ASA status		
- I	8	2
- II	14	8
- III	10	4
- IV	12	8
- V	6	1
- E	26	13
Surgical procedure		
- Colic or C-section	28	13
- Other surgery	22	10
Recumbency		
- Dorsal	45	19
- Left lateral	4	1
- Right lateral	1	3
Sex		
- Stallions	12	8
- Geldings	18	8
- Mares	20	7

Body conformation		
- Warmblood	20	9
- Thoroughbred	0	1
- Draft	3	4
- Pony	3	2
- Miscellaneous	24	7
Age (months)	125 (18-346)	160 ± 75
Time from induction (minutes)	39 (8-192)	52 ± 22
Body weight (kg)	531 (170-715)	540 (420-914)

C-section, caesarean section.



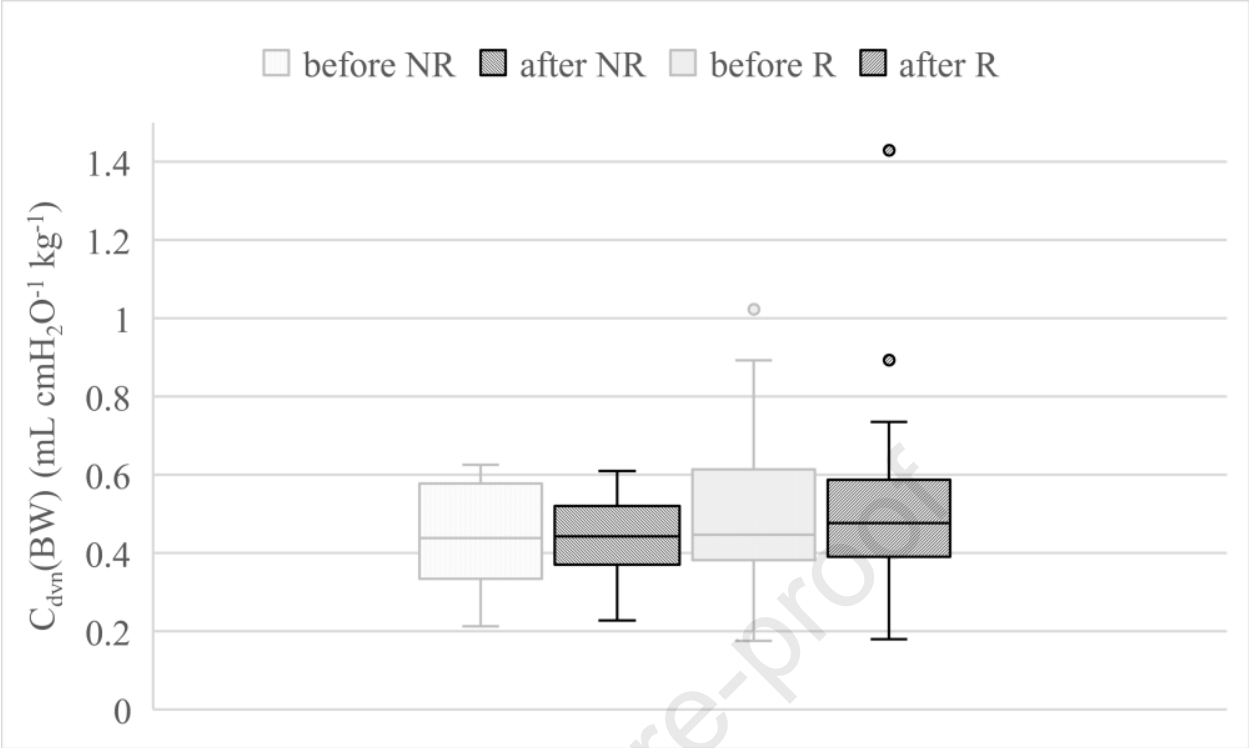


Figure 1 Flow diagram illustrating the recruitment of the 73 horses included in the study, their American Society of Anesthesiologists (ASA) status, and the type of surgical procedure. ARM, alveolar recruitment manoeuvre; C-section, caesarean section.

Figure 2 Box and whisker plots presenting the evolution of **(a)** the dynamic compliance relative to body weight [C_{dyn}(BW)], **(b)** the arterial to end-tidal carbon dioxide difference [$P(a\text{-}E')CO_2$], **(c)** the estimated ratio of dead space to tidal volume (est.V_D/V_T) and **(d)** the estimated shunt fraction (F-shunt) in hypoxaemic horses responsive (R) and non-responsive (NR) based on a ≥ 1.2 increase (i.e. ≥ 20% increase) in arterial partial pressure of oxygen after inhaled salbutamol.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: