



Impact of Aerosolised Salbutamol on Physiological Function During Equine Inhalation Anaesthesia

A Retrospective Review of Cardiovascular Function and Arterial Oxygen Saturation

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Abstract

Hypoxaemia is a common complication in equine general anaesthesia, primarily caused by ventilation-perfusion mismatch and atelectasis. While aerosolised salbutamol, a β_2 -adrenergic agonist, is widely used to improve oxygenation, its efficacy and impact on haemodynamic variables remain debated. This retrospective study aimed to evaluate clinical use of salbutamol in horses under general anaesthesia, focusing on its effect on cardiovascular parameters, indications, administration and to explore if salbutamol was effective at different degrees of hypoxemia based on baseline values of saturation.

Medical records from 33 cases receiving salbutamol during general inhalation anaesthesia at the SLU University Animal Hospital (UDS) met the inclusion criteria. Data collected included anaesthetic protocols, administered doses, and monitored heart rate (HR), systolic (SYS), diastolic (DIA) and mean arterial blood pressure (MAP) and saturation (SpO₂). Statistical analyses compared pre- and post-administration values using Friedman tests with Dunn's post hoc comparisons.

Salbutamol dosing, duration of parameter monitoring after drug administration and individual alterations in collected parameters varied widely. A significant improvement in SpO₂ was observed in mildly hypoxaemic horses (baseline SpO₂ 90-94%) at 10 and 15 minutes ($P < 0.0001$) post-administration, but not in severely hypoxaemic (SpO₂ <90%) or non-hypoxaemic (SpO₂ $\geq 95\%$) horses. No significant changes in HR or MAP were detected, contrasting with experimental studies in non-hypoxaemic horses.

In conclusion, salbutamol improved saturation in mildly hypoxaemic horses but showed inconsistent efficacy in severe hypoxaemia, with no significant cardiovascular effects observed in these cases. These results might indicate that the severity of hypoxaemia may influence salbutamol's effect on oxygenation and cardiovascular parameters. The greater impact in less severe hypoxaemic horses raises questions regarding the drug's optimal indication, suggesting it as a preventive measure rather than a rescue intervention when aiming to promote oxygenation. Future research should aim to determine salbutamol's mechanism of action, its effect in hypoxaemic clinical patients and haemodynamic variables and compare its efficacy with other oxygenation strategies. If the desired effect is achieved, salbutamol might be a cost-effective and practical technique promoting a safe general anaesthesia for the patient. However, clinicians should take careful consideration when electing salbutamol for treatment and be prepared to adjust the treatment strategy depending on individual patient response.

Keywords: β_2 -adrenergic agonist, cardiovascular parameters, heart rate, horses, hypoxaemia, inhalation anaesthesia, mean arterial blood pressure, saturation

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Abbreviations

Abbreviation	Description
ABP	Arterial blood pressure
ARM	Alveolar recruitment manoeuvre
PiNO	Pulsed inhaled nitrous oxide
BPM	Beats per minute
CO	Cardiac output
CRI	Constant rate infusion
ECG	Electrocardiography
FiO ₂	Fraction of inspired oxygen
HR	Heart rate
IPPV	Intermittent positive pressure ventilation
IVFT	Intravenous fluid therapy
MAP	Mean arterial blood pressure
MDI	Microdose inhaler
PaO ₂	Partial arterial oxygen pressure
PEEP	Positive end expiratory pressure
PIP	Peak inspiratory pressure
RAO	Recurrent airway disease
TIVA	Total intravenous anaesthesia
UDS	SLU University Animal Hospital
V/Q mismatch	Ventilation-perfusion mismatch

1. Introduction

The administration of general anaesthesia in the equine patient is widely regarded as particularly challenging, potentially displaying more complications than those encountered in any other domestic animal, stated by Clarke et al. (2014). The same authors further describe cardiopulmonary dysfunctions as common and challenging to avoid. Hypoxaemia is a recognised complication, due to anaesthetically induced lung atelectasis and pulmonary shunt (Nyman et al. 1990). No ideal treatment technique exists, nevertheless administration of salbutamol aerosol during general anaesthesia to improve oxygenation is common, despite demonstrated varying efficacy, adverse cardiovascular effects and unknown mechanism of action (Patschova et al. 2010; Casoni et al. 2014).

1.1 Hypoxaemia in the equine patient

Hypoxemia, is a risk factor regarding equine perianaesthetic mortality and its effect on the brain, cardiopulmonary systems, muscles, wound healing and surgical site infections may be responsible (Auckburally & Nyman 2017). Hypoxaemia are defined as a partial arterial oxygen pressure (PaO_2) $<60\text{mmHg}$ (Auckburally & Nyman 2017; Reed 2022) or saturation (SpO_2) $<95\%$ and severe cases $<90\%$ (Grubb et al. 2020). Reed (2022) identifies five basic causes of hypoxaemia: ventilation-perfusion mismatch (V/Q mismatch), shunt, hypoventilation, diffusion impairment and low inspired oxygen.

Among these ventilation-perfusion mismatch is considered the primary cause according to Nyman and Hedenstierna (1989). The alveolar-arterial oxygen tension difference develops rapidly after induction and tends to be more or less constant (Clarke et al. 2014). This indicates perfusion of relatively under ventilated lung regions, whereas a shunt represents the most severe form of ventilation-perfusion mismatch. In a shunt, blood enters the left side of the heart without participating in gas exchange, as it perfuses entirely unventilated regions of the lung (Nyman & Hedenstierna 1989; Reed 2022). Clarke et al. (2014) emphasise that this venous-arterial shunt promotes marked arterial hypoxemia.

The ventilation-perfusion mismatch is primarily caused by atelectasis of dependent lung regions (Nyman et al. 1990). Magnusson and Spahn (2003) describes three mechanisms leading to atelectasis, with compression atelectasis, caused by pressure-induced collapse of the alveoli, as the determined primary cause. Absorption atelectasis occurs as more gas is absorbed into the blood than that entering alveoli, and loss of surfactant resulting in an alteration in alveolar distension (Magnusson & Spahn 2003). The equine anatomy has an athletic adaption beneficial for ventilation and perfusion when standing, however to a

disadvantage when in dorsal recumbency as the lung is more prone to compression (Hedenstierna et al. 2005) and leads to large areas of alveolar atelectasis (Auckburally & Nyman 2017). The right-to-left pulmonary shunt increases significantly (Nyman et al. 2012) from 1% in the standing horses to an estimated 33% in horses positioned in dorsal recumbency (Nyman & Hedenstierna 1989).

1.2 Other treatment options for hypoxaemia

Treatment of hypoxaemia can be done through ventilatory measures, such as mechanical ventilation, increasing the inspired oxygen concentration or administration of either drugs or other gases (Auckburally & Nyman 2017). However, increasing fraction of inspired oxygen (FiO_2) is not always effective (K.W. Clarke et al. 2014b; Auckburally & Nyman 2017; Reed 2022). This is particularly true when shunting is present as atelectasis is the predominant cause of ventilation-perfusion mismatch. Hence, no shunted blood comes in contact with the oxygen in the alveoli, leading to a minimal response to oxygen supplementation (Nyman & Hedenstierna 1989). In addition, Dugdale et al. (2020) note that the administered fresh gas might already be pure oxygen, making an increase impossible. The same author further raises caution against using high oxygen concentrations as this can exacerbate absorption atelectasis. Auckburally and Nyman (2017) however mentions no advantages in decreasing FiO_2 partway through anaesthesia. This is based on a study by Hubbell et al. (2011) of mechanically ventilated horses in dorsal recumbency receiving FiO_2 of 0.5 instead of >0.95 , where no change in shunt fraction or alveolar dead space ventilation was observed.

Mechanical ventilation strategies may successfully treat hypoxemia during anaesthesia (Auckburally & Nyman 2017). Early onset of mechanical ventilation benefits oxygenation, as it is more effective in maintaining arterial oxygen pressure rather than reinflating a substantial amount of collapsed alveoli to again participate in gas exchange (Moens 2013; Reed 2022). Although intermittent positive pressure ventilation (IPPV) controls hypercapnia relatively well, the effect on oxygenation is unpredictable according to Moens (2013). This is a possible result of over-ventilation of the already expanded alveoli (Clarke et al. 2014). In addition to an incapacity to inverse atelectasis, using IPPV may also worsen pulmonary shunt and hypoxaemia as it increases intrathoracic pressure and thereby forces more pulmonary blood into regions with atelectasis (Moens 2013). The venous return is also decreased, meaning a reduced cardiac output and further reduced pulmonary perfusion (Hodgson et al. 1986).

Utilising positive end expiratory pressure (PEEP) to improve low PaO_2 can prevent alveolar collapse and thereby promote oxygenation. However the

challenges with mechanical ventilation remains (Moens 2013). Moens (2013) describes the evidence of its efficacy in limiting the PaO₂ decrease in horses as limited but convincing. However, the supporting evidence in human studies and other animal species is more extensive. A significantly enhanced oxygenation has been demonstrated when using IPPV with modest PEEP compared to not using PEEP, thus early IPPV with moderate PEEP can represent a beneficial strategy in optimising gas exchange in haemodynamically stable horses as concluded by Moens (2023). The "Open lung concept" is a newer ventilatory strategy aiming to actively opening up collapsed alveoli and keep them open (Dupont et al. 2022). This is achieved by initially applying a high peak inspiratory pressure (PIP) to reinflate the alveoli, also called an alveolar recruitment manoeuvre (ARM) followed by sustained PEEP to prevent recollapse (Moens 2013; Dupont et al. 2022). However, the higher intra-thoracic pressures required to re-inflate collapsed alveoli and maintain them long enough to significantly improve PaO₂ is challenging (Auckburally 2021).

Administering pulsed inhaled nitrous oxide (PiNO) to anaesthetised equine patients has been shown to successfully improve PaO₂ levels, with benefits extending into the recovery period (Clarke et al. 2014). Auckburally (2021) has proved the assumed redistribution in pulmonary perfusion through regional vasodilation, hence the blood flow shifts from atelectatic to ventilated lung areas, thereby significantly improving V/Q mismatch. Furthermore, PiNO may be beneficial for oxygenation in both spontaneously breathing and mechanically ventilated patients, given that the blood pressure and cardiac output are maintained during mechanical ventilation.

Clenbuterol is a β_2 agonist used for bronchodilation, however it is known to cause both positive inotropic and chronotropic effects as stated by Dugdale et al. (2020). The same author describes the occurrence of tachycardia as a result of vasodilation and direct effects on Cardiac β_2 receptors. Nevertheless, this increases the myocardial oxygen demand (Dugdale et al. 2020) and can explain the following fall in PaO₂ seen in some cases (Clarke et al. 2014). Clenbuterol also causes sweating, lacrimation, lightening of the anaesthetic plane and muscle tremors (Dugdale et al. 2020). Lee et al. (1998) observed no PaO₂ improvement in the experimental study of intravenously administered clenbuterol to horses during inhalation anaesthesia. However, tachycardia, elevated cardiac output, increased muscle perfusion, sweating and increased oxygen consumption occurred. Dodam et al. (1993) demonstrated an increased shunt fraction and enhanced hypoxaemia in horses under total intravenous anaesthesia (TIVA) and Clarke et al. (2014) discourage the use of clenbuterol due to too many side effects.

1.3 Salbutamol

Salbutamol is a selective β_2 -adrenergic receptor agonist used in human medicine to treat acute bronchospasm caused by asthma and symptomatic relief is achieved due to its potent smooth muscle relaxant properties (Marques & Vale 2022). This also applies to treatment of Recurrent airway disease in horses (RAO) where salbutamol is widely used and considered safe and effective in improving pulmonary ventilation (Derksen et al. 1999). However, as Patschova et al. (2010) point out, the bronchodilatation in these patients is preceded by bronchoconstriction. No bronchodilation or ventilation improvement occurs in clinically normal horses (Rush et al. 1999). Dupont et al. (2024) describe salbutamol as the most commonly used β_2 -adrenergic agonist with an improving effect on oxygenation in equine patients under general anaesthesia (Robertson & Bailey 2002; Patschova et al. 2010; Casoni et al. 2014; K.W. Clarke et al. 2014b; Dupont et al. 2022).

Robertson and Bailey (2002) studied the effect of aerosolised salbutamol in hypoxaemic equine patients under general anaesthesia and showed almost doubled PaO_2 values post administration. Dupont et al. (2024) presented significantly higher PaO_2 values at both 15 and 30 minutes after salbutamol administration in arterial hypoxaemic anaesthetised horses. In a study comparing efficacy of single-breath continuous positive airway pressure manoeuvre and aerosolised salbutamol in hypoxemic anaesthetised horses concluded that both methods had comparable success rates in improving oxygenation and dynamic compliance. However salbutamol increased PaO_2 in a greater percentage and also significantly decreased estimated shunt fraction (Dupont et al. 2022). Patschova et al. (2010) demonstrated a significantly increased heart rate (HR), cardiac output (CO) and oxygen delivery without change in lung ventilation, compliance or amount of pulmonary shunt. Additionally, pulmonary arterial blood pressure was significantly lower in subjects receiving salbutamol. Patschova et al. (2010) conclude that the drug can contribute to positive effects on arterial oxygenation. Clark-Price et al. (2022) administered salbutamol in a controlled study to non-hypoxaemic anaesthetised horses via inhalation and demonstrated an association with increased PaO_2 compared to baseline values.

The exact mechanism by which salbutamol promotes oxygenation has not been determined (Patschova et al. 2010; Casoni et al. 2014; Dupont et al. 2022, 2024). β -adrenergic receptors are expressed in a variety of cell types and equine tracheal smooth muscle has been demonstrated by Törneke (1999) to primarily contain β_2 -adrenoceptors. The same study also suggested a small proportion of β_2 -adrenergic receptors in the equine myocardium, however the β_1 subtype was predominant. This perspective is partially supported by Horn et al. (2002), although their data suggest no evidence of a significant population of co-existing β_2 -adrenoceptors in the myocardium. Clarke et al. (2014) and Reed (2022) notes that salbutamol

exhibits agonistic effects on the β_1 -adrenergic receptor, nonetheless it is more selective for β_2 receptors, making bronchodilation its primary effect. The reported $\beta_2:\beta_1$ selectivity is 1375:1 (Johnson et al. 1993 see Robertson & Bailey 2002). Clarke et al. (2014) describes the studied results of salbutamol administration as variable, confirmed by Patschova et al. (2010) who describe the individual variations in effects as large. Casoni et al. (2014) define the large inter individual variation in response to β -adrenoreceptors in vivo as well known. Törneke (1999) mentions a great individual variety in density of β_2 -adrenoceptors, not only in the airways, but also in the myocardium, something that might contribute to treatment failures (Dupont et al. 2022).

1.4 Speculations regarding the mechanism of salbutamol

The mechanism of action behind the effects is however discussed. Robertson and Bailey (2002) failed to determine the mechanism of action in their study on anaesthetised horses, however stated the possibility of salbutamol's bronchodilating effect opening bronchioles in perfused lung regions, thereby resulting in an improved partial pressure of arterial oxygen as this allows uptake of oxygen by blood in the mentioned areas. They further mentioned a possible increased perfusion, secondary to an elevated cardiac output. This is despite no measurements of either cardiac output or ventilation-perfusion relationships being made. However, a significant contribution of cardiovascular factors on the observed improvement in arterial oxygenation was concluded unlikely as no alterations in heart rate or mean arterial blood pressure (MAP) were observed (Robertson & Bailey 2002).

Dupont et al. (2022) could not detect clinically relevant effects on haemodynamic variables and heart rate remained unchanged when salbutamol aerosol was administered to hypoxaemic anaesthetised horses. Nevertheless, a significantly decreased estimated shunt fraction and improved dynamic compliance were seen, also supporting the hypothesis of salbutamol altering respiratory mechanics (Dupont et al. 2024).

Dugdale et al. (2020) states that the thought of bronchodilation and opening of bronchioles and alveoli as causes for the enhanced oxygenation is a more former thought, and that the β_2 agonists are now thought to act primarily by promoting vasodilation in areas with under perfused alveoli, thereby improving ventilation-perfusion matching.

Patschova et al. (2010) partly agree when discussing the results of their study in anaesthetised horses receiving salbutamol contributing to an increase of cardiac output and oxygen delivery without change in lung ventilation, compliance or amount of pulmonary shunt. They assume that salbutamol contributed to a

positive effect on haemodynamics and heart activity, resulting in an increased cardiac output. This increase would enhance lung perfusion and decrease pulmonary arterial blood pressure, suggesting a vasodilation in pulmonary vessels in alignment with the statement of Dugdale et al. (2020) as the cause of improved arterial oxygenation. However, pulmonary shunt values remained constant and the concluded assumption of Patschova et al. (2010) was that no effect on the ventilation-perfusion ratio had taken place. Further, in contrast to Robertson and Bailey (2002) and more in alignment with Dugdale et al. (2020), Patschova et al. (2020) mention the mechanism of bronchodilation or opening of collapsed lung areas as unlikely. This decreased pulmonary shunting and increased dynamic compliance was absent. A significant increase in oxygen delivery was observed at the same time point as the maximum measured cardiac output following salbutamol administration, indicating its contribution to oxygen delivery at greater extent than improved PaO₂/FiO₂-ratio (Patschova et al. 2010).

Clark-Price et al. (2022) also acknowledge the haemodynamic alterations post salbutamol administration as possible mechanisms increasing PaO₂-levels by elevating heart rate and thereby increasing cardiac output, thus increasing regional pulmonary vasodilation and perfusion to ventilated alveoli. Furthermore, they advocate that the minimal alteration in anatomical dead space contradicts bronchodilation, possibly absent due to an already maximal branchial expansion caused by the inhalant agent's directly relaxant effect. Another explanation mentioned is an increase in anatomical dead space alongside a concurrent decrease in alveolar dead space, resulting in a negligible difference in the ratio of dead space to tidal volume.

The described possible haemodynamic alterations seen with salbutamol usage consist of increased inotropy, chronotropy or heart rate according to Clark-Price et al. (2022), who also demonstrated a significant increase of heart rate in anaesthetised horses administered salbutamol. In addition, Patschova (2010) showed a significant elevation of heart rate and cardiac output. In contrast, neither Dupont et al. (2022) nor Robertson and Bailey (2002) observed any clinically relevant change in heart rate or blood pressure variables. The adverse effects on heart rate caused by salbutamol are frequently mentioned in literature, although in varying degrees of severity. For instance, Dupont et al. (2024), Clarke-Price et al. (2022) advocate that the alterations are rare or mild, respectively. Casoni et al. (2014) urges to careful consideration when using salbutamol regarding the cardiovascular adverse effects. The described tachycardia from salbutamol inhalation is most likely attributed to systemic absorption leading to activation of extrabronchially located β_1 and β_2 receptors (Robertson & Bailey 2002; Casoni et al. 2014). Casoni et al. (2014) suggest β_1 adrenoreceptor activity causing the chronotropic effects, despite the β_2 -selectivity, as the receptor is prevalent in the equine myocardia. Another possibility the study mentions is that individuals

possessing a larger number of β_2 receptors might respond more strongly to salbutamol than those with fewer receptors, hence aligning with the large individual variations in receptor density proved by Törneke (1999). Clarke-Price et al. (2022) compare these chronotropic effects caused by salbutamol with those seen in human medicine.

Another documented adverse effect linked to salbutamol administration in horses is sweating, as shown in the studies by Clarke-Price et al. (2022) and Roberson and Bailey (2002) where 50% and approximately 70%, of the subjects were affected. This effect occurs as adrenergic action on β_2 receptors activates the equine sweat gland (Clark-Price et al. 2022).

1.5 Administration and dosing of salbutamol

The 2 $\mu\text{g kg}^{-1}$ dose of salbutamol improves oxygenation in horses under general anaesthesia (Robertson & Bailey 2002; Patschova et al. 2010; Casoni et al. 2014; Reed 2022; Clark-Price et al. 2022; Dupont et al. 2022, 2024). Robertson and Bailey rounded the dose to the nearest 45kg, whereas Patschova et al. (2010) and Dupont et al. (2024,2022) used the nearest 50kg. The aerosol is usually administered under general anaesthesia into the endotracheal tube via a metered dose inhaler canister through a port at the Y-piece of the breathing circuit (Reed 2022; Clark-Price et al. 2022). Each actuation of the canister is to be performed at the inspiratory phase of the ventilator cycle (Clarke et al. 2014; Reed 2022; Dupont et al. 2022, 2024). The stated time of onset is fast, around five to twenty minutes (Clarke et al. 2014) and the duration of effect is 30 minutes to 3 hours (Derksen et al. 1999). Clark-Price et al. (2022) demonstrated an increased PaO_2 of at least 40 minutes.

2. Aim and research questions

The aim of this master's thesis was to investigate the cardiovascular effects associated with the administration of salbutamol to equine patients undergoing general anaesthesia by comparing values of relevant physiological parameters measured in patients before and after drug administration and to explore if salbutamol was effective at different baseline values of SpO₂, i.e. degrees of hypoxemia. The retrospective journal study addressed the following research questions:

- What is the indication and administration technique for salbutamol and why is it used in equine anaesthesia?
- What cardiovascular effects are associated with salbutamol administration in equine patients under general anaesthesia?

3. Material and method

3.1 Identifying subjects by physical anaesthetic protocols

Suitable anaesthetics of equine patients treated with salbutamol were identified by physical anaesthetic records stored by SLU University Animal Hospital (UDS). All records dated within 2.5 years from the time of data collection, February 2025, were searched for administrations of salbutamol or Ventoline. Proper anaesthetic protocols were cross-referenced with digital records in ProVet Cloud (Nordhealth, Finland) to collect monitoring data and written notes. Data collection of body weight, age, procedure demanding the anaesthesia, anaesthetic protocol containing administered drugs and doses and monitoring of HR, SpO₂%, diastolic (DIA) and systolic blood pressure (SYS) as well as MAP was to be collected.

Data collection was mainly conducted for three weeks. Inclusion criteria was physiological adult horses receiving salbutamol during general inhalation anaesthesia with proper monitoring provided. Exclusion criteria included foals or patients under 10 months of age, general anaesthesia maintained by TIVA and incomplete anaesthetic records including monitoring data during general anaesthesia. The protocols were anonymised of owner information and photographed to be stored on a portable USB stick.

3.2 Anaesthetic monitoring data

The anaesthetic monitoring data provided in UDS's medical records consists of an automatically generated PDF sheet from the anaesthetic machine and ventilator (Tafonius, Vetronic Services, UK). These include graphed parameters; HR, respiratory rate, SYS, DIA, MAP measurements and temperature. Remaining parameters are presented as numerical values in a table for every five minutes from the start of monitoring. These include inspired, expired and the set concentration of Isoflurane, concentration of Nitrous oxide and oxygen, fresh gas flow, End-tidal carbon dioxide concentration, SpO₂, Tidal volume during mechanical ventilation, tidal volume during spontaneous breathing and Peak inspiratory Pressure during mechanical ventilation. The graph consists of a x-axis representing the time, with marks at five-minutes intervals from the start of monitoring. The y-axis represents the value of the graphed parameters, with each mark corresponding to a value of 10. All graphed parameters are represented by a symbol.

The automatically generated anaesthetic records provided by the Tafonius are based on a slow-data file (sd-file), where all events and values of ventilatory and physical parameters are logged continuously every five seconds. These files are stored in the Tafonius unit. The sd-files were exported as CSV files from the Tafonius software to a portable USB stick and anonymised by removal of owner information. The files were then opened in Excel (Microsoft Excel for Mac, version 16.95.1) and the parameters mean values were collected at the time point for salbutamol administration and then repeated with five minute intervals. Extreme values indicating measure failure are excluded.

3.3 Administration of salbutamol

The aerosolised salbutamol (Ventoline Evohaler) was administered synchronously at inspiration through a microdose inhaler (MDI) adapter connected to the endotracheal tube. Each compression of the salbutamol canister administered a dose of 100µg. Three compressions were done per inspiration, usually for five succeeding breaths or according to recommended dose.

3.4 Data analysis

Statistical analyses were performed using GraphPad Prism 10.4.2 (GraphPad Software, San Diego, CA, USA). Freidman's test compared the values at different time points with the baseline values for each monitor parameter. A confidence interval of 95% was applied, and $p < 0.05$ was considered statistically significant. If a significant difference was detected, Dunn's multiple comparisons post hoc test was applied.

4. Results

4.1 Data collection

A total of 52 anaesthetic records involving the administration of salbutamol were identified. This included 51 equine patients as one individual had received salbutamol during anaesthesia on two different occasions. After applying the exclusion criteria, a total of 19 subjects were excluded. Four cases were excluded based on the anaesthetic protocol and 15 due to inadequate monitoring.

The physical anaesthetic protocols contained information including the procedure, staff information, body weight, administered drugs and their route and time of administration, as well as dosage. Time of induction and intubation, start and end of anaesthetic gas administration, ventilation technique, and arterial catheter placement were also provided.

The three available Tafonius machines at UDS were searched for anaesthesia data corresponding to the collected patients. Twelve patients were excluded due to the absence of recorded monitoring data, including both the graphed anaesthetic record and the sd-file. Three additional patients were excluded as only the graphed anaesthetic record was available, with no corresponding sd-file.

Two anaesthetic records and their sd-file lacked patient identifiers but were confirmed to belong to the respective patients and the specific anaesthesias. This is based on alignment with the date, time for start and stop of isoflurane administration, procedure, identification of anaesthetist and surgeon and the specific Tafonius unit used. The specific Tafonius units had not been used for any other anaesthesias on these specific dates and times. One of the automatic anaesthetic records provided by the Tafonius unit was also included in the patient's digital record, as entered by the anaesthetist.

Two other automatic anaesthetic records and their sd-file contained correct patient identifiers but incorrect dates and time. Both cases were recorded in October 2022 but incorrectly dated to January 2009, predating the patients' births. The documented drug administration times noted in the text and the time ratio of isoflurane administration start and stop in the Tafonius anaesthetic protocols aligned with the physical anaesthetic protocols, confirming the correct sd-file for these cases. Both patients had only been anaesthetised at UDS during these specific occasions. The correct timing for salbutamol administration was determined by proceeding from the recorded times of Isoflurane administration. The time discrepancy represents a difference of 7 hours and 39 minutes, respectively 8 hours, for the two files.

The values for each parameter were collected by marking all measured values at the correct minute and recording the mean value calculated by Excel. Selected time points included a zero value, the minute of salbutamol administration, followed by values at five-minute intervals post administration, up to a maximum of 85min for some cases.

The parameters analysed were HR, SpO₂, SYS, DIA and MAP measurements. All measurements were provided by the Tefonius ventilator equipment. SpO₂ and arterial blood pressure measurements typically had 12 measured values per minute, while HR was determined by measurements from all three measuring sources, the pulse oximeter, arterial blood pressure and electrocardiography (ECG), typically yielding 36 values per minute. All three measurement techniques were included to provide the mean HR when available to minimise measurement errors and enhance reliability.

Extreme separate values indicating measure failure were excluded, such as values of zero or numbers twofold of the remaining values measured the same minute. Identification was facilitated by the high frequency of measurements, recorded every five seconds.

Once the mean values for each selected minute were collected, they were organised into separate tables for each of the five parameters (SpO₂, SYS, DIA, MAP, and HR) in Excel. These tables were used for further analysis and visualisation of trends over time

4.2 Subjects

Of the 51 horses initially receiving salbutamol under general inhalation anaesthesia during the given timeframe, 32 horses and 33 anaesthesia met the criteria to be included in the study. Of these, 14 were mares, 10 were geldings and 8 stallions. The most common type of breed was warmblood and both the breed distribution and sex is displayed within table 1. There were large variations in age within the group, as presented in figure 1.

Sex	Number (n=32)	Breed	Number (n=32)
Geldings	10	Warmblood	20
Mares	14	Coldblood	7
Stallions	8	Pony	3
		Unknown/Cross	2
		breed	

Table 1. Patient descriptive data regarding sex and breed type

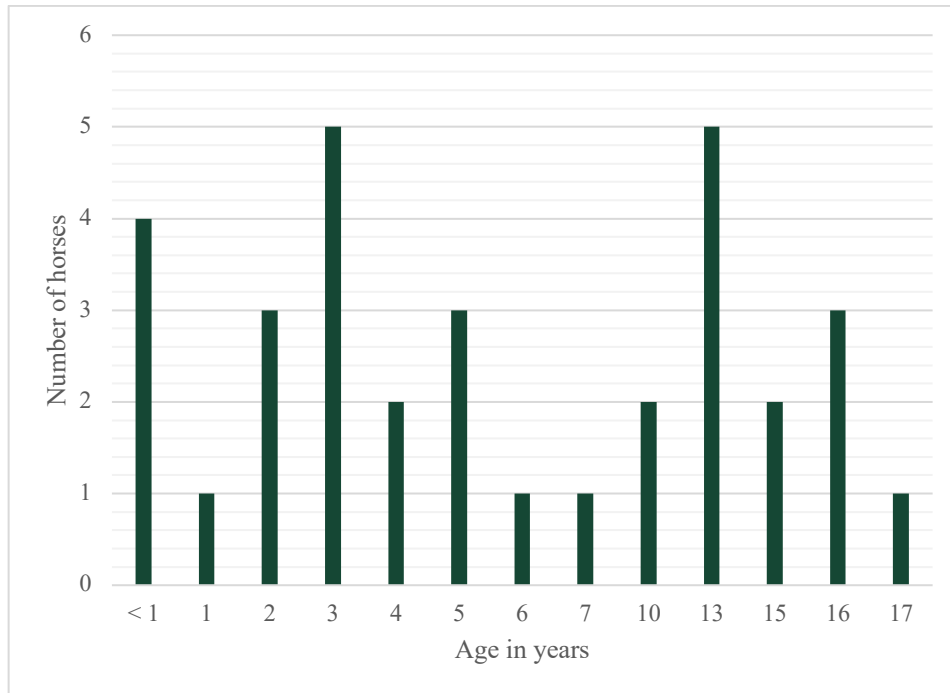


Figure 1. Age distribution in the study population

The mean $\pm$ standard deviation (mean $\pm$ sd) age was 7 ± 6 years with a minimum of 9 months and maximum at 17 years of age. Orthopaedic procedures were the most common cause of general anaesthesia, shown in table 2.

Table 2. Surgical procedures as cause of anaesthesia

Procedures	Number (n=33)
Orthopaedic	16
Colic	7
Wounds	5
Castration	5

4.3 Monitoring

A total of 33 cases had provided sd-files with adequate monitoring data. The digital records were searched for record notes commenting the anaesthesia or salbutamol effect and nine cases had no written notes available. All but one case had blood gas analyses from the anaesthesia accessible.

Of the 24 cases with anaesthetic notes commenting the anaesthesia, six notes did not mention an administration of salbutamol. When the administration was mentioned, six of these notes did not evaluate the effect. The most common indication mentioned for salbutamol administration was hypoxaemia or low

oxygenation, followed by low saturation or PaO₂. Four notes did not mention any indication for the drug administration. The majority of notes acknowledging salbutamol administration also addressed the effect. A satisfactory effect was commented in 11 cases and a mild effect in 2 cases. Of the cases with an addressed effect, three cases also used ventilatory strategies in combination with the drug administration and two of these also administered PiNO. Two anaesthetists estimated no effect from salbutamol.

There was a large variation in available monitoring data regarding HR, arterial blood pressure (ABP) and SpO₂%, as displayed in table 3. Of the 33 included cases of anaesthesia utilising salbutamol, 8 cases had one or more parameters monitored for 20 minutes or less after salbutamol was administered. Two cases also had one repetitive dose of salbutamol administered. The documented monitoring of HR and SpO₂% for the two cases was 15 and 25 minutes, respectively, post the second administration, whereas the ABP was only monitored for 10 minutes after the dose was given. Two patients had no ABP monitoring available. Furthermore, this meant that their mean HR was based on measures provided by only the pulse oximeter and ECG.

Table 3. Duration of monitoring of HR, ABP and SpO₂% available post salbutamol administration. Second time administrations are excluded.

Monitoring of HR (min post drug administration)	Number of cases (n=33)	Monitoring of ABP (min post drug adm)	Number (n=33)	Monitoring of SpO ₂ % (min post drug adm)	Number (n=33)
None	0	None	2	None	1
≤ 20 minutes	5	≤ 20 minutes	8	≤ 20 minutes	5
21-30 minutes	3	21-30 minutes	7	21-30 minutes	4
31-40 minutes	9	31-40 minutes	3	31-40 minutes	8
41-50 minutes	5	41-50 minutes	4	41-50 minutes	5
51-60 minutes	3	51-60 minutes	2	51-60 minutes	3
> 60 minutes	8	> 60 minutes	7	> 60 minutes	7

4.4 Anaesthetic protocols

All anaesthetic protocols included the NSAID Flunixin (1.1mg/kg) as a preemptive analgesic agent in the premedication. The majority of anaesthesias included acepromazine (0.02-0.05mg/kg, Plegicil) and romifidine (0.08-0.12mg/kg, Sedivet) or xylazine (0.5-1mg/kg, Xysol) in combination with butorphanol (0.01-0.05mg/kg, Butomidor) or morphine (0.05-0-15mg/kg) for sedation. Antibiotics were administered during most anaesthesias, mostly benzylpenicillin sodium (12mg/kg Geepenil,) but some patients received gentamicin (6.6mg/kg, Gentaject). All inductions were initiated with midazolam (0.03-0.1mg/kg) combined with ketamine (2-2.4mg/kg). 8 horses were given thiopental at induction. All anaesthesias was maintained with isoflurane as inhalant agent, used intravenous fluid therapy (IVFT) with ringeracetate or Infusolec and constant rate infusion (CRI) of dobutamine (0.5-5ug/kg/min). Table 4 summarises the agents used for premedication.

Premedication agent	Number (n=33)
Flunixin	33
Plegicil	27
Xylazine	6
Romifidine	27
Butomidor	16
Methadone	1
Morphine	18

Table 4. Drug agents used in the premedication and the number of anaesthetic protocols utilising each agent

Rescue drugs most commonly used intraoperatively was ketamine and thiopental administered as bolus doses. CRIs of butorphanol (0.04mg/kg/h, Butomidor) or romifidine (20-40ug/kg/h, Sedivet) was administered in 13 cases. All intraoperative drug administrations are presented in table 5. The mean±sd duration of inhalation anaesthesia was 2 hours and 40 minutes ± 4 hours and 6 minutes, from gas administration start and stop. Four anaesthesias used PiNO prior to salbutamol administration and two of these cases noted an unsatisfactory effect of PiNO in the records.

Table 5. Administered boluses and CRIs under general anaesthesia

Intraoperative bolus adm	Number (n=33)	Number doses adm within 30min of salbutamol	CRIs intraoperatively	Number (n=33)
Dexmedetomidine	1		Lidocaine	9
Morphine	1		Butomidor CRI 0.04mg/kg/h	9
Thiopental	6		Dobutamine 0.5-5ug/kg/min	33
Ketamine	10	6	Dexmedetomidine 0.05mg/kg	2
Xylazine	1	1	Romifidine 20-40ug/kg/h	4
Ephedrine	2	1	Ketamine	1

The mean $\pm$ sd dose (μ g/kg) of salbutamol (Ventoline Evohaler, 100 μ g/dose) administered in the collected cases was 2.83 μ g/kg $\pm$ 0.80 μ g/kg with a maximum dose of 5.78 μ g/kg and minimum of 1.88 μ g/kg, see table 6. One case had no dose of salbutamol noted in either the anaesthetic protocol or digital record, but the time of administration. A total of 68% of the cases received a dose >25% above the dose of 2 μ g/kg recommended in literature and 32% of all salbutamol cases received a dose higher then 50% of the recommended dose. The observed mean $\pm$ sd time of salbutamol administration from inhalant agent start was 1 hour and 8 minutes $\pm$ 34 minutes. Two horses received a repetitive administration of salbutamol under the same anaesthesia. The first horse received its repetitive dose of 1 hour and 15 minutes after the first. The second horse received its repetitive administration only 25 minutes from the first.

Case	Administered dose $\mu\text{g/kg}$	% difference from recommended dose (2 $\mu\text{g/kg}$)
1	2.10	5%
2	2.54	27%
3	2.27	13%
4	3.14	57%
5	2.69	34%
6	3.31	66%
7	3.08	54%
8	2.00	0%
9a	2.17	9%
9b	2.88	44%
10	2.62	31%
11	2.94	47%
12	2.45	22%
13	3.26	63%
14	3.28	64%
15	Unknown	Unknown
16	2.73	36%
17	2.16	8%
18	2.67	33%
19	3.11	55%
20	2.98	49%
21	2.63	32%
22	1.78	-11%
23	2.62	31%
24	2.47	24%
25	2.61	31%
26	4.59	129%
27	4.12	106%
28	2.34	17%
29	3.33	67%
30	5.75	187%
31	2.00	0%
32	1.98	-1%

Table 6. Table presenting the salbutamol doses administered for each case, summarising the administered dose in $\mu\text{g/kg}$ rounded to two decimal places and difference (%) from dose of 2 $\mu\text{g/kg}$ recommended in the literature.

4.5 SpO₂ alterations

The mean±sd SpO₂% at time of salbutamol administration was 91%±3.7%. The lowest baseline SpO₂% was 77% and the highest 98%. An overall improvement of baseline mean value was observed over the first 20 minutes, however not significant, followed by a slight decrease for the succeeding 20 minutes. By 45 minutes post salbutamol administration, a small insignificant peak at mean±sd saturation of 94.7±3.4% was observed before another small decrease for 10 minutes. This pattern was repeated after the text peak at 60 minutes post administration. After another 15 minutes, at 75 minutes post administration, the maximum mean±sd value of 96±1.4% was observed. However, this mean±sd value was based on four remaining cases and not significant. Of the 25 patients monitored 30 minutes after salbutamol administration, 20% had no improvement in saturation at this time point from their individual baseline value. The mean±sd SpO₂% every ten minutes up to one hour after salbutamol administration are presented in table 7.

Mean ±sd	T ₀	T ₁₀	T ₂₀	T ₃₀	T ₄₀	T ₅₀	T ₆₀
SpO ₂ %	91±3.7	93.5±3.3	94.4±3.1	93.6±4.1	94.2±3.3	94.4±3.6	95.5±2.8

Table 7. Saturation before (T₀) and after (T₁₀, T₂₀, T₃₀, T₄₀, T₅₀, T₆₀) salbutamol administration

A significant improvement in saturation was determined at 10 and 15 minutes (p-value<0.0001) post salbutamol administration, provided that the baseline SpO₂ was 90-94%%. This is presented in figure 2. A baseline saturation of either less than 90% or 95% or higher led to no significant improvement, see figure 2. Of the salbutamol doses administered a majority of 62% were given at a saturation between 90-94%, and 29% of the administrations occurred at a saturation of 90% or less, see table 8. 9% of the doses was administered at a saturation of 95% or higher.

SpO ₂ % at T ₀	Number (n=34)
<90%	10
90-94%	21
≥95%	3

Table 8. Distribution of baseline values in saturation before (T₀) salbutamol administration within the study population

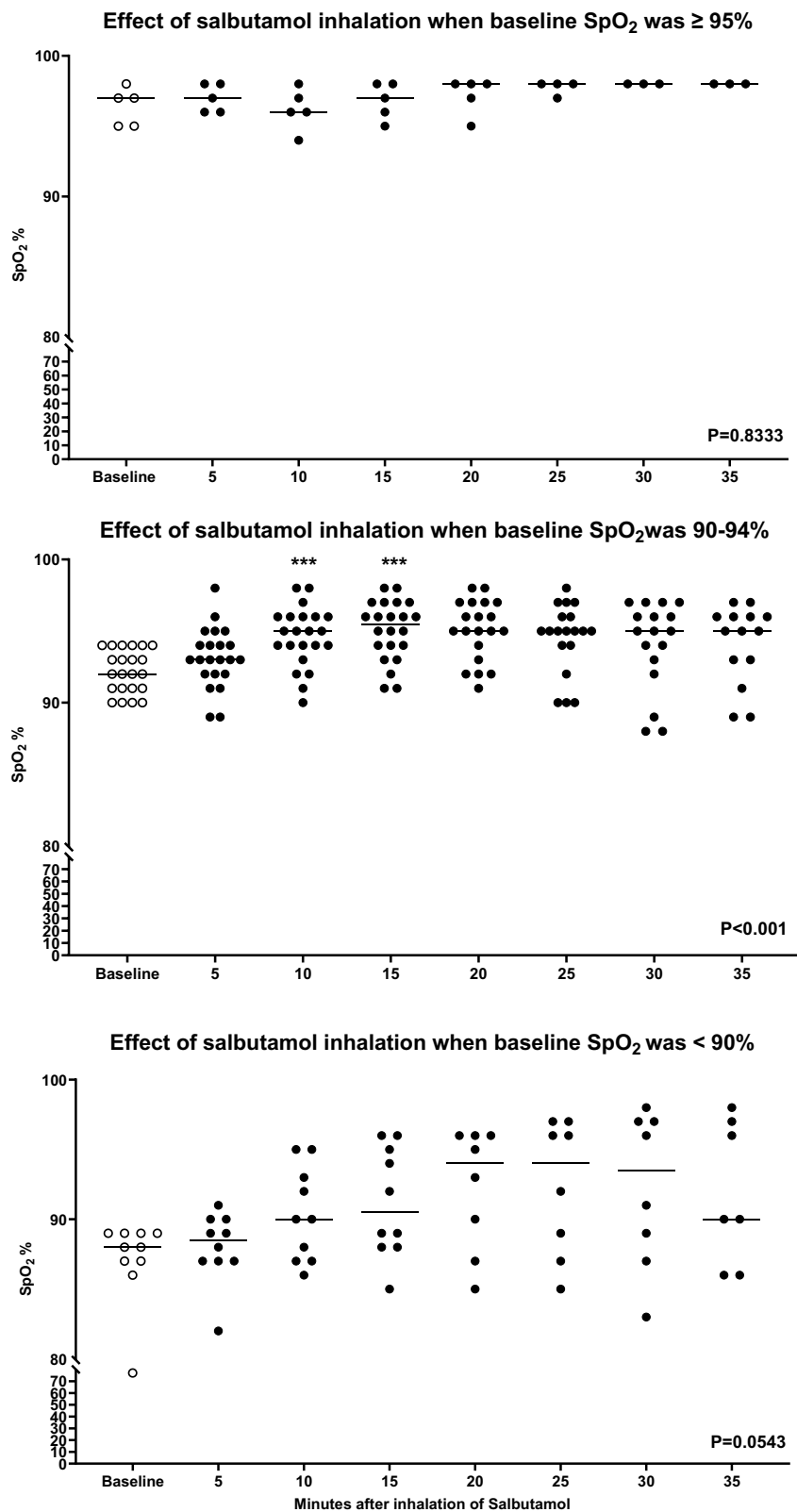


Figure 2. Effect of salbutamol inhalation when baseline was $\geq 95\%$ ($p=0,8333$) 90-94% ($p=<0,0001$) and $<90\%$ ($p=0.0543$). *** Significant difference ($p=<0,0001$) between baseline value and value 10 and 15 minutes post drug administration.

The two doses given as a repetitive dose were administered at a saturation of 93% and 92% respectively, see figure 4. The first case had the drug administered after a decrease of 3% during the prior 10 minutes and was succeeded by an increase of 3% during the following 15 minutes. In contrary, the second case had the repetitive dose administered after an increase of 2% since the preceding 10 minutes and was followed by a decrease of 1% over the subsequent 15 minutes.

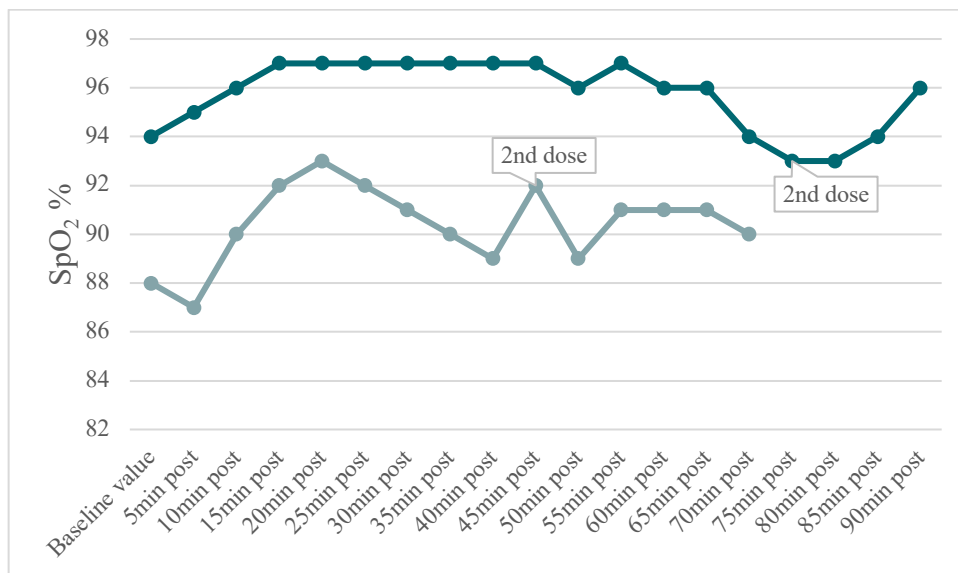


Figure 3. Graph of saturation in patients receiving a repetitive dose of salbutamol

4.6 Heart rate alterations

4.6.1 General heart rate alterations

The mean $\pm$ sd baseline value of heart rate was 40 $\pm$ 7 beats per minute (bpm). The lowest baseline HR was constituted of 28bpm and the maximum at 58bpm. One case had no HR measured at time of drug administration, hence the first measured value was provided five minutes after the salbutamol was given. No significant alterations in HR were observed. The mean $\pm$ sd HR five minutes post drug administration for all subjects was 39 $\pm$ 9bpm, a small decrease from baseline, succeeded by a steady increase to the maximum of 46 $\pm$ 13 bpm 40 minutes after salbutamol administration, however not significant. Of the 27 cases still monitored after 30 minutes from drug administration, 63% had an increased HR from the baseline value. A total of 10 cases had an increase in HR of $\geq 10\%$ and a majority of these had an increase of $\geq 20\%$. One case had no change in HR from the baseline after 30 minutes. A decrease in HR from baseline value was observed in 9 cases at the same time point, the majority of them had a decrease of 10% or less.

Of the 19 cases still monitored 40 minutes after salbutamol administration, 68% showed a nonsignificantly higher bpm than the baseline. Eleven of the cases showed an bpm $\geq 10\%$ above baseline and five of these had an bpm $\geq 20\%$ higher. Five cases had a lower bpm 40 minutes after administration compared to baseline, the majority with a decrease of 10% or less. The mean $\pm$ sd HR every ten minutes up to one hour after salbutamol administration are presented in table 9. The overall effect on HR every five minutes up to 80 minutes are summarised in figure 5.

Table 9. Heart rate (bpm) before (T_0) and after (T_{10} , T_{20} , T_{30} , T_{40} , T_{50} , T_{60}) salbutamol administration

Mean $\pm$ sd	T_0	T_{10}	T_{20}	T_{30}	T_{40}	T_{50}	T_{60}
bpm	40 $\pm$ 7	41 $\pm$ 8	41 $\pm$ 9	42 $\pm$ 11	46 $\pm$ 13	43 $\pm$ 12	41 $\pm$ 11

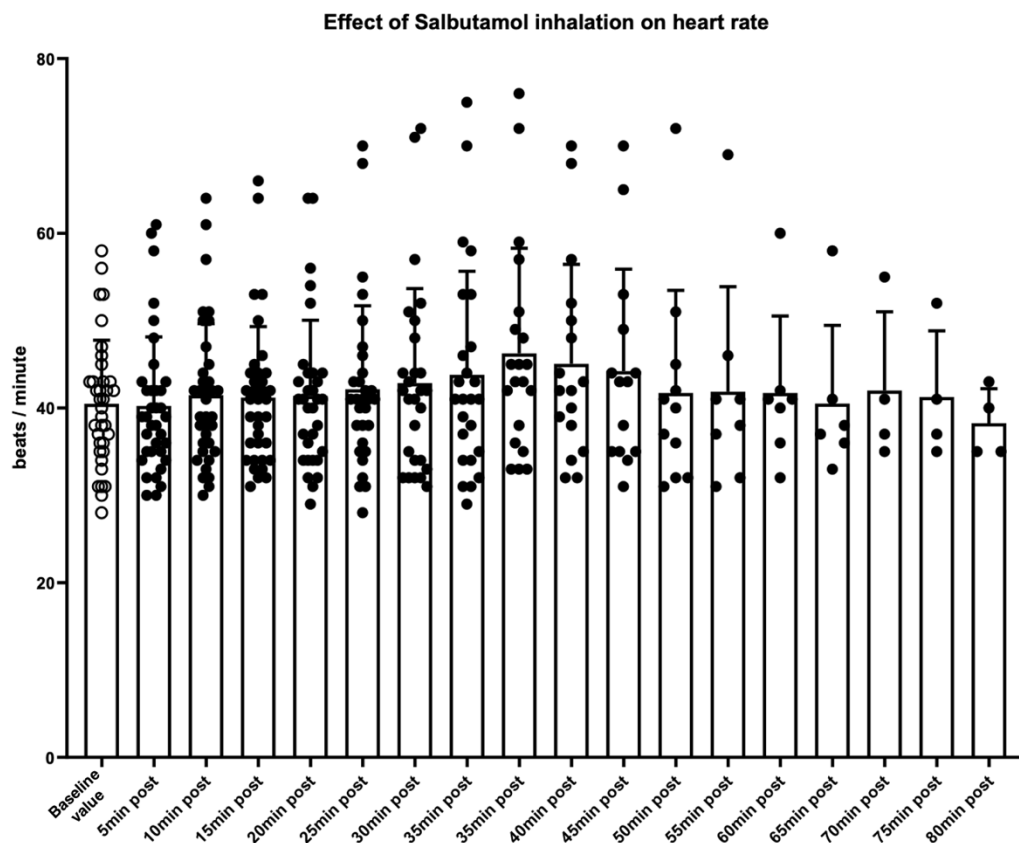


Figure 4. Effect of salbutamol on heart rate after salbutamol administration

The largest individual HR elevation was 158% from the initial value of 19bpm to 49bpm 80 minutes post drug administration and the last measurement provided. This individual's initial value was from 5 minutes after salbutamol was given, as no baseline value was measured. Not only was the last measurement increased,

but also at the timepoints 30 minutes and 40 minutes, displaying bpm 68% respectively 58% higher than the initial measured value. This case did not provide any SpO₂ measurements. Another large individual elevation of 90% from baseline value was observed, from 31 bpm to 59 bpm measured at both 35 and 40 minutes post drug administration. A third case displayed an increase of 43% at 40 minutes after salbutamol was given, from 53bpm to 76 bpm.

The two cases receiving a repetitive dose of salbutamol both had a similar rise in bpm the second dose as the rise in bpm seen after the first. The first case had a baseline value of 34 bpm at the timepoint of the first salbutamol administration with a following increase of 15% in bpm 15 minutes after administration. The second dose was given at 35bpm and 15 minutes after administration a rise of 20% in bpm was measured. The second case had a baseline HR of 41bpm and the HR was 5% higher after 15 minutes. The second dose was given at a HR of 43 bpm and was 2% higher after 15 minutes.

Some cases displaying an insignificant increase in HR also showed a succeeding decrease, some HR even lower than the baseline value. These cases had a mean HR peak of 11% from baseline value and the following mean percental decrease from baseline HR was 13%. The mean time point of the HR peak was 15 minutes post salbutamol administration. After 20 minutes following the measured peaks in these cases the mean decrease was 28% in HR. Seven cases had an increase succeeded by a steady, but insignificant, decrease until the last measurement. Two cases had a decrease in HR five minutes after the measured peak HR but then displayed a return to the peak HR 10 minutes after the first. The first case with a peak 7% above the baseline value had no more measurements and displayed a last HR 7% lower than the baseline value. However, the other case displayed a repetitive decrease to again be followed by a third peak. All three peaks in this case were of 72bpm, 29% higher than the baseline bpm. After the third peak the HR steadily decreased until the last measurement, a HR 29% lower than the baseline.

4.6.2 Heart rate and differences in dosing

Due to the large variations in dosing, an eventual correlation between an elevated HR and a higher dose of salbutamol administered was explored. No significance was proved between higher dose and increased HR post drug administration, see figure 7. However, those cases with an elevated HR from values before drug administration had received a higher dosing. Hence, a tendency of a higher dose causing a higher HR may be present.

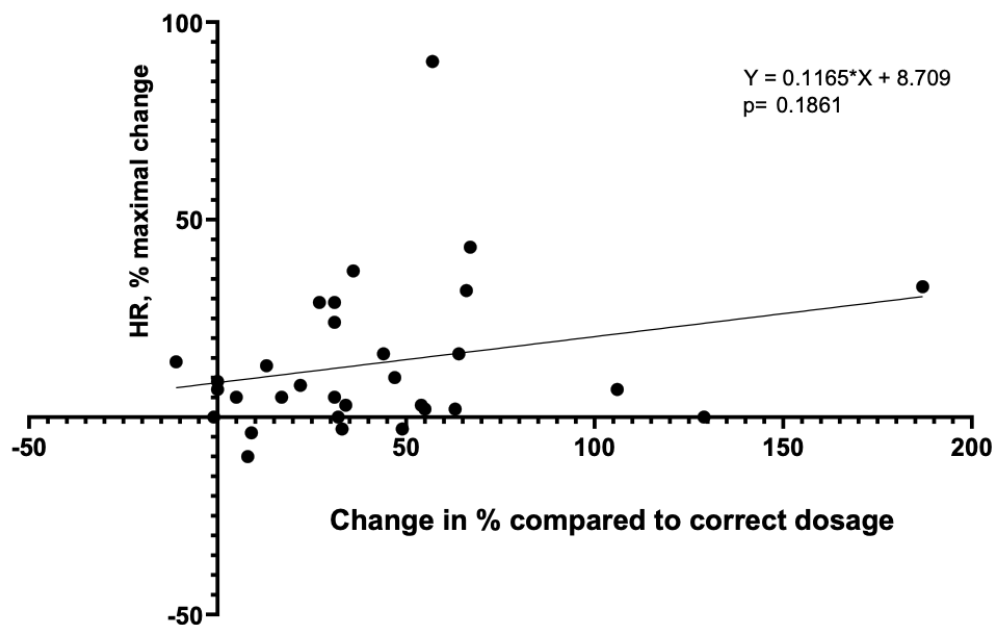


Figure 5. Change in heart rate compared to dosage. The y-axis represents maximal heart rate change from baseline value in % and the x-axis change in administered dose in % from correct dosage (2µg/kg)

4.6.3 Heart rate and age

Of the 10 cases with a maximum elevation in HR of 20% or more from baseline value, the mean±sd age was 8.5±5 years. However the variation was large, and the minimum and maximum age within this group was two and thirteen years. Half of the horses was thirteen years old. The cases of a maximum HR elevation of 10-19% had a mean±sd age of 8.2±5.9 years, with ten months and sixteen years as minimum respectively maximum age. Of the cases with the smallest maximum elevation in HR, under 10%, had a mean±sd age of 6.3±6.2 years. Amongst this group, the youngest individual was ten months and the oldest seventeen years.

4.7 Blood pressure alterations

The mean±sd baseline value of SYS, DIA and MAP was 107±14, 63±15 and 78±15 mmHg respectively. The minimum and maximum baseline values of DIA was 32 and 94mmHg, SYS 77 and 138mmHg and MAP 48 and 113mmHg. One case had no BP measurements at all and one case had only measurements provided for the last 10 minutes of monitoring. Another case had no baseline ABP and the first measurement was provided first 5 minutes after drug administration. A third case had a 10-minute window of missing BP measurements in the beginning of monitoring.

Table 10. Systolic (SYS), diastolic (DIA) and mean arterial blood pressure (MAP) before (T₀) and after (T₁₀, T₂₀, T₃₀, T₄₀, T₅₀, T₆₀) salbutamol administration

Mean $\pm$ sd mmHg	T ₀	T ₁₀	T ₂₀	T ₃₀	T ₄₀	T ₅₀	T ₆₀
SYS	107 $\pm$ 14	108 $\pm$ 12	111 $\pm$ 14	110 $\pm$ 11	107 $\pm$ 11	108 $\pm$ 14	108 $\pm$ 14
DIA	63 $\pm$ 15	62 $\pm$ 14	64 $\pm$ 12	67 $\pm$ 15	67 $\pm$ 17	68 $\pm$ 17	62 $\pm$ 13
MAP	78 $\pm$ 15	78 $\pm$ 13	81 $\pm$ 12	83 $\pm$ 13	82 $\pm$ 15	81 $\pm$ 14	78 $\pm$ 12

A first peak in mean SYS at the timepoint of 20 minutes after drug administration was observed, as seen in table 11, followed by a steady decrease until returning to the baseline mean after another 20 minutes. The first peak in both mean DIA and MAP was observed 35 minutes after drug administration, for DIA this was also the highest peak whereas the highest mean MAP was observed 85 minutes after drug administration, also presented in figure 8. This was also the last observed measurement based on the three cases still monitored at this time point.

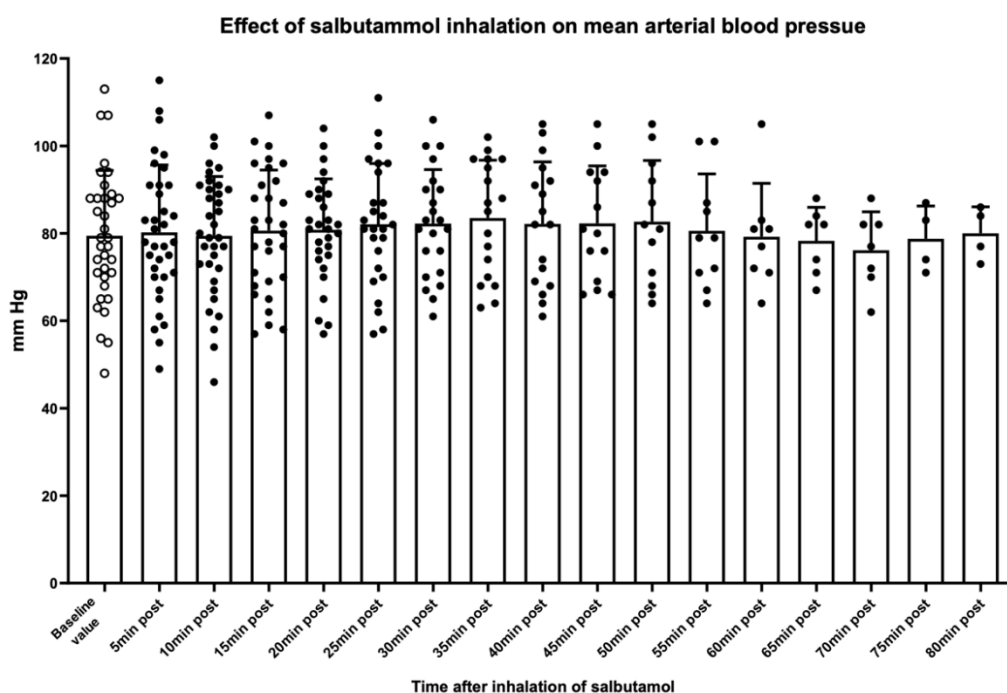


Figure 6. Effect of salbutamol on mean arterial blood pressure after salbutamol administration.

Of all cases with MAP measurements 30 minutes after drug administration 63% had an elevation from baseline values. The mean percentual change in MAP from baseline values was an elevation of 8%. At this time point, the maximum individual elevation was 46% higher than the baseline. Of the cases with a decrease in MAP from baseline values at this time point, only one had a decrease of over 10% and the mean decrease within this group was 5%.

5. Discussion

The aim of this master's thesis was to investigate the administration, indications and cardiovascular effects and arterial oxygen saturation associated with the administration of salbutamol to equine patients undergoing general anaesthesia. This was performed by comparing relevant monitored parameters from medical records provided before and after drug administration in patients.

The retrospective chart review enables a resource-efficient and ethically advantageous approach to evaluate salbutamol's utilisation and effect on anaesthetised horses as no additional interventions or interaction with the subjects are required. Administered drugs, including salbutamol, are administered as a treatment to maintain a safe anaesthesia meeting the individual patient's needs without experimental interest. This also implies an indirect evaluation of routines at UDS. For instance if the aim of administering salbutamol, to provide an enhanced oxygenation, is accomplished or not. Many cases had to be excluded due to inadequate monitoring provided. This would be possible to avoid with a controlled experimental study design, thereby promoting study population size and significance in suspected trends. However, these results regarding scarce monitoring may act as a clear indicator of insufficient routines, risking patient safety and opportunities to communicate individually anaesthetic challenges. Access to digital medical records constitutes the main material requirement, aligning with sustainable research practices. In addition, despite the large number of excluded cases, the retrospective study design allowed data collection from cases anaesthetised over a much larger time frame than that possible when conducting an experimental study.

An experimental study design with a controlled anaesthetic protocol would also minimise the number of cases having received drugs with a possible effect on the cardiovascular parameters administered at time points risking interference with the effect of salbutamol. This may have altered with the results in this study. The large variation in salbutamol dosing might also have altered the possibilities to explore the presence of individual variations in effect of salbutamol, something widely discussed in the literature.

The collection of the provided monitoring data may also affect this study's results. The decision to only collect data from the slow-data files was made as it provided numerical values during a full minute. A rule-based approach had to be created and implemented if the graphed monitoring was to be used. This would mean three additional cases to the study population, however as no numerical values was provided, the accuracy of estimating the values and thereby the trend over time would be questionable.

The study population had relatively large variations regarding breed, age, body weight, surgical procedures and sex. This facilitates application of the results

upon the target population, adult horses receiving salbutamol under general inhalation anaesthesia to promote oxygenation. These population variations also reflect those seen in the experimental studies done by Dupont et al. (2024), Dupont et al. (2022) and Robertson and Bailey (2002).

The variations in anaesthetic protocols were expected, as conducted to meet individual needs. However, the extreme variations in salbutamol dosing within the same facility, 1,88-5,78µg/kg, was surprising. The literature seems to generally agree to the prescribed dose of 2µg/kg. The reasons for prescribing such different doses within the same surgical facility might be due to personal preferences and experiences among the veterinarians or differences in subjective assessment of the hypoxaemic severity. Close teamwork may imply the absence of formal prescriptions of dose or delegations in administration technique from the responsible veterinarians, hence an insufficient knowledge among nurses can influence the administered dose. When conducting an experimental study design with a consistent salbutamol dose administered to each subject, as in the studies done by Robertson and Bailey (2002), Patschova et al. (2010) and Dupont et al. (2022, 2024), the effects are not only more comparable between subjects or subject groups within the same study, but also between different studies. These comparable results are beneficial for future composing of studies to fill the knowledge gaps identified by previous researchers. As the described presence of side effects and the mechanism of action of salbutamol being unknown, these large variations in dose observed in this study might contribute to risking patient safety. As the basic principle to toxicology emphasises, the dose makes the poison.

The practised administration technique of salbutamol described by the personnel at UDS was in well alignment with the literature. However, as Casoni (2014) states, a variety of factors may influence the actual dose of drug delivered to the patients. Mentioned considerations are differences in canister filling and humidity degree of the endotracheal tube's lumen, different flow of carrier gas. This may explain, or partly participate to, the large individual variations described within literature and also observed in this data.

Administering salbutamol is widely suggested intervention to treat hypoxaemia under general anaesthesia. Reed (2022) as well as Auckburally and Nyman (2017) defines hypoxaemia as $\text{PaO}_2 < 60\text{mmHg}$ which Grubb et al. (2020) equalises with a SpO_2 of $< 95\%$ and severe cases with SpO_2 of $< 90\%$. When communicated in anaesthetic notes, the indication for salbutamol administration at UDS seems to be hypoxia or low saturation, thereby aligning with the literature. The majority of the cases receiving salbutamol had hypoxaemia, 62% of the doses took place during mild hypoxaemia with a SpO_2 of 90-94% and 29% at a time of severe hypoxaemia ($\text{SpO}_2 < 90\%$). Three of the salbutamol administrations took place without present hypoxaemia. As a significant improvement in saturation only

could be found in cases with baseline values 90-94%, a discussion regarding correct indication for salbutamol are induced. Salbutamol seems to literally be considered a rescue drug for hypoxaemia, and not a prophylaxis. On one hand, the equine patient at risk of hypoxaemia or already in a state of less severe hypoxaemia, might escalate into severe hypoxaemia which increases the importance of prevention. For these patients, this result might help indicate salbutamol administration, hopefully increasing oxygenation and hinder development of hypoxaemia early in the process. On the other hand, the patients with severely low PaO₂ or saturation constitutes a patient group where effective intervention is critical. In the study done by Dupont et al. (2024), the subjects received salbutamol when reaching an PaO₂ of <100mmHg and 60% of the cases presented a significant improvement after 15 and 30 minutes post administration. Hence, the horses was not considered hypoxaemic. This PaO₂ threshold was also used in the study done by Dupont et al. (2022) where salbutamol was compared with continuous positive airway pressure manoeuvre on improving oxygenation. In this study, 22 of 28 horses showed a higher PaO₂ after salbutamol administration, however not significant. Robertson and Bailey (2002) is the only available study aiming to investigating the effect of salbutamol in hypoxaemic horses, presenting a significant improvement in PaO₂ after salbutamol administration, however using a PaO₂ threshold of <70mmHg. Clarke-price et al. (2022) brings this issue to attention and discusses the many studies investigating the effect of salbutamol in non-hypoxaemic horses and states that the effect may perform differently in clinical patients where profound derangements in pulmonary gas exchange and atelectasis prevail. The data from the clinical patients in this study partly display the point made by Clarke-Price et al. (2022), where the difference in results between baseline values of less severe versus severe hypoxaemia are clear. The varying effect in patients with different degrees of hypoxaemia at the time point of drug administration constitutes a perspective to study further. This in order to evaluate the effect in our most critical patients in the greatest need of hypoxaemic prevention and treatment.

The same principle translates to investigating the cardiovascular effects in clinical patients experiencing hypoxaemia. An increase in HR following salbutamol administration has been both described (Casoni et al. 2014) and significantly proven by multiple studies, for instance Patschova et al. (2010) and Clark-Price et al. (2022). Dupont et al. (2024) noted a significant increase in MAP. These experimental studies used non hypoxaemic subjects and the case report by Casoni et al. (2014) included only one hypoxaemic horse of five. Patschova et al. (2010) also proved a significant increase in CO following salbutamol administration. In contrast, neither Dupont et al. (2022) or Robertson and Bailey (2002) observed any significant change in HR or MAP, in alignment with the results observed in our data. However, none of the subjects included

experienced hypoxaemia as the drug administration took place at PaO₂ thresholds of <70 and <100mmHg in the mentioned studies. Hence not considered of clinical relevance, small elevations of mean HR and MAP are presented in a descriptive figure after salbutamol administration in the study by Dupont et al. (2022).

The previously described large individual variations in both desired and side effects of salbutamol are also observed in this thesis. Hence the non-experimental study design, many variables varied between the cases included. Anaesthetic protocols, dose-differences of both salbutamol and other drugs, degrees of hypoxaemia at time point of salbutamol administration and different conditions demanding general anaesthesia. As previously mentioned, the mechanism of action is repeatedly discussed as well as the cause of varying effects on oxygenation and haemodynamic parameters. Individual distribution of β -adrenoreceptors or tendency for agonistic effect on β_1 receptors may play a part in variations of both desired and side effects, one possible explanation for the ranging effects observed in this data. The possible errors in administration of salbutamol aerosol could also alter the absorbed amount of the drug. However, in this thesis no correlation could be seen between HR alterations and dose of salbutamol administered, despite the large dose span. Nor any correlation between HR and age. Still, differences in dosing or age as well as individual sensitivity might affect both desired and undesired effects caused by salbutamol. As no significant increase in neither HR or MAP was displayed and no ventilatory parameters was measured, speculations regarding suspected mechanism behind the saturation improvement remains challenging. An increased CO initiating the enhanced oxygenation, as Patschova et al. (2010) and Dugdale et al. (2020) suggests, would presume an accompanying increase in HR and MAP. This was not observed in this thesis.

Salbutamol is not the only treatment strategy for hypoxaemia with varying effect or degree of adverse effects. However, salbutamol is considered inexpensive and the administration technique easy to learn and simple to use (Dupont et al. 2022), in contrast to PiNO for instance, which requires a special device not yet available for routine clinical use according to Clarke et al. (2014). This may explain salbutamol's extensive use, despite the unpredictable effects and the vaguely explored gaps in knowledge of the substance, raising important ethical concerns. Nevertheless, to maintain patient safety, conscious considerations should be made when electing salbutamol as treatment strategy for the hypoxaemic equine patient. As both desired and adverse effects varies, other treatment options should be available, as well as actions to manage possible haemodynamic alterations. If the desired effect is achieved, salbutamol might be an economically sustainable technique promoting a safe general anaesthesia for the patient.

6. Conclusion

This study set out to evaluate the clinical use of salbutamol in anaesthetised horses, focusing on its administration practices, indications, and cardiovascular effects. The findings revealed expressive variability in dosing, with salbutamol administered at doses ranging from 1.88 to 5.78 µg/kg. Thereby far exceeding the commonly recommended 2 µg/kg. This inconsistency suggested a lack of clinically standardised protocols, potentially influenced by individual clinician preferences or subjective assessments of hypoxaemia severity. The administration of the aerosol employed involved connecting the drug canister to an MDI adapter attached to the endotracheal tube and compression timed to inspiration.

This study has identified a significant improvement in saturation when administered to mildly hypoxaemic horses (SpO₂ 90-94%). However, its efficacy in severe hypoxaemia (SpO₂ <90) was less consistent, raising questions about its optimal indication and use - whether as a preventive measure or a rescue intervention. In clinical practise salbutamol was primarily administered to hypoxaemic horse with indication motivated as “hypoxaemia”, “low oxygenation”, “low saturation” or “low PaO₂”.

Contrary to findings from experimental studies in non-hypoxaemic horses, this study failed to detect significant increases in HR or MAP following salbutamol administration. This discrepancy may indicate that hypoxaemia might influence the drug’s haemodynamic effects, warranting further investigation.

While salbutamol remains a practical and cost-effective option for managing hypoxaemia, its variable effects require clinicians to carefully evaluate its use, consider alternative techniques, and be prepared to manage potential side effects should they arise.

Future research should focus on determine the mechanisms of action, further evaluate effects in clinical and truly hypoxaemic patients as well as the impact on haemodynamic systems and finally consider comparative studies with other oxygenation strategies to optimise treatment of the hypoxaemic horse under general anaesthesia.

In conclusion, salbutamol is a valuable but inconsistently effective tool to promote the challenging oxygenation in the equine anaesthetised patient. Clinicians should weigh its benefits against potential limitations and remain prepared to adjust treatment strategies based on individual patient responses.

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Popular science summary

Anaesthetising horses is challenging as complications are common. Hypoxaemia, low oxygen level in the arterial blood, is a frequent complication caused by many factors, for instance the horses anatomy. When standing awake, the large lungs are effectively ventilated as air reaches every lung area and the vessels allows blood to pass the same areas and absorb the oxygen. When anaesthetised and laying down, the pressure from inner organs prevents both air and blood to reach some lung areas, severely depressing the bloods oxygen levels. Different techniques, all with benefits and limitations, are available to treat the hypoxaemia. However, no perfect strategy exists. Salbutamol is a drug used to treat asthma in both humans and horses as it can widen the airways, yet also commonly used to treat hypoxaemia in anaesthetised horses. It is unknown how the drug works, the effectiveness in promoting oxygenation varies a lot among patients and some studies, but not all, have shown large increases in heart rate (HR) and blood pressure after the drug has been administered. Some researchers suggests that salbutamol helps widening small airways despite the high pressure from laying down, thereby increasing the oxygen levels by affecting the lung itself. Other studies with significant increase in HR and blood pressure propose that this helps the blood reaching the more challenging areas to reach in the anaesthetised horse laying down.

The drug is administered by inhalation through attaching the drug canister to a special adapter connected to the patients breathing tube. By compressing the canister at time of inhalation a dose of the aerosol is released into the patients' airways.

The aim of this study was to investigate the alterations in heart and blood vessels associated with salbutamol administration in anaesthetised horses and to explore if different degrees of hypoxemia based on saturation at time of administration affected its effectiveness. These aspects were explored by research questions also investigating the drugs indication, administration technique and use in horse anaesthesia.

Medical records from SLU University Animal Hospital (UDS) were searched for anaesthetised horses given salbutamol. A total of 33 cases meeting the inclusion criteria was identified. The data was collected from automatically generated files provided by the monitoring equipment and mean values for HR, arterial blood pressure (ABP) and saturation (SpO₂) was collected at the time point for salbutamol administration and then repeated with five minute intervals. Statistical analyses were done with the Freidmans test and Dunn's multiple comparisons post hoc test was applied when detecting a significant difference. Patient breed type, age, cause of anaesthesia, anaesthetic protocol and duration of monitoring after salbutamol administration varied between the cases. A large

variation in salbutamol dose was observed, from 1,88 to 5.78 µg/kg and 68% of the cases was given a dose >25% higher than the recommended 2µg/kg. A significant increase in SpO₂ was observed in mildly hypoxaemic horses (baseline SpO₂ 90-94%) at 10 and 15 minutes (p-value<0,0001) after salbutamol was given. No significant improvement was observed in severe hypoxaemic cases (SpO₂<90%). Despite a positive trend in mean HR up to 40 minutes following salbutamol administration, no significant increase was observed. Of the cases still monitored after 40 minutes, 68% had higher HR than the baseline values. The variation between individuals was large. No correlation between elevated HR and higher dose or age was seen. No significant alterations in ABP following salbutamol were observed.

These results raise question regarding salbutamol's effect depending on the severity of hypoxaemia and whether the drug should be given to prevent a beginning, or treat a present, hypoxaemia. Many experimental studies administered salbutamol to non-hypoxaemic patients, including those demonstrating a significant increase in HR and ABP. Conducting an experimental study with controlled administration times and doses might have given more study subjects and less interference from salbutamol dose differences and other drugs administered. However, a retrospective design allowed cases anaesthetised over a larger time frame and insight of the use of salbutamol in clinical patients.

As no significant elevation in HR or ABP was observed and no parameters related to lung function was measured in this study, no clue can be identified to contribute to the ongoing speculations about the mechanism behind salbutamol's effect on oxygenation.

In conclusion, this study identified a significant improvement in SpO₂ in mildly hypoxaemic horses, but not in cases of severe hypoxaemia. No significant increase in HR or ABP was observed in contrast to experimental studies on non-hypoxaemic horses. Severity of hypoxaemia may therefore influence the drugs effect on both oxygenation and heart and blood vessels, an aspect in need of further investigation. While salbutamol can be a practical tool to treat hypoxaemic horses, the personnel should consider other options, weight the benefits and limitations of salbutamol as well as being prepared to manage the individual patient's response.

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