The effects of inhalation salbutamol administration on systemic and pulmonary hemodynamic, pulmonary mechanics and oxygen balance during general anaesthesia in the horse

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ABSTRACT: This research aimed to determine the effect of aerosolized salbutamol administration on systemic and pulmonary hemodynamic, pulmonary mechanics and oxygen balance in healthy horses during general anaesthesia. Six healthy Thoroughbreds (body weight range 471–587 kg) underwent two general anaesthesias in dorsal recumbency with and without aerosolized salbutamol administration in randomized order with a one month washout period. The anaesthesia was induced by 1.1 mg/kg of xylazine, 0.02 mg/kg of diazepam and 2.2 mg/kg of ketamine, maintained with isoflurane in oxygen and air and horses were mechanically ventilated. Measurement of arterial and pulmonary arterial blood pressures, cardiac output and arterial and mixed venous blood gas analysis was carried out. Spirometry was performed using a Horse-lite. After achieving a steady state, baseline (T_0) values of cardiac output, systemic and pulmonary arterial blood pressures, heart rate, dynamic compliance, airway resistance and arterial and mixed venous blood gas values and pH were recorded in both groups. In the S-group (salbutamol), 2 μg/kg of aerosolized salbutamol were administered synchronously with inspirium into the tracheal tube. In both groups data were recorded at 15, 30, 45 and 60 min (T_{15}, T_{30}, T_{45}, T_{60}) after the baseline. PaO_2/FiO_2 ratio, oxygen consumption (VO_2), oxygen delivery (DO_2), pulmonary shunt values were calculated. Data were tested for normality and compared within each group: T_0 value with T_{15}, T_{30}, T_{45}, T_{60} values using Wilcoxon's test with Bonferoni correction (significance level 0.0125). For each time point, comparisons were made between the S- and C-groups (control) using Wilcoxon's test. In the S-group, there was a significant increase in values (mean ± SD) of cardiac output (l/min), T_0 (38 ± 7), a peak at T_{15} (64 ± 25.5), significantly higher values persisted throughout the period of anaesthesia; heart rate (beats/min), T_0 (32 ± 2), T_{15} (40 ± 6), T_{30} (38 ± 5); DO_2 (l/min), T_0 (5.8 ± 0.8), a peak at T_{15} (9.6 ± 3.2), significantly higher values persisted until the end of anaesthesia and VO_2 (l/min), T_0 (1.1 ± 0.5), T_{30} (1.6 ± 0.7) and T_{45} (1.8 ± 0.5). In the C-group, there was a significant decrease in values of PaO_2/FiO_2 ratio from T_0 (176 ± 67) to a minimum at T_{60} (114 ± 36) and in DO_2 from T_0 (6 ± 2.3) to a minimum at T_{60} (4.3 ± 1.2). A comparison of the S- and C-groups did not reveal any difference in the baseline data. Subsequently, significantly higher values of cardiac output, heart rate, DO_2, and the PaO_2/FiO_2 ratio were found in the S-group compared to the C-group. Pulmonary arterial blood pressure was significantly lower in the S-group. Aerosolized salbutamol administration in healthy horses during general anaesthesia caused hemodynamic changes which resulted in an elevation of oxygen delivery. It can have a positive effect on arterial oxygenation, but the effect varies between individuals.

Keywords: horse; hypoxaemia; salbutamol; general anaesthesia; arterial oxygenation

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General anaesthesia in the horse is accompanied by gas exchange impairment and development of hypoxaemia (Hall et al., 1968; Gillespie et al., 1969; Steffey et al., 1977; Trim and Wan, 1990; Whitehair and Willits, 1999). A decrease in PaO_2 and elevation of $PaCO_2$ is greater during spontaneous ventilation compared to mechanical ventilation (Hall et al., 1968; Gillespie et al., 1969).

Alteration of blood gas values and an increased alveolar-to-arterial oxygen gradient are the results of a ventilation and perfusion (V/Q) mismatch. This is a consequence of redistribution of perfusion caused by the force of gravity, redistribution of inspired gas and hypoventilation of the dependent lung, a decrease in cardiac output, development of atelectasis and an increase in pulmonary shunt (Hall et al., 1968; Gillespie et al., 1969; Nyman et al., 1990; Trim and Wan, 1990; Moens et al., 1995, 1998). Atelectasis formation in dependent lung regions is considered to be the main cause of impaired arterial oxygenation (Nyman et al., 1990; Moens et al., 1995). The extent of hypoxaemia is also influenced by body position during anaesthesia, age, body weight, shape of the abdominal contour and amount of abdominal contents (Steffey et al., 1977; Moens et al., 1995; Whitehair and Willits, 1999).

Intermittent positive pressure ventilation (IPPV) with the addition of positive end expiratory pressure (PEEP) or a combination of differential ventilation with selective PEEP of the dependent lung is effective in improving arterial oxygenation (Moens et al., 1994, 1998). The disadvantage of the latter technique is the technical difficulty involved. Implementation of a "recruitment manoeuvre" during IPPV allows opening of the collapsed lung areas and results in a significant increase in PaO_2 and decrease in pulmonary shunt (Wettstein et al., 2006). However, high inspiratory pressure and PEEP are accompanied by a depression of hemodynamic and cardiac output (Moens et al., 1998; Wettstein et al., 2006).

Pulsed delivery of nitric oxide synchronized with inspirium was shown to successfully increase PaO_2 values and decreased the amount of pulmonary shunt (Heinonen et al., 2001).

Studies concerned with the systemic or inhalant use of β_2 adrenergic agonists in hypoxaemic anaesthetized horses have reported controversial results. During inhalation anaesthesia, intravenous administration of clenbuterol was described to elicit an elevation in PaO_2. Adverse effects were also observed; tachycardia and profuse sweating (Gleed and Dobson, 1990; Keegan et al., 1991). Dodam et al. (1993) found no improvement in PaO_2 values after intravenous administration of clenbuterol in horses during total intravenous anaesthesia. Conversely, PaO_2 decreased as a result of β_2 receptor stimulation, vasodilatation, and an increase in heart rate and oxygen consumption. In the experimental study of Lee et al. (1998), intravenous administration of clenbuterol failed to produce any improvement in PaO_2 and caused a temporary increase in heart rate, cardiac output and muscle perfusion in horses during inhalation anaesthesia. Sweating also occurred. The sympathomimetic effects of clenbuterol, led to an increase in oxygen consumption.

Salbutamol is a selective β_2 adrenergic agonist; its inhalant administration is used in human medicine in patients suffering from primary pulmonary hypertension (Spiekerkoetter et al., 2002) or asthma (Wong et al., 1990).

A clinical study by Robertson and Bailey (2002), showed that administration of aerosolized salbutamol in horses under inhalation anaesthesia with PaO_2 values less than 9.3 kPa, led to an increase in these values within 20 min of treatment. The exact mechanism of action was not determined in that study.

The aim of our experimental study was to determine the effect of inhalation salbutamol administration on systemic and pulmonary hemodynamics, oxygen balance and pulmonary mechanics during general anaesthesia in healthy horses.

MATERIAL AND METHODS

The project for this experimental study (No. 1/2008) was approved by the Ethical Committee of the University of Veterinary and Pharmaceutical Sciences Brno and by the Ministry of Education, Youth and Sports of the Czech Republic.

Experimental animals

Six healthy Thoroughbreds with left *arteria carotis communis* raised subcutaneously were included in this experimental cross-over blind study; two stallions, three geldings and one mare. Their body weight ranged between 471 and 587 kg (median: 497). The age ranged between 5 and 10 years (median: 5.5). Horses were considered healthy on the basis of physical examination, haematology and basic serum biochemistry which were evaluated before general anaesthesia.

Anaesthetic protocol and instrumentation

Each horse underwent two general anaesthesias in dorsal recumbency, with and without aerosolized salbutamol administration (Ventolin; Glaxo Group Ltd, Greenford, Great Britain), in randomized order, with a one month washout period.

A venous catheter (Secalon T; Becton Dickinson Critical Care Systems Pte Ltd, Singapore) was placed into the right jugular vein before the induction of anaesthesia. Horses were sedated with 1.1 mg/kg of xylazine (Xylapan 2%; Vetoquinol Biowet, Gorzow Wlkp, Poland) intravenously and anaesthesia was induced with 0.02 mg/kg of diazepam (Apaurin; Krka, Novo Mesto, Slovenia) and 2.2 mg/kg of ketamine (Narketan 10%; Vetoquinol SA, Lure Cedex, France) intravenously. After orotracheal intubation with an endotracheal tube (Smiths Medical Pm Inc, Waukesha, USA) of suitable diameter, horses were transported to the operating theatre, placed in dorsal recumbency and connected to a large animal circle system (Stephan GmbH, Gackenbach, Germany). IPPV in a control pressure setup with peak inspiratory pressure 20–25 cm H_2O was used. Maintenance of anaesthesia was achieved with isoflurane (Aerrane; Baxter SA, Lessines, Belgium) in oxygen and air. The aim was to reach a fraction of inspired oxygen (FiO_2) of 0.60 but this parameter varied between 0.53 and 0.60. The actually reached values were noted and used for calculations. Ventilation was set to attain end tidal values of CO_2 (Et CO_2) between 5 kPa and 6 kPa and an Et value of isoflurane at 1.4%. At the beginning of anaesthesia, horses received a bolus of 1 l of colloids (Voluven; Fresenius Kabi, Bad Homburg, Germany) and supportive therapy continued by a constant rate infusion of crystalloids (Infusio Ringeri Mediekos; In Mediec, Luhacovice, Czech Republic) at a rate of 10 ml/kg/h.

An arterial catheter (Surflo 22 G; Terumo, Leuwen, Belgium) was placed into the right *arteria facialis* for arterial blood sample withdrawal which was performed anaerobically using special syringes (Monovette 2 ml LH; Sarstedt, Nümbrecht, Germany). A second arterial catheter (BD Arterial Cannula with FloSwitch; BD, Swindon, Great Britain) was placed into the raised left *arteria carotis communis* for systemic blood pressure and lithium dilution cardiac output measurements. An arterial catheter was connected to a pressure transducer, which was zeroed at the level of the right atrium.

An 8.5 F introducer (Intro-Flex; Baxter Healthcare Co, Irvine, USA) was placed into the right jugular vein, near the *apertura thoracis cranialis* for the introduction of a 7 F Swan-Ganz catheter (Swan-Ganz; Edwards Lifesciences, Irvine, USA) for pulmonary arterial blood pressure measurement and blood sample withdrawal. The distal port of the catheter was placed in the pulmonary artery and its position was confirmed by the characteristic shape of the pressure curve on a Datex-Ohmeda monitor (Datex-Ohmeda S/5; Datex-Ohmeda Inc, Madison, USA). The introducer was placed according to Seldinger's method (Seldinger, 1953). A pressure transducer for pulmonary arterial blood pressure measurement was set at the level of the right atrium.

Lithium dilution cardiac output measurements were performed using a commercial machine (LiDCOplus; LiDCO Ltd, London, Great Britain) and lithium chloride (LiCl; LiDCO Ltd, London, Great Britain) at a concentration of 0.15 mmol/ml was used at a dose of 0.03 mg/kg and administered intravenously. A calculated bolus of LiCl increased by the dead space value of the catheter was delivered through the jugular catheter. The measurement procedure was performed according to the manufacturer's instructions.

Blood gas analysis of arterial and mixed venous blood samples was performed using a Blood Gas analyzer with the CO-Ox module (Rapidlab 855; Bayer, Germany).

Monitoring

The following parameters were monitored continuously during anaesthesia: heart rate, ECG, SpO_2, systemic and pulmonary arterial blood pressures, Fi and Et of O_2, CO_2 and isoflurane, capnography and respiratory rate. Spirometric measurements of respiratory pressures and volumes were performed using Horse-lite, a Pitot-based flow meter (Moens et al., 2009) and dynamic compliance and airway resistance were calculated.

Experimental protocol

After steady state achievement (45 min), the following baseline values (T_0) were recorded in both the salbutamol group and the control group respectively: heart rate, arterial and mixed venous blood gas values and pH, systemic and pulmonary arterial

blood pressures, dynamic compliance, airway resistance and cardiac output. From this data, the following values were calculated according to the formulas below: PaO_2/FiO_2 ratio, oxygen delivery (DO_2), oxygen consumption (VO_2) and pulmonary shunt (Qs/Qt).

PaO_2/FiO_2 ratio = PaO_2/FiO_2/0,133
$DO_2 = ctO_2(a) \times Qt$
$VO_2 = ctO_2(a–v) \times Qt$
$Qs/Qt = ctO_2(c) – ctO_2(a)/ctO_2(c) – ctO_2(v)$

where:
$ctO_2(a)$ = arterial oxygen content
$ctO_2(v)$ = mixed venous oxygen content
$ctO_2(a–v)$ = arterial-mixed venous oxygen content difference
Qt = cardiac output
0.133 = conversion factor kPa to mmHg

In the salbutamol group, 2 µg/kg of aerosolized salbutamol were administered synchronously with inspirium into the tracheal tube using a microdose inhaler (MDI) adapter with a spacer (AeroChamber; Trudell Medical International, Ontario, Canada). The MDI adapter was connected between the tracheal tube and the Horse-lite which was attached to the Y-piece of the anaesthetic circle system. Salbutamol was administered at the onset of inspirium. The salbutamol inhaler was pressed 2–3 times during each inspirium, one press for each 50 kg of body weight. This step was omitted in the control group.

In both groups all data mentioned above were recorded at 15, 30, 45 and 60 minutes (T_{15}, T_{30}, T_{45}, T_{60}) after the baseline.

Statistical analysis

The following parameters were statistically analysed: cardiac output, heart rate, systemic and pulmonary arterial blood pressure (systolic, diastolic and mean), PaO_2/FiO_2 ratio, oxygen delivery, oxygen consumption, pulmonary shunt, dynamic compliance and airway resistance. Data were tested for normality and compared within each group: T_0 value with T_{15}, T_{30}, T_{45} and T_{60} values using Wilcoxon's test with Bonferoni correction (significance level 0.0125). For each time point (T_0, T_{15}, T_{30}, T_{45}, T_{60}), comparisons were made between the salbutamol and the control group using Wilcoxon's test in the PC programme KyPlot.

RESULTS

Results are presented in Tables 1 to 5 as means ± SD.

In the salbutamol group, a statistically significant difference ($P < 0.05$) was found between T_0 and T_{15}, T_{30}, T_{45}, T_{60} values for the following param-

Table 1. Hemodynamic parameters (cardiac output, heart rate, pulmonary and systemic arterial blood pressure) before (T_0) and after (T_{15}, T_{30}, T_{45}, T_{60}) salbutamol administration (salbutamol group) – comparison of T_0 value with T_{15}, T_{30}, T_{45}, T_{60} values

Parameter	T_0	T_{15}	T_{30}	T_{45}	T_{60}
Cardiac output (l/min)	38 ± 7	64 ± 25.5 $P = 0.031$	59.8 ± 23.4 $P = 0.031$	55.3 ± 19 $P = 0.031$	50.4 ± 9.4 $P = 0.046$
Heart rate (beats/min)	32 ± 2	40 ± 6 $P = 0.046$	38 ± 5 $P = 0.046$	34 ± 2 N.S.	32 ± 1 N.S.
Systolic pulmonary arterial blood pressure (mmHg)	26 ± 4	26 ± 2 N.S.	25 ± 2 N.S.	25 ± 3 N.S.	24 ± 2 N.S.
Diastolic pulmonary arterial blood pressure (mmHg)	12 ± 3	9 ± 1 N.S.	7 ± 4 N.S.	8 ± 3 N.S.	7 ± 2 $P = 0.031$
Mean pulmonary arterial blood pressure (mmHg)	16 ± 3	15 ± 2 N.S.	13 ± 3 N.S.	13 ± 2 N.S.	12 ± 2 $P = 0.049$
Systolic arterial blood pressure (mmHg)	80 ± 13	90 ± 13 N.S.	94 ± 13 N.S.	94 ± 14 N.S.	93 ± 10 N.S.
Diastolic arterial blood pressure (mmHg)	46 ± 10	56 ± 14 N.S.	60 ± 14 N.S.	58 ± 12 N.S.	58 ± 7 $P = 0.046$
Mean arterial blood pressure (mmHg)	60 ± 12	70 ± 16 N.S.	74 ± 15 N.S.	73 ± 14 N.S.	73 ± 9 N.S.

N.S. = not significant

Table 2. Hemodynamic parameters (cardiac output, heart rate, pulmonary and systemic arterial blood pressure) in the control group – comparison of T_0 value with T_{15}, T_{30}, T_{45}, T_{60} values

Parameter	T_0	T_{15}	T_{30}	T_{45}	T_{60}
Cardiac output (l/min)	37.4 ± 12.7	35.4 ± 10.1 N.S.	30.1 ± 5.4 N.S.	30 ± 5.9 N.S.	29.4 ± 3.7 N.S.
Heart rate (beats/min)	30 ± 2	30 ± 2 N.S.	30 ± 1 N.S.	31 ± 4 N.S.	31 ± 3 N.S.
Systolic pulmonary arterial blood pressure (mmHg)	28 ± 5	28 ± 4 N.S.	27 ± 3 N.S.	27 ± 4 N.S.	27 ± 4 N.S.
Diastolic pulmonary arterial blood pressure (mmHg)	13 ± 4	13 ± 2 N.S.	15 ± 2 N.S.	17 ± 4 $P = 0.039$	16 ± 5 N.S.
Mean pulmonary arterial blood pressure (mmHg)	20 ± 4	20 ± 3 N.S.	21 ± 3 N.S.	22 ± 4 N.S.	22 ± 4 N.S.
Systolic arterial blood pressure (mmHg)	77 ± 11	76 ± 13 N.S.	86 ± 14 $P = 0.046$	88 ± 12 $P = 0.045$	87 ± 12 $P = 0.045$
Diastolic arterial blood pressure (mmHg)	45 ± 11	45 ± 9 N.S.	56 ± 14 $P = 0.046$	59 ± 12 $P = 0.045$	58 ± 11 $P = 0.049$
Mean arterial blood pressure (mmHg)	58 ± 11	58 ± 10 N.S.	68 ± 14 $P = 0.045$	72 ± 13 $P = 0.046$	70 ± 12 $P = 0.045$

N.S. = not significant

eters. Cardiac output significantly increased from the baseline to a maximum value at T_{15} followed by a moderate decrease, but with significantly higher values at T_{30}, T_{45} and T_{60} when compared to the baseline. A transient increase in heart rate was noted at T_{15} and T_{30}; the following values at T_{45} and T_{60} were without any significant difference from the baseline. Diastolic and mean pulmonary arterial blood pressure decreased after salbutamol administration but a significant decrease was only recorded at T_{60} (Table 1). Oxygen delivery significantly increased from T_0 to a maximum value at T_{15}, subsequent values at T_{30}, T_{45} and T_{60} slightly decreased but were still significantly higher than the baseline. There was a significant increase in oxygen consumption at T_{30} and T_{45} compared to the baseline. Other values of VO_2 were not significantly different from T_0 despite their apparent increase (Table 3).

In the control group, a statistically significant difference was recorded between T_0 and T_{15}, T_{30}, T_{45}, T_{60} values for the following parameters. Systemic arterial blood pressure significantly increased at T_{30}, T_{45} and T_{60} when compared to the baseline (Table 2). The PaO_2/FiO_2 ratio significantly decreased between T_0 and all subsequent time points, with the minimum value at T_{60}. Oxygen delivery decreased, with significantly lower values at T_{30}, T_{45} and a minimum value at T_{60} when compared to the baseline (Table 3).

In a comparison between the salbutamol and control groups (Table 5), there was no significant difference in any parameter at the baseline. Subsequently, a statistically significant difference was found between the salbutamol and control group in the following parameters. There were significantly higher values for cardiac output and oxygen delivery after salbutamol administration than in the control group at T_{30}, T_{45} and T_{60}. Heart rate was significantly higher at T_{15} and T_{30} after salbutamol administration. The PaO_2/FiO_2 ratio was significantly higher after salbutamol administration than in the control group at T_{15}, T_{45} and T_{60}, while there was no significant difference at T_{30} despite a higher value in the salbutamol group. Diastolic and mean pulmonary arterial blood pressure was significantly lower after salbutamol administration than in the control group at T_{15}, T_{30}, T_{45} and T_{60}.

DISCUSSION

A statistically significant increase in cardiac output following salbutamol administration was recorded, reaching a maximum value fifteen minutes after administration. The increased cardiac output lasted for the whole monitoring period. At the same time, a transitory increase in heart rate occurred following salbutamol administration at T_{15} and T_{30} while heart rate was stable in the control

Table 3. Oxygen balance (PaO_2/FiO_2 ratio, DO_2, VO_2, Qs/Qt) in the salbutamol and control groups – comparison of T_0 value with T_{15}, T_{30}, T_{45}, T_{60} values within each group

Parameter	T_0		T_{15}		T_{30}		T_{45}		T_{60}	
	salbutamol	control	salbutamol	control	salbutamol	control	salbutamol	control	salbutamol	control
PaO_2/FiO_2	158 ± 32	176 ± 67	178 ± 52 N.S.	151 ± 56 $P = 0.031$	172 ± 37 N.S.	138 ± 56 $P = 0.031$	180 ± 43 N.S.	121 ± 41 $P = 0.031$	181 ± 47 N.S.	114 ± 36 $P = 0.031$
DO_2 (l/min)	5.8 ± 0.8	6.0 ± 2.3	9.6 ± 3.2 $P = 0.031$	5.4 ± 1.8 N.S.	8.9 ± 2.5 $P = 0.031$	4.4 ± 1.0 $P = 0.046$	8.3 ± 1.9 $P = 0.031$	4.3 ± 1.1 $P = 0.046$	7.6 ± 0.8 $P = 0.031$	4.3 ± 1.2 $P = 0.046$
VO_2 (l/min)	1.1 ± 0.5	1.4 ± 0.4	1.7 ± 0.6 N.S.	1.3 ± 0.2 N.S.	1.6 ± 0.7 $P = 0.031$	1.2 ± 0.2 N.S.	1.8 ± 0.5 $P = 0.046$	1.3 ± 0.2 N.S.	1.5 ± 0.5 N.S	1.4 ± 0.3 N.S.
Qs/Qt (%)	23 ± 4	19 ± 4	25 ± 4 N.S.	23 ± 4 N.S.	25 ± 7 N.S.	22 ± 4 N.S.	20 ± 3 N.S.	23 ± 6 N.S.	23 ± 5 N.S.	25 ± 8 N.S.

N.S. = not significant

Table 4. Spirometric measurements (dynamic compliance and airway resistance) in the salbutamol and control groups – comparison of T_0 value with T_{15}, T_{30}, T_{45}, T_{60} values within each group

Parameter	T_0		T_{15}		T_{30}		T_{45}		T_{60}	
	salbutamol	control	salbutamol	control	salbutamol	control	salbutamol	control	salbutamol	control
Dynamic compliance (l/kPa)	3.6 ± 0.4	3.5 ± 0.4	3.5 ± 0.4 N.S.	3.3 ± 0.4 N.S.	3.4 ± 0.4 N.S.	3.4 ± 0.3 N.S.	3.2 ± 0.3 N.S.	3.3 ± 0.5 N.S.	3.2 ± 0.3 N.S.	3.5 ± 0.5 N.S.
Airway resistance (kPa/l/s)	0.36 ± 0.05	0.38 ± 0.07	0.38 ± 0.07 N.S.	0.39 ± 0.14 N.S.	0.43 ± 0.11 N.S.	0.4 ± 0.15 N.S.	0.41 ± 0.13 N.S.	0.42 ± 0.13 N.S.	0.38 ± 0.13 N.S.	0.36 ± 0.13 N.S.

N.S. = not significant

Table 5. Comparison between the salbutamol and control group at each time point (hemodynamic parameters, oxygen balance and spirometric measurements)

Parameter	T_0		T_{15}		T_{30}		T_{45}		T_{60}	
	salbutamol	control	salbutamol	control	salbutamol	control	salbutamol	control	salbutamol	control
Cardiac output (l/min)	38 ± 7	37.4 ± 12.7	64 ± 25.5	35.4 ± 10.1	59.8 ± 23.4	30.1 ± 5.4	55.3 ± 19	30 ± 5.9	50.4 ± 9.4	29.4 ± 3.7
	N.S.		N.S.		$P = 0.031$		$P = 0.031$		$P = 0.031$	
Heart rate (beats/min)	32 ± 2	30 ± 2	40 ± 6	30 ± 2	38 ± 5	30 ± 1	31 ± 4	34 ± 2	31 ± 3	32 ± 1
	N.S.		$P = 0.031$		$P = 0.029$		N.S.		N.S.	
Systolic pulmonary arterial blood pressure (mmHg)	26 ± 4	28 ± 5	26 ± 2	28 ± 4	25 ± 2	27 ± 3	25 ± 3	27 ± 4	24 ± 2	27 ± 4
	N.S.		N.S.		N.S.		N.S.		N.S.	
Diastolic pulmonary arterial blood pressure (mmHg)	12 ± 3	13 ± 4	9 ± 1	13 ± 2	7 ± 4	15 ± 2	8 ± 3	17 ± 4	7 ± 2	16 ± 5
	N.S.		$P = 0.029$		$P = 0.031$		$P = 0.031$		$P = 0.030$	
Mean pulmonary arterial blood pressure (mmHg)	16 ± 3	20 ± 4	15 ± 2	20 ± 3	13 ± 3	21 ± 3	13 ± 2	22 ± 4	12 ± 2	22 ± 4
	N.S.		$P = 0.030$		$P = 0.031$		$P = 0.031$		$P = 0.031$	
Systolic arterial blood pressure (mmHg)	80 ± 13	77 ± 11	90 ± 13	76 ± 13	94 ± 13	86 ± 14	94 ± 14	88 ± 12	93 ± 10	87 ± 12
	N.S.		$P = 0.045$		N.S.		N.S.		N.S.	
Diastolic arterial blood pressure (mmHg)	46 ± 10	45 ± 11	56 ± 14	45 ± 9	60 ± 14	56 ± 14	58 ± 12	59 ± 12	58 ± 7	58 ± 11
	N.S.		N.S.		N.S.		N.S.		N.S.	
Mean arterial blood pressure (mmHg)	60 ± 12	58 ±11	70 ± 16	58 ± 10	74 ± 15	68 ± 14	73 ± 14	72 ± 13	73 ± 9	70 ± 12
	N.S.		N.S.		N.S.		N.S.		N.S.	
PaO_2/FiO_2	158 ± 32	176 ± 67	178 ± 52	151 ± 56	172 ± 37	138 ± 56	180 ± 43	121 ± 41	181 ± 47	114 ± 36
	N.S.		$P = 0.031$		N.S.		$P = 0.031$		$P = 0.031$	
Qs/Qt (%)	23 ± 4	19 ± 4	25 ± 4	23 ± 4	25 ± 7	22 ± 4	20 ± 3	23 ± 6	23 ± 5	25 ± 8
	N.S.		N.S.		N.S.		N.S.		N.S.	
VO_2 (l/min)	1.1 ± 0.5	1.4 ± 0.4	1.7 ± 0.6	1.3 ± 0.2	1.6 ± 0.7	1.2 ± 0.2	1.8 ± 0.5	1.3 ± 0.2	1.5 ± 0.5	1.4 ± 0.3
	N.S.		N.S.		N.S.		N.S.		N.S.	
DO_2 (l/min)	5.8 ± 0.8	6 ± 2.3	9.6 ± 3.2	5.4 ± 1.8	8.9 ± 2.5	4.4 ± 1	8.3 ± 1.9	4.3 ± 1.1	7.6 ± 0.8	4.3 ± 1.2
	N.S.		N.S.		$P = 0.031$		$P = 0.031$		$P = 0.031$	
Dynamic compliance (l/kPa)	3.6 ± 0.4	3.5 ± 0.4	3.5 ± 0.4	3.3 ± 0.4	3.4 ± 0.4	3.4 ± 0.3	3.2 ± 0.3	3.3 ± 0.5	3.2 ± 0.3	3.5 ± 0.5
	N.S.		N.S.		N.S.		N.S.		N.S.	
Airway resistance (kPa/l/s)	0.36 ± 0.05	0.38 ± 0.07	0.38 ± 0.07	0.39 ± 0.14	0.43 ± 0.11	0.4 ± 0.15	0.41 ± 0.13	0.42 ± 0.13	0.38 ± 0.13	0.36 ± 0.13
	N.S.		N.S.		N.S.		N.S.		N.S.	

N.S. = not significant

group during the whole monitoring period. Based on the results and the fact that in our study we have excluded hemodynamic medication support, we assume that inhalation salbutamol administration had a positive influence on heart activity through chronotropic and inotropic action with the result being an increase in cardiac output. The chronotropic action of salbutamol was recorded in the first half of the monitoring period while the inotropic action of salbutamol persisted throughout the whole monitoring period. This is proved by the fact that heart rate returned to basal values but cardiac output remained at an increased level for the whole period of anaesthesia. The inotropic mechanism for an increase in cardiac output following inhalation salbutamol administration is described by Spiekerkoetter et al. (2002) in human patients with primary pulmonary hypertension. An increase in the inotropic state following intravenous salbutamol administration was also recorded by Insulander et al. (2004). The chronotropic action of salbutamol is derived from direct stimulation of β_2 receptors in the heart and from the baroreceptor reflex that results from peripheral vasodilatation caused by the influence on β_2 vascular receptors (Insulander et al., 2004). Studies in human medicine (Wong et al., 1990; Bennet et al., 1994; Insulander et al., 2004) describe the action of inhalation or intravenous salbutamol administration similarly: heart rate increase, peripheral vasodilatation and a decrease in diastolic arterial blood pressure caused by the above mentioned mechanisms.

In our study, systemic arterial blood pressure was stable following salbutamol administration which corresponds with a clinical study conducted by Robertson and Bailey (2002). When compared to the baseline we recorded a slight increase that was not statistically significant. This stability of systemic arterial blood pressure following salbutamol administration, despite the increased cardiac output, can be attributed to changes in systemic vascular resistance. We did not measure central venous pressure and therefore calculate systemic vascular resistance, but if cardiac output, systemic arterial blood pressure and systemic vascular resistance are interrelated, then an increase in cardiac output at stable, or in our study, slightly increased, blood pressure could be accompanied by some degree of decrease in systemic vascular resistance. In the control group of horses, the low cardiac output was compensated for by an increase in systemic arterial blood pressure, possibly caused by an increased systemic vascular resistance. We did not record any decrease in systemic arterial blood pressure in our experimental horses following salbutamol administration which was however observed in human patients in studies conducted by Wong et al. (1990), Bennet et al. (1994) and Insulander et al. (2004). In a study on horses, Lee et al. (1998) also recorded a short-term decrease in systemic arterial blood pressure following intravenous administration of clenbuterol which lasted on average for 5 min. Dodam et al. (1993) recorded a decrease in mean arterial blood pressure as well as a decrease in mean pulmonary arterial blood pressure plus peripheral and pulmonary vascular resistance following intravenous administration of clenbuterol to horses undergoing total intravenous anaesthesia. We assume that in our study a decrease in systemic vascular resistance and peripheral vasodilatation occurred, but the absence of any decrease in systemic arterial blood pressure may be explained by compensation due to high cardiac output.

A decrease in diastolic and mean pulmonary arterial blood pressure following salbutamol administration was recorded, but the results were insignificant with the exception of T_{60} values. These results might be caused by individual variation in the decrease rates of pulmonary arterial blood pressure for each horse following salbutamol administration. However, comparing the two groups revealed significantly lower values of diastolic and mean pulmonary arterial blood pressure after salbutamol administration than in the control group. In a study conducted by Spiekerkoetter et al. (2002), the inhalation salbutamol administration in human patients with primary pulmonary hypertension caused an increase in cardiac output which was combined with a decrease in pulmonary and systemic vascular resistance, but the mean pulmonary arterial blood pressure did not change. The decrease in pulmonary vascular resistance could occur as a reaction to the increase in cardiac output or as a result of vasodilatation caused by the effect of salbutamol on β_2 receptors in pulmonary vessels or by a combination of both mechanisms. A certain vasodilatation effect of β_2-agonists administered by inhalation may be expected (Spiekerkoetter et al., 2002). In contrast with the study conducted by Spiekerkoetter et al. (2002), we recorded a decrease in diastolic and mean pulmonary arterial blood pressure while cardiac output was increased following salbutamol administration in horses undergoing general anaesthesia. This decrease might

be a result of vasodilatation of pulmonary vessels which is caused by the effect on β_2 receptors in combination with a reaction to high cardiac output. The presence of β_2 receptors in pulmonary vessels in mice and rats and their contribution to the mechanism of vasodilatation was proven in studies conducted by Leblais et al. (2008) and Pourageaud et al. (2005).

Cardiovascular changes observed following inhalation salbutamol administration support the idea that salbutamol is absorbed in the systemic blood circulation and influences heart activity and hemodynamics. This is further supported by the sweating which occurred in all horses following salbutamol administration and is in contrast with the control group where no such sweating was recorded. The idea of systemic absorption is also mentioned in a report of Robertson and Bailey (2002). The dose and method of administration of salbutamol in our study correspond to the dose and method of administration in the study conducted by Robertson and Bailey (2002), but they recorded sweating only in some patients (approximately 10%) which is in contrast with our experimental horses. Sweating in horses as a result of administration of β_2 agonists is also described in studies by Keegan et al. (1991) and Lee et al. (1998).

The PaO_2/FiO_2 ratio increased insignificantly following salbutamol administration but comparison of the two groups revealed significantly higher values in the salbutamol group than in the control group. The results clearly indicate a positive influence of salbutamol on the PaO_2/FiO_2 ratio. In the clinical study of Robertson and Bailey (2002) a more distinct improvement of arterial oxygenation was recorded following inhalation salbutamol administration, almost double the basal PaO_2 values were recorded. Based on the results of this study, the PaO_2/FiO_2 ratio increased from 66 to 127, which represents a 92% improvement, while the improvement in our study was only 12%. This can be explained by the fact that in our study we maintained constant ventilation parameters and excluded medication for hemodynamic support while in the study of Robertson and Bailey (2002) the goal to increase PaO_2 was achieved by increased intensity of ventilation and in cases of low blood pressure, by inotropic support with dobutamin prior to salbutamol administration. The increase in cardiac output caused by the effect of dobutamin did not improve arterial oxygenation (Swanson and Muir, 1986) but the combination with increased ventilation and salbutamol might intensify the effect of salbutamol. Robertson and Bailey (2002) assume that the mechanism for improvement in PaO_2 values includes bronchodilatation of the small bronchioles in the perfused lung areas in combination with increased cardiac output. The bronchodilatation action of salbutamol is known from studies in human patients (Wong et al., 1990; Bennet et al., 1994) and horses (Derksen et al., 1999). However, bronchodilatation in these cases is preceded by bronchoconstriction. Robertson and Bailey (2002) do not assume that cardiovascular factors contributed significantly to the improvement in arterial oxygenation, because no changes in heart rate and mean arterial blood pressure were observed either before or after salbutamol administration. They admit the possibility of a transitory improvement in pulmonary perfusion even though they did not measure cardiac output and the distribution of ventilation and perfusion. We assume that in our study salbutamol had a positive effect on hemodynamics and heart activity that led to increased cardiac output. This increase caused higher perfusion of the lungs and the decrease in pulmonary arterial blood pressure suggests that vasodilatation occurred in the pulmonary vessels. It is difficult to determine if the increase in the PaO_2/FiO_2 ratio occurred as a result of an improved V/Q ratio caused by salbutamol or only through an increase in cardiac output and pulmonary perfusion. As the pulmonary shunt values remained constant, we assume that there was no effect on the V/Q ratio and that improved pulmonary perfusion, in connection with a decrease in pulmonary arterial blood pressure, resulted in improved arterial oxygenation. The insignificant increase in the PaO_2/FiO_2 ratio following salbutamol administration could also be attributed to an insufficient number of values as the number of horses in both groups was the minimum required for statistical calculations. Other factors related to the effect of salbutamol, especially individual variability, might also contribute to the overall result.

A significant increase in oxygen delivery was observed following salbutamol administration with the maximum value recorded at T_{15}. This increase occurred at the same time as the maximum cardiac output. Based on the formula for calculating oxygen delivery and the above mentioned connection between increased oxygen delivery and cardiac output, we assume that the increase in oxygen delivery occurred mostly as a result of increased cardiac

output and, to a lesser extent, as a result of the improved PaO_2/FiO_2 ratio. The decrease in oxygen delivery in the control group could be related to low cardiac output and the level of arterial oxygenation which could also be observed as decreasing PaO_2/FiO_2 ratio values.

Oxygen consumption increased following salbutamol administration, whereas in the control group oxygen consumption was constant. However, a comparison between the groups revealed no significant difference which suggests that the extent of increase in oxygen consumption following salbutamol administration is not relevant and the resultant effect of its administration is positive. An increase in oxygen consumption following intravenous administration of clenbuterol was also recorded in studies conducted by Dodam et al. (1993) and Lee et al. (1998).

No statistically significant change in the amount of pulmonary shunt was recorded in either group. In contrast to this in a study conducted by Dodam et al. (1993), administration of clenbuterol caused an increase in pulmonary shunt and at the same time an increase in the proportion of dead space ventilation. Increased pulmonary shunt resulted in a decrease in PaO_2. In our study, we did not have at our disposal any device for measuring the ventilation-perfusion ratio, we were able to determine only the perfusion component and the ventilation component is missing. Therefore we could not determine the changes in the ventilation-perfusion ratio after salbutamol administration. But the possible causes of different results in pulmonary shunt in our study include the type of anaesthesia: inhalation anaesthesia vs. total intravenous anaesthesia, method of drug administration: inhalation vs. intravenous and different β_2 agonist: salbutamol vs. clenbuterol.

The results of spirometric measurements performed in our study did not reveal any changes in either the salbutamol group or the control group. The values for dynamic compliance and airway resistance were stable for both groups. These results are limited by the fact that they were obtained from horses with no muscle relaxation. Even though total compliance is dependent on the compliance of the chest, diaphragm, abdominal wall and lungs, muscle relaxation is required for monitoring changes in compliance of the lungs which limits the influence of other components. However, provided that the values obtained for the salbutamol and control group did not differ, we may assume that inhalation salbutamol administration does not have any influence on ventilation parameters.

The results of our study confirm the onset and duration of salbutamol action observed in the study by Robertson and Bailey (2002). However, we assume that the primary effect of salbutamol was seen in hemodynamics but based on our results, the mechanism of bronchodilatation or opening of collapsed lung areas is unlikely as this effect would be accompanied by a decrease in pulmonary shunt and an increase in dynamic compliance.

In our study, we recorded individual variability in response to inhalation salbutamol administration which was reflected in the values recorded for cardiac output, pulmonary arterial blood pressure, oxygen delivery, oxygen consumption, PaO_2/FiO_2 ratio and systemic arterial blood pressure. This fact may be possibly attributed to individual differences in β_2 receptor presence which are described in a study on horses conducted by Torneke (1999). Significant individual differences were also recorded in responses to β-adrenergic agonist administration (Torneke et al., 1998).

Inhalation salbutamol administration to healthy horses under general anaesthesia, which were artificially ventilated, resulted in an increase in cardiac output and oxygen delivery. Oxygen consumption was also slightly increased, but not to an extent that should overweigh the positive actions of salbutamol. Individual variations were large. It is necessary to assess the V/Q ratio and its changes following salbutamol administration in order to determine the exact mechanism of salbutamol action. Further clinical studies are warranted to study the mechanism of action in compromised patients.

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