AJVR

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Cardiac output affects the response to pulsed inhaled nitric oxide in mechanically ventilated anesthetized ponies determined by CT angiography of the lung

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Received January 23, 2023
Accepted March 27, 2023

doi.org/10.2460/ajvr.23.01.0005

OBJECTIVE
To measure changes in regional lung perfusion using CT angiography in mechanically ventilated, anesthetized ponies administered pulsed inhaled nitric oxide (PiNO) during hypotension and normotension.

ANIMALS
6 ponies for anesthetic 1 and 5 ponies for anesthetic 2.

PROCEDURES
Ponies were anesthetized on 2 separate occasions, mechanically ventilated, and placed in dorsal recumbency within the CT gantry. Pulmonary arterial, right atrial, and facial arterial catheters were placed. During both anesthetics, PiNO was delivered for 60 minutes and then discontinued. Anesthetic 1: hypotension (mean arterial pressure < 70 mmHg) was treated using dobutamine after 30 minutes of PiNO delivery. Following the discontinuation of PiNO, dobutamine administration was discontinued in 3 ponies and was continued in 3 ponies. The lung was imaged at 30, 60, and 105 minutes. Anesthetic 2: hypotension persisted throughout anesthesia. The lung was imaged at 30, 60, and 90 minutes. At all time points, arterial and mixed venous blood samples were analyzed and cardiac output ($\dot{Q}t$) was measured. Pulmonary perfusion was calculated from CT image analysis.

RESULTS
During PiNO delivery, perfusion to well-ventilated lungs increased if ponies were normotensive, leading to increased arterial oxygenation, reduced alveolar dead space, and reduced alveolar to arterial oxygen tension gradient. When PiNO was stopped and dobutamine administration continued, alveolar dead space and venous admixture increased, in contrast to when dobutamine and PiNO were both discontinued.

CLINICAL RELEVANCE
If PiNO is administered to mechanically ventilated, anesthetized ponies with concurrent hypotension and low $\dot{Q}t$, this must be supported to achieve favorable redistribution of pulmonary perfusion to improve pulmonary gas exchange.

Equine anesthesia is associated with the development of numerous complications that may be implicated in this species' high perioperative mortality rate.[1,2] Hypoventilation, hypotension (mean arterial pressure [MAP] < 70 mmHg), and hypoxemia (PaO_2 < 60 mmHg), occur relatively frequently during general anesthesia in horses, necessitating interventional treatment.[3] These complications occur as a consequence of the administration of anesthetic drugs and the physical effects of recumbency.[4–6]

Mechanical ventilation (MV) is often used to counteract hypoventilation, but this may further aggravate the cardiovascular effects of general anesthesia.[6–8]

Hypotension (and poor cardiac output) is usually managed using infusions of dobutamine, a synthetic catecholamine with beta-1 agonistic activity.[9] The improvement in cardiac contractility leads to increased cardiac output and blood pressure in healthy horses.[4]

Hypoxemia in anesthetized horses usually results from profound ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch and the development of a large right-to-left intrapulmonary shunt.[5] Treatment strategies using modifications to the open lung concept, to reinflate atelectatic lung regions, have been largely successful. However, these techniques can have

additional detrimental effects on blood pressure and cardiac output.[3] Furthermore, MV and the application of positive-end expiratory pressure (PEEP) may increase intrapulmonary shunt, presumably by forcing blood downwards, to dependent regions of the lung that are atelectatic, worsening pulmonary gas exchange.[10,11]

Alternative solutions have been described that manipulate pulmonary perfusion rather than manage ventilation. The administration of pulsed inhaled nitric oxide (PiNO) to anesthetized horses, improves perfusion to ventilated lungs and reduces perfusion to atelectatic lung (reduced intrapulmonary shunting), and $\dot{V}/\dot{Q}$ matching is enhanced.[12–14] This movement of blood has been quantified using gamma scintigraphy in horses,[12] and using CT angiography (CTA) in ponies.[13] The beneficial effect of PiNO on oxygenation indices in anesthetized horses has been described in numerous studies.[14–19] However, if PiNO is administered to mechanically ventilated horses exhibiting concurrent hypotension, PiNO is ineffective.[20] This is in contrast to hypotensive, spontaneously breathing horses, presumably because of differing respiratory mechanics between the 2 modes of ventilation. Moreover, the administration of dobutamine to improve cardiac output and pulmonary perfusion in combination with nitric oxide (NO) during MV, appears to optimize the effect of NO.[21]

This study aimed to document the effect of PiNO on pulmonary perfusion using CTA in mechanically ventilated, anesthetized ponies during periods of hypotension and normotension achieved using an infusion of dobutamine. We hypothesized that the delivery of PiNO during periods of hypotension would not redistribute pulmonary perfusion, compared with the delivery of PiNO during dobutamine administration.

Materials and Methods

This experiment was a prospective, experimental study. The local Ethical Committee on Animal Experiments in Uppsala, Sweden, approved this study, which included 6 healthy ponies (5 Shetland ponies and 1 crossbreed pony; 1 mare, 3 geldings, and 2 stallions) with a mean weight of 190 kg (150–241 kg) and a mean age 12 years (range = 4–18 years). Health status was confirmed on clinical examination and complete blood analysis.

Anesthesia

Ponies were anesthetized on 2 separate occasions using the same protocol. Food was withheld for 12 hours before general anesthesia and water was provided ad libitum until the point of venous catheterization. Premedication was with acepromazine (0.03 mg/kg^{-1}) intramuscularly (IM) approximately 45 minutes before induction to general anesthesia. After subcutaneous infiltration with lidocaine, a catheter (14 G X 90 mm) was placed into the left jugular vein and two sheath introducers (8.5 Fr) into the right jugular vein. Further premedication was with xylazine (1.1 mg/kg^{-1}) and butorphanol (0.025 mg/kg^{-1}), administered intravenously (IV). General anesthesia was induced using ketamine (2.2 mg/kg^{-1}) and diazepam (0.05 mg/kg^{-1}), mixed in the same syringe, and given IV. Once unconsciousness was attained, the trachea was intubated with a size 20 mm endotracheal tube, and the pony hoisted onto an appropriately padded CT table with the head facing the CT gantry. The fore and hind limbs were allowed to fall into natural positions with padding inserted between the lower antebrachium and the metacarpal bone. The endotracheal tube was connected to a large animal anesthetic circuit and machine. Inserted between the breathing system and the endotracheal tube was an arrangement of pitot tubes for measurement of lung volumes and flow and a simple ball-valve tap to facilitate a breath-hold during CT acquisition. General anesthesia was maintained using isoflurane vaporized in oxygen with an inspired oxygen fraction (FIO_2) of approximately 0.9. IV fluid therapy was administered throughout anesthesia using a balanced isotonic crystalloid solution, and ponies were mechanically ventilated throughout both anesthetics. Tidal volume and rate were adjusted to maintain $PaCO_2$ between 45 and 68 mmHg and peak inspiratory pressure (PIP) was kept below 30 cmH_2O. At the end of the experiment, anesthesia was terminated and the pony was hoisted into a padded stall and allowed to recover. Analgesia was provided at this time with flunixin meglumine (1.1 mg/kg^{-1}) IV and morphine (0.1 mg/kg^{-1}) IM.

Instrumentation and hemodynamic analysis

The facial artery was catheterized (18 G X 32 mm) for sampling arterial blood and measurement of systemic blood pressure. A thermodilution catheter (7F X 110 cm) was inserted into the pulmonary artery via one of the pre-placed introducers. This catheter was used for sampling of mixed venous blood and measurement of mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output ($\dot{Q}t$) by thermodilution. A pigtail, multi-hole catheter, was similarly inserted through the other pre-placed introducer, advanced into the right ventricle, and then retracted into the right atrium. This catheter was used for injection of both iodinated contrast medium and ice-cold saline for $\dot{Q}t$ measurement using thermodilution. Catheters were positioned using pressure waveform guidance and simultaneous ECG analysis. Pressures were measured by connecting catheters to calibrated transducers and saline-filled columns. The transducers were zeroed to atmospheric pressure and positioned at the level of the scapulohumeral joint.

A multiparameter monitor was connected to each pony to measure the ECG (Lead I), heart rate (HR), arterial hemoglobin oxygen saturation using pulse oximetry (SpO_2), end-tidal (ET), and an inspired fraction (FI) of carbon dioxide (CO_2), oxygen (O_2) and anesthetic vapor, respiratory rate

(*f*R), tidal volume (TV), PIP, systolic (SAP), MAP and diastolic (DAP) arterial blood pressures, MPAP, PCWP, and $\dot{Q}t$.

Thermodilution was used to determine $\dot{Q}t$. During the expiratory pause, the same person injected a 20 mL bolus of ice-cold saline through the pigtail catheter by hand. A minimum of 3 measurements were made at each data collection point and the average was recorded.

Blood gas measurements

At each data collection point, arterial and mixed venous blood samples were simultaneously collected into heparinized syringes, from the facial arterial and the Swan-Ganz catheters, respectively, and analyzed immediately using a standard electrode technique (ABL 90 flex, Radiometer). Arterial pH (pHa), PaO_2, $PaCO_2$, arterial oxygen saturation (SaO_2), hemoglobin concentration ([Hb]), mixed venous oxygen tension ($P\bar{v}O_2$), and oxygen saturation ($S\bar{v}O_2$) were measured. Blood gases were corrected for temperature.[22]

Nitric oxide delivery

Delivery of PiNO during each anesthetic was achieved using an airway pressure-triggered device (Datex-Ohmeda Research Unit), which intermittently delivered a volumetric dose of NO from the beginning of inspiration for 30% to 45% of the total inspiratory time. The device was connected to a cylinder supply of 2000 ppm NO in N_2 (AGA). The approximate dose of NO delivered during each breath was 2.5–5.0 μM.

Groups

During both anesthetics, hypotension (MAP between 44 and 52 mmHg) was allowed to develop over the initial 60 minutes of anesthesia while the ponies were being instrumented. For the following 60 minutes, PiNO was then delivered. In the first experiment (treatment group, n = 6), data were collected after 30 minutes of PiNO (time point T1). Dobutamine was then administered as a variable rate infusion (0.5 to 5.0 $\mu g \cdot kg^{-1} \cdot in^{-1}$) to maintain MAP between 70 and 80 mmHg for 30 minutes and data was collected again (time point T2). PiNO was then discontinued and dobutamine was discontinued in 3 ponies and was continued in 3 ponies. Data were collected after 45 minutes after PiNO cessation (time points T3a and T3b, respectively).

In the second experiment (control group, n = 5), hypotension (MAP 44 to 59 mmHg) was allowed to develop as described but was not treated and persisted throughout the entire anesthetic. Data were collected at 30 (time point C1) and 60 minutes (time point C2) of PiNO delivery. PiNO was discontinued and data was collected again after 30 minutes (time point C3).

CT data acquisition

A complete description of the CT angiography technique is reported elsewhere.[13] In brief, dynamic axial scans were acquired at each time point using a third-generation, 64-slice multi-detector CT scanner (Somatom Definition AS, Siemens Medical Systems) at exposures of 70 mAs and 120 kV, slice thickness 15.0 mm and rotation time 0.33 seconds. Iodinated contrast agent (Omnipaque 300 mg/mL^{-1} GE Healthcare) was injected directly into the right atrium using the multi-hole pigtail catheter using an automated injector (Medrad Stellant dual syringe CT injection system, Bayer AG). CT scans were acquired with breath held at peak inspiration using the plumbing ball valve. Each scan sequence lasted 50 seconds. DICOM files as a series of 166 images at 3 per second were exported to Osirix (v.5.8.5 64-bit). CT images were analyzed using ImageJ (v1.49, National Institute of Health). Lung regions were delineated using threshold windows: for atelectatic lung 100 to −100 Hounsfield Units (HU); for poorly ventilated lung −100 to −500 HU; and for normally ventilated lung −500 to −1000 HU.[23] Calculations of perfusion were made using the methodology described previously,[13] and perfusion values are presented as milliliter blood $minute^{-1}$ $gram\ tissue^{-1}$.

Calculated data

Oxygen content of end capillary ($Cc'O_2$), arterial (CaO_2), and mixed venous ($C\bar{v}O_2$) blood were calculated as $CxO_2 = (1.36 \times [Hb] \times SxO_2) + (0.003 \times PxO_2)$, where *x* is c′, a or $\bar{v}$; PAO_2 was used to calculate $Cc'O_2$.

Alveolar oxygen tension (PAO_2) was calculated using the alveolar gas equation: $PAO_2 = FIO_2$ (barometric pressure − water vapor pressure) - $PACO_2/RQ$.[24] Where: alveolar carbon dioxide tension ($PACO_2$) is substituted with $PaCO_2$ and respiratory quotient (RQ) is taken as 0.8. Oxygen delivery (DO_2) was calculated as $CaO_2 \times \dot{Q}t$.

Venous admixture ($\dot{Q}s/\dot{Q}t$) was calculated using the Berggren shunt formula:[25]

$$\dot{Q}s/\dot{Q}t = (Cc'O_2 - CaO_2)/(Cc'O_2 - C\bar{v}O_2).$$

The cardiac index (CI) was calculated as $\dot{Q}t$/body weight in kilograms. Minute ventilation (V_E) was calculated as *f*R × TV. Alveolar dead space Vd/Vt was calculated as $(PaCO_2\text{-}ETCO_2)/PaCO_2$. Alveolar-arterial oxygen tension difference ($P(A\text{-}a)O_2$) was calculated as $PAO_2 - PaO_2$. The oxygen extraction ratio, OER, was calculated as $C(a - \bar{v})O_2/CaO_2$.

Statistical analysis

Data for each pony were collected during 2 anesthetics: control (C) and treatment (T). During each anesthetic, data were collected at 3 time points, denoted 1, 2, and 3. Thus, there were 6 measurements per pony: C1, C2, and C3 and T1, T2, and T3 (a or b). Dobutamine was only given at measurement T2. Because there were several observations per pony, data were analyzed using the mixed procedure of the SAS/STAT software (SAS Institute Inc).[26] The fixed part of the model included anesthetic (C or T), time, and the anesthetic*time interaction. The pony

was set as a random factor. In a post hoc comparison, the average for measurements C1, C2, and T1 was compared with the T2 value; that is, the observation with active treatment was compared with the average of the untreated observations using linear contrasts. The assumptions were checked using diagnostic plots. No apparent deviations from normality or homoscedasticity were detected.

For time points after PiNO discontinuation (C3 and T3a or b), descriptive data are included. No statistical analysis was performed due to the small number of ponies included at these time points.

Results

Distribution of perfusion

In the control experiment, perfusion to all lung regions did not change over time during PiNO administration. In the treatment experiment, perfusion to well-ventilated lung regions (−500 to −1000 HU) increased significantly when dobutamine was administered. Perfusion to poorly ventilated lung regions (−100 to −500 HU), and atelectatic lung regions did not change significantly **(Table 1)**.

During the treatment experiment, the 6 ponies were divided into 2 further subgroups once PiNO was discontinued. In the first subgroup in which hypotension developed again, perfusion to the atelectatic lung (100 to −100 HU) decreased. In the second subgroup in which normotension was maintained, perfusion to the atelectatic lung did not change. These results were not tested statistically due to the small number of ponies within each subgroup.

Physiological data

In the control group **(Table 2)**, there were no significant differences in any physiological parameters or any of the calculated data recorded over the entire experimental period.

In the treatment group **(Table 3)**, there was a significant interaction when delivering PiNO and administering dobutamine: MAP, MPAP, $\dot{Q}t$, HR, PaO_2, DO_2, and [Hb] all increased and Vd/Vt and $P(A\text{-}a)O_2$ decreased. There were also significant differences over time between time points T1 and T2: MPAP, $\dot{Q}t$, HR, PaO_2, DO_2, $\dot{Q}s/\dot{Q}t$, and [Hb] increased and $P(A\text{-}a)O_2$ decreased.

During the treatment experiment, the 6 ponies were divided into 2 further subgroups once PiNO was discontinued. In the second subgroup in which dobutamine administration continued and normotension was maintained, $\dot{Q}s/\dot{Q}t$ and Vd/Vt increased compared with the previous measurement. This correlated with a fall in PaO_2. These results were not tested statistically due to the small number of ponies within each subgroup.

Table 2—Physiological parameters during control experiment in mechanically ventilated anesthetized ponies.

Anaesthesia 1 – Control group

Variable	C1 n = 5	C2 n = 5	C3 n = 5
MAP (mmHg)	56 ± 6	54 ± 3	54 ± 1
MPAP (mmHg)	15.6 ± 3.5	15.6 ± 2.5	14.7 ± 1.5
$\dot{Q}t$ (L/min)	10.5 ± 3.3	8.9 ± 0.7	8.2 ± 0.9
HR (beats/min)	42 ± 6	40 ± 4	39 ± 2.1
V_E (L/min)	20.3 ± 1.6	20.3 ± 4.1	19.8 ± 2.0
$PaCO_2$ (kPa)	6.8 ± 1.3	6.9 ± 1.5	7.5 ± 1.8
Vd/Vt (%)	19 ± 3	22 ± 4	25 ± 6
$\dot{Q}s/\dot{Q}t$ (%)	28 ± 4	28 ± 4	37 ± 5
$P(A\text{-}a)O_2$ (kPa)	37.1 ± 5.9	39.1 ± 8.8	46.0 ± 14.5
PaO_2 (kPa)	39.2 ± 10.1	38.3 ± 10.1	35.8 ± 16.9
SaO_2 (%)	96.5 ± 0.4	96.5 ± 0.4	96.1 ± 1.0
DO_2 (L/min)	1.09 ± 0.28	0.96 ± 0.20	0.85 ± 0.20
[Hb] (g/L)	74.0 ± 14.1	75.0 ± 16.7	73.0 ± 14.1
ETiso (%)	1.5 ± 0.2	1.8 ± 0.2	1.6 ± 0.2

See Table 1 for group descriptions. DO_2 = Oxygen delivery; ETiso = End-tidal isoflurane concentration; [Hb] = Hemoglobin concentration; HR = Heart rate; MAP = Mean arterial blood pressure; MPAP = Mean pulmonary arterial pressure; $P(A\text{-}a)O_2$ = Alveolar-arterial oxygen tension difference; $PaCO_2$ = Arterial partial pressure of carbon dioxide; PaO_2 = Arterial partial pressure of oxygen; $\dot{Q}s/\dot{Q}t$ = Shunt fraction; $\dot{Q}t$ = Cardiac output; SaO_2 = Arterial oxygen saturation; Vd/Vt = Alveolar dead space; V_E = Minute volume.

Table 1—Distribution of perfusion in different lung regions in mechanically ventilated anesthetized ponies during two different anesthetics.

	Distribution of perfusion (mL blood/min/gram tissue)					
						T3a
Lung region	C1	C2	C3	T1	T2*	*T3b*
−500 to −1000 (HU)	3.9 ± 1.2	3.7 ± 0.9	2.9 ± 0.4	4.1 ± 0.8	7.0 ± 3.3†	3.6 ± 1.3 *6.1 ± 0.4*
−100 to −500 (HU)	4.5 ± 1.1	4.4 ± 0.9	3.0 ± 0.4	4.3 ± 1.0	6.7 ± 2.1	3.3 ± 0.4 *4.7 ± 0.5*
100 to −100 (HU)	3.8 ± 1.4	2.5 ± 0.9	2.0 ± 0.5	1.7 ± 1.4	2.7 ± 0.7	1.5 ± 0.3 *2.7 ± 0.2*

Control experiment time points: C1 = Hypotension and pulsed inhaled nitric oxide (PiNO) delivery for 30 min; C2 = Hypotension and PiNO delivery for 60 min; C3 = Hypotension and PiNO discontinued for 30 min. Treatment experiment time points: T1 = Hypotension and PiNO delivery for 30 min; T2 = Normotension (mean arterial pressure 70–80 mmHg achieved with dobutamine) and PiNO delivery for 60 min; T3a = Hypotension and PiNO discontinued for 45 min; T3b = Normotension (continued dobutamine administration) and PiNO discontinued for 45 min.

A significant interaction was seen between the distribution of perfusion to lung regions and the effect of dobutamine during concurrent pulsed inhaled nitric oxide, *$P < .001$. Difference in perfusion compared with the previous measurement, †$P < .021$. Time points T3a and T3b were not tested statistically.

Table 3—Physiological parameters during treatment experiment in mechanically ventilated anesthetized ponies.

Anaesthesia 2 – Treatment group

Variable	T1 n = 6	T2 n = 6	T3a n = 3 *T3b n = 3*
MAP* (mmHg)	54 ± 2	76 ± 2	46.7 ± 1.5 *72.7 ± 1.5*
MPAP* (mmHg)	8.2 ± 2.8	13.7 ± 3.9†	9.3 ± 4.2 *18.7 ± 0.6*
$\dot{Q}t$* (L/min)	9.1 ± 2.2	17.2 ± 4.5†	7.7 ± 0.8 *20.4 ± 0.6*
HR * (beats/min)	41 ± 4	53 ± 9 †	39 ± 6 *68 ± 15*
V_E (L/min)	19.0 ± 4.3	19.1 ± 4.1	16.4 ± 2.2 *22.1 ± 3.9*
$PaCO_2$ (kPa)	6.9 ± 1.1	7.4 ± 1.0	6.3 ± 1.4 *8.3 ± 0.6*
V_D/V_T * (%)	27 ± 4	25 ± 2	27 ± 1 *33 ± 3*
$\dot{Q}s/\dot{Q}t$ (%)	26 ± 7	33 ± 6‡	25 ± 9 *43 ± 4*
$P(A\text{-}a)O_2$ * (kPa)	37.3 ± 9.6	22.8 ± 5.5‡	30.8 ± 19.2 *34.0 ± 9.7*
PaO_2 * (kPa)	37.8 ± 10.1	51.8 ± 5.5†	46.4 ± 21.6 *40.2 ± 0.8*
SaO_2 (%)	96.7 ± 0.3	96.8 ± 0.2	96.7 ± 0.3 *96.6 ± 0.0*
DO_2 * (L/min)	0.93 ± 0.21	2.8 ± 0.9‡	0.91 ± 0.17 *3.2 ± 0.17*
[Hb]* (g/L)	81.3 ± 8.4	114.5 ± 8.4‡	81.0 ± 5.3 *112.3 ± 7.2*
ETiso (%)	1.3 ± 0.3	1.3 ± 0.1	1.3 ± 0.3 *1.2 ± 0.1*

See Table 1 for group descriptions.

Statistical comparisons were performed for T1 and T2. A significant interaction was seen between the effect of dobutamine and concurrent pulsed inhaled nitric oxide, *$P < .001$. Significantly different compared with the previous measurement, †$P < .05$, ‡$P < .01$.

Discussion

Using CTA, we have demonstrated that when blood pressure and $\dot{Q}t$ are supported with dobutamine, the effect of PiNO on $\dot{V}/\dot{Q}$ matching is optimized in mechanically ventilated anesthetized ponies: perfusion to ventilated regions of lung increases leading to improvements in oxygenation. During periods of hypotension and MV, the redistribution of perfusion to the ventilated lung when PiNO is delivered, is lost.

Mechanical ventilation can affect oxygenation in several ways. Global $\dot{Q}t$ is adversely affected due to cyclical increases in intrathoracic pressure via its effects on mean cardiac filling pressures,[7] and a reduction in venous return via compression of major intrathoracic veins.[27] Hypoxemia may develop as a direct consequence of low $\dot{Q}t$, because $S\bar{v}O_2$ decreases as more oxygen is extracted by the tissues.[27] Positive intrathoracic pressure can also adversely affect $\dot{V}/\dot{Q}$ matching by: over-ventilating well-ventilated regions of the lung and reducing blood supply to these areas through increased pulmonary vascular resistance (PVR),[28] and; driving blood downwards towards atelectatic regions of the lung, so increasing $\dot{Q}s/\dot{Q}t$.[5,29] Compounding all of these effects is the fall in global $\dot{Q}t$ during general anesthesia that may, in turn, reduce perfusion to well-ventilated regions of the lung and increase alveolar dead space.[30] In the ponies supported with dobutamine in this study, the resulting increase in $\dot{Q}t$ minimized the negative cardiovascular effects of MV on the response to PiNO delivery and agrees with a previous study.[20] However, in the latter study, regional pulmonary perfusion was not measured. In this present study, we were able to demonstrate that when PiNO was delivered to ponies with dobutamine administered concurrently, pulmonary blood was redistributed to well-ventilated regions of the lung, leading to improvements in oxygenation. When blood pressure was not supported, PiNO had no effect on regional pulmonary perfusion or on indices of oxygenation.

The administration of PiNO has been shown to reduce PVR in anesthetized ponies but this is of little clinical significance.[15] However, PiNO may offset the increase in PVR that is observed with MV as described above and minimize the negative effects on $\dot{V}/\dot{Q}$ matching. Furthermore, the administration of dobutamine has been shown to reduce PVR whilst at the same time, augmenting $\dot{Q}t$.[31] These additive, vasodilatory effects within the pulmonary vasculature may explain the superior response to PiNO during dobutamine administration. The interaction between dobutamine and continuously inhaled NO has been reported in humans with pulmonary hypertension.[21] In this latter study, a complementary effect was described with augmented $\dot{Q}t$ and pulmonary vasodilation in well-ventilated lung regions, leading to improved $\dot{V}/\dot{Q}$ matching. In this present study, we have shown that by giving PiNO and dobutamine together, perfusion to aerated lung regions improves; therefore, optimizing $\dot{V}/\dot{Q}$ matching, which is supported by improvements in PaO_2, $\dot{Q}s/\dot{Q}t$, and DO_2.

The relatively wide range of $PaCO_2$ values observed in this study may have affected PVR. However, the independent effects of CO_2 on the equine pulmonary vasculature have not been described, and there are contradictory reports on other species. In hypoxaemic dogs, PVR was elevated in the presence of increased CO_2,[32] whilst in isolated rat lungs, PVR decreased in response to hypercapnia.[33] In previous studies, we have compared spontaneously breathing ponies with those that were mechanically ventilated. In those experiments, $PaCO_2$ was lower in the MV group but no differences in PVR were observed regardless of ventilation mode, suggesting that $PaCO_2$ had little influence on the overall results.[14]

In this study, hypotension and poor $\dot{Q}t$ affected the expected response to PiNO based on previous work where indices of oxygenation improve.[14–19] However, this poor response to PiNO agrees with a previous study in anesthetized horses.[20] In anesthetized humans with nitroprusside-induced hypotension, gas exchange is adversely affected: $\dot{Q}s/\dot{Q}t$

and Vd/Vt increase due to vasodilation of pulmonary vessels in dependent lung regions and a fall in PVR.[34,35] It is possible that this effect of hypotension during anesthesia may counteract the response to PiNO. However, when hypotension is induced with isoflurane, gas exchange is not affected significantly, suggesting that nitroprusside itself, may have an effect on pulmonary gas exchange rather than hypotension per se.[36] Because hypotension in the ponies in this present study was induced with isoflurane, it seems unlikely that hypotension alone was responsible for the lack of response to PiNO; more, it was the combination of MV and hypotension.

In the past, it has been demonstrated that dobutamine improves $\dot{Q}t$, systemic vascular resistance, and PVR in horses.[37,38] Despite this, in anesthetized horses, it has been shown that supporting $\dot{Q}t$ using dobutamine has little effect on pulmonary gas exchange.[39] In the latter part of the treatment group experiment, we discontinued PiNO in all 6 ponies and then allowed hypotension to develop in three ponies, but continued dobutamine administration in the remaining 3 ponies. This was to differentiate between the effect of PiNO on pulmonary gas exchange and simply an effect of dobutamine alone. We found that perfusion to atelectatic lung regions and $\dot{Q}s/\dot{Q}t$ increased when dobutamine was administered after discontinuation of PiNO, although this was not tested statistically due to the small number of ponies at these time points. As the vasodilatory effect of PiNO in well-ventilated lung regions waned, dobutamine appeared to drive blood toward dependent lung regions. Dobutamine does impair oxygenation in humans by increasing $\dot{Q}s/\dot{Q}t$ and $\dot{V}/\dot{Q}$ mismatch.[40,41] The correlation between increased $\dot{Q}t$ and increased $\dot{Q}s/\dot{Q}t$ has also been documented in pigs[42] and dogs.[43,44] The impairment in gas exchange associated with increased $\dot{Q}t$, either through exercise or pharmacological means, may be associated with the recruitment of intrapulmonary shunt vessels in humans,[45] dogs,[46] cats, and rabbits.[47] In the equine lung, there are conflicting reports regarding the presence of intrapulmonary arteriovenous shunts,[48,49] but their potential existence may offer an additional explanation as to why dobutamine does not improve pulmonary gas exchange in this species.

There were some limitations to this study. Due to the size of the CT gantry, this study was limited to ponies up to a certain size. Although pulmonary physiology is similar between horses and ponies, the magnitude of gas exchange derangements is known to be associated with body mass and dimensions of the thorax.[50] This may be a reason why none of the ponies studied developed significant hypoxemia during anesthesia (PaO_2 < 60 mmHg). However, this study aimed to document the effect of PiNO on regional pulmonary perfusion during periods of hypotension and mechanical ventilation and to compare this during treatment with dobutamine. We were able to show that there was a significant effect on pulmonary perfusion and oxygenation indices when $\dot{Q}t$ was supported with dobutamine in conjunction with the delivery of PiNO.

When anesthetized ponies are hypotensive and mechanically ventilated, the effect of PiNO on regional pulmonary perfusion and $\dot{V}/\dot{Q}$ matching is disrupted. To optimize the effect of PiNO on gas exchange and $\dot{V}/\dot{Q}$ matching, $\dot{Q}t$ must be supported during periods of mechanical ventilation.

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