Journal of Zoo and Wildlife Medicine 48(4): 1016–1025, 2017

EVALUATION OF BLOOD GAS VALUES IN ANESTHETIZED SOUTHERN WHITE RHINOCEROS (*CERATOTHERIUM SIMUM*) VENTILATED WITH A NOVEL DEMAND VENTILATOR IN A ZOOLOGICAL PARK SETTING

Mark Jeon, B.S., Khursheed R. Mama, D.V.M., Dipl. A.C.V.A.A., Jeffrey R. Zuba, D.V.M., Nadine Lamberski, D.V.M., Dipl. A.C.Z.M., James E. Oosterhuis, D.V.M., Meredith M. Clancy, D.V.M., M.P.H., Katie W. Delk, D.V.M., Dipl. A.C.Z.M., Matthew E. Kinney, D.V.M., Dipl. A.C.Z.M., Patrick J. Morris, D.V.M., Dipl. A.C.Z.M., and Francisco Olea-Popelka, D.V.M., Ph.D.

Abstract: Rhinoceros conservation efforts are essential to the survival of the species. One such effort is focused on using advanced reproductive technologies to produce viable northern white rhinoceros (*Ceratotherium simum cottoni*) embryos for implantation into southern white rhinoceros (*Ceratotherium simum simum*) surrogates. Anesthesia may be required to facilitate necessary procedures in these surrogate rhinoceros, but commonly reported side effects including hypercapnia and hypoxemia limit anesthetic recumbency time due to animal safety concerns. Although many interventions have been attempted, success in improving these physiologic parameters to date is mixed. The objective of this report is to describe arterial pH (pHa), blood gas (PaO_2 and $PaCO_2$), bicarbonate, base excess, lactate, and cardiovascular (heart rate, direct arterial blood pressure) values recorded in seven intubated and ventilated female southern white rhinoceros anesthetized for reproductive examinations in a zoological park setting. Anesthetic induction was accomplished using etorphine, medetomidine, butorphanol, and midazolam. The primary hypotheses were that PaO_2 and $PaCO_2$ would improve after intubation and mechanical ventilation. Induction and recovery observations were also summarized. Physiologic and laboratory data were analyzed using a mixed linear regression model using ranks. Statistical significance was set at $P < 0.05$. The PaO_2 increased significantly ($P < 0.001$) following ventilation from a median value of 58 (range, 38–67) to 123 (range, 42–184) mm Hg. The $PaCO_2$ significantly ($P = 0.003$) decreased from 63 (range, 55–73) to 52 (range, 30–75) mm Hg, with a corresponding improvement ($P = 0.068$) in pHa from 7.33 (7.25–7.34) to 7.37 (7.24–7.58) units. Intubation and ventilation improve respiratory parameters and may facilitate safe prolongation of anesthetic duration in white rhinoceros.

Key words: Anesthesia, blood gas, *Ceratotherium simum*, intubation, mechanical ventilation, white rhinoceros.

INTRODUCTION

The increasing rate of rhinoceros poaching for their horns threatens the survival of the species. The northern white rhinoceros (*Ceratotherium simum cottoni*) is on the brink of extinction, with only three nonreproductive animals left in the world. As part of the conservation mission of the San Diego Zoo Safari Park, collaborative efforts are underway to preserve and propagate this rhinoceros subspecies. One such effort is focused at using advanced reproductive technologies to produce viable northern white rhinoceros embryos and implant the same in southern white rhinoceros (*Ceratotherium simum simum*) surrogates.[28]

A safe and reliable anesthetic protocol is essential for the management of these surrogate animals and other rhinoceros requiring care that cannot be provided to them awake or under sedation. Due to their large size and unique anatomy and physiology, rhinoceros pose significant anesthetic challenges. Hypercapnia resulting from drug- and recumbency-induced hypoventilation and hypoxemia secondary to hypoventilation and ventilation–perfusion abnormalities are commonly observed.[5,8,16,20,33] Severe hypoxemia has been suspected as a cause of anesthesia-related mortality.[20] Oxygen insufflation has been used to alleviate hypoxemia with an early report of transient improvement in oxygenation with oxygen administration (66 L/min) via the nostril.[16] Subsequent studies have evaluated the influence of intratracheal (via naso-tracheally placed equine nasogas-

From the Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, 300 W Drake Rd, Fort Collins, Colorado 80523, USA (Jeon, Mama, Olea-Popelka); and Harter Veterinary Medical Center, San Diego Zoo Safari Park, 15500 San Pasqual Valley Rd, Escondido, California 92027, USA (Zuba, Lamberski, Oosterhuis, Clancy, Delk, Kinney, Morris). Present address (Delk): North Carolina Zoo, 4401 Zoo Parkway, Asheboro, North Carolina 27205, USA. Correspondence should be directed to Dr. Mama (kmama@colostate.edu).

tric tube) oxygen (30 L/min). Although oxygenation improved, no change or worsening hypoventilation and acidemia was reported, emphasizing the need for ventilatory support.[5,14]

Because oxygen administration is not always possible in the field setting, efforts to alleviate respiratory compromise in rhinoceros receiving potent mu opioid agonist drugs have evaluated partial reversal (of respiratory depression) using the kappa agonist/mu antagonist drugs nalbuphine[20], nalorphine,[20] and recently, butorphanol.[8,14,33] Small improvements in oxygenation were noted after intravenous administration of nalorphine.[20] Butorphanol administration similarly was reported by some to improve oxygenation in rhinoceros slightly or transiently.[8,14] Others, however, did not find any benefit of administering butorphanol and hypothesize animal size may have influenced results.[33] A recent report suggests some improvement in both oxygenation and ventilation following butorphanol administration in etorphine- and midazolam-anesthetized rhinoceros.[31] Despite improvement in PaO_2, however, overall values remained critically low (mean PaO_2, 44.2 mm Hg), and carbon dioxide tensions stayed elevated (mean $PaCO_2$, 65.3 mm Hg).[31]

Despite these respiratory side effects and the availability of alternate anesthetic and immobilization protocols,[26,30,35] techniques using potent opioids with tranquilizers remain the mainstay of rhinoceros anesthesia. Therefore, there is a need to assess clinical interventions that improve patient safety during anesthesia. This report describes arterial pH (pHa), blood gas ($PaCO_2$, PaO_2), bicarbonate, base excess and lactate values, and selected cardiovascular parameters (heart rate, direct arterial blood pressure) summarized over 10-min intervals during anesthesia in seven intubated and mechanically ventilated female southern white rhinoceros. Changes in values for these parameters following oro-tracheal intubation and mechanical ventilation were also assessed. The primary hypotheses were that PaO_2 and $PaCO_2$ would improve after intubation and mechanical ventilation. Induction and recovery observations and additional physiologic parameters are also summarized.

MATERIALS AND METHODS

Animals and data collection

Data were retrospectively obtained from the anesthetic records of seven female southern white rhinoceros anesthetized at the San Diego Zoo Safari Park (33.0974°N, 116.9957°W; 136 m [447 ft] above sea level; barometric pressure [BP], 745 mm Hg) between February and April 2016.

Animals and preanesthetic preparation

Rhinoceros ranged in age from 4.75 to 8 yr and weighed between 1,252 and 2,000 kg. Available food was reduced by 50% 18 hr prior to the procedure; water was removed 6 hr prior to the procedure.

Darting and induction

On the morning of the procedure, rhinoceros scheduled for anesthesia were isolated in a boma familiar to them. Four of seven rhinoceros received diazepam (10 mg tablets, Actavis Pharma Inc., Parsippany, New Jersey 07054, USA; 0.15–0.21 mg/kg p.o.) in cooked yam or banana pieces 1–3 hr prior to the procedure. Rhinoceros were darted in the neck muscle using a 3.0-ml plastic dart (DanInject LLC, Austin, Texas 78753, USA) with a 60-mm uncollared and unbevelled needle (DanInject LLC) using a compressed air rifle (DanInject LLC) from a concealed location. Animals received a combination of etorphine HCl (10 mg/ml, Wildlife Pharmaceuticals Inc., Windsor, Colorado 80550, USA; 0.0018–0.0024 mg/kg i.m.) and butorphanol tartrate (30 mg/ml, Intervet Inc. d/b/a Merck Animal Health, Summit, New Jersey 07901, USA; 0.020–0.024 mg/kg i.m.), maintaining a ratio of 10 mg butorphanol to 1 mg etorphine; midazolam (50 mg/ml, Wildlife Pharmaceuticals Inc.; 0.015–0.020 mg/kg i.m.); and medetomidine HCl (20 mg/ml, Wildlife Pharmaceuticals Inc.; 0.020–0.024 mg/kg i.m.).

Time when the dart made contact with the animal was recorded as time zero ($t = 0$). In one animal, the dart provided approximately 50% of the intended volume. However, the animal was sufficiently sedated to allow administration of a combination of propofol (10 mg/ml, Abbott Laboratories, North Chicago, Illinois 60064, USA; 0.28 mg/kg i.v.), ketamine (100 mg/ml, MWI, Boise, Idaho 83705, USA; 0.17 mg/kg i.v.), and medetomidine (20 mg/ml, Wildlife Pharmaceuticals Inc.; 0.0056 mg/kg i.v.) in an auricular vein to facilitate recumbency and subsequent intubation. Propofol (10 mg/ml, Abbott Laboratories; 0.25–0.33 mg/kg i.v.) was titrated to facilitate intubation following recumbency in the six remaining rhinoceros.

Time to first effects (high stepping followed by somnolence and head pressing) was recorded. When safe, a blindfold and ear plugs were placed. Ropes and body straps were then used to assist all

Figure 1. Mega-vertebrate demand ventilator.

animals into recumbency. Time of blindfold and strap placement was noted, as was the time to lateral recumbency. All rhinoceros were maintained in lateral recumbency (four in left lateral and three in right lateral).

Cardiovascular and respiratory parameters

Heart rate and rhythm (via electrocardiogram) and direct arterial blood pressure following placement of a 22-gauge, 1-inch medial auricular arterial catheter (Terumo Corporation, Binan, Laguna 4026, Philippines) were continuously monitored and recorded at 1- to 3-min intervals during recumbency using a multiparameter monitor (Smiths Medical ASD, Inc., St. Paul, Minnesota 55112, USA).

Following placement, the arterial catheter was used to obtain blood for subsequent hematology and serum biochemistry analysis. Samples for measurement of pHa, blood gases (PaO_2 and $PaCO_2$), and lactate were also collected before and at multiple time points after intubation and ventilation of each rhinoceros. Calculated bicarbonate and base excess values were also recorded. Blood was analyzed using a portable iSTAT blood gas analyzer (Abbott Point of Care Inc., Union City, California 94587, USA) and CDG4+ and CDG8+ (Abbott Point of Care Inc.) cartridges. Values were not corrected for body temperature. An auricular venous catheter (18 or 20 gauge 1.88 inch, Terumo Corporation) was placed; patency was maintained by administration of lactated Ringers solution (1 L, Abbott Laboratories).

Intubation using a 30-mm internal diameter cuffed oro-tracheal tube (MWI) was initiated once the animal was sufficiently relaxed in lateral recumbency. This was performed manually using a 0.312-cm × 2-m polyoxymethylene rod (Piedmont Plastics, San Diego, California 92126, USA) as a guide and a hydraulic wedge jack (Harbor Fright Tools, San Diego, California 92126, USA) to open the jaws. Time to placement of the endotracheal tube from darting was recorded. Mechanical ventilation was initiated immediately on intubation using a mega-vertebrate demand ventilator (In Case of Anesthesia, La Jolla, California 92037, USA) (Fig. 1). A 125-ft^3 (H cylinder) containing compressed medical oxygen (Airgas USA, LLC, Randor, Pennsylvania 19087, USA) powered the ventilator with the drive gas pressure of 70 PSI to generate an expected fraction of inspired oxygen (FiO_2) of 40%. Inspiratory pressure and respiratory rate ranged from 25 to 35 cm H_2O and 5 to 12 breaths per minute, respectively.

Anesthetic recovery

Reproductive evaluations included rectal palpation and ultrasonography. When concluded, antagonists including naltrexone (50 mg/ml, Diamondback Drugs, Scottsdale, Arizona 85251, USA; 0.1–0.24 mg/kg i.v.) and atipamezole HCl (25 mg/ml, Wildlife Pharmaceuticals Inc.; 0.14–0.22 mg/kg) were administered using an 18-gauge, 3.5-in spinal needle (BD, Franklin Lakes, New Jersey 07417, USA) in the neck musculature in six rhinoceros and half i.m. and i.v. in one animal. Two rhinoceros also received flumazenil (0.1 mg/ml, West-ward Pharmaceutical Corporation, Eatontown, New Jersey 07724, USA; 0.0011–0.0012 mg/kg i.v. [one animal] or i.m. [one animal]). Times from darting to administration of reversal drugs and from reversal to extubation, sternal recumbency, and ambulation were recorded. One rhinoceros noted to be sedate and unresponsive to auditory or tactile stimulation approximately 5 hr after initial reversal and recovery received a second dose of atipamezole (0.01 mg/kg, i.v.) in the auricular vein.

Statistical analysis

Physiologic and laboratory parameters and timed induction and recovery data are summarized using standard descriptive statistics (mean, standard deviations, median, ranges, 95% confidence intervals [Cis], and first (Q1) and third (Q3) quartiles) and graphed to assess the data distribution.

Due to the small sample size, nonparametric statistical tests were used. To adjust for the effect of time and repeated measurements within a rhinoceros, median values were analyzed with a mixed linear regression model using ranks. This model was also used to compare pHa and blood gas values before and after intubation. Statistical

Table 1. Induction ($n = 6$) and recovery times ($n = 7$) for seven female southern white rhinoceros (*C. simum*).

Descriptive Statistics	Initial effects	Ability to place blindfold and straps	Recumbency with ability to approach the animal	Reversal drug administration	Extubation	Time to sternal recumbency	Ambulatory
Mean	4.1	8.3	11.4	71.6	72	75.8	77.8
SD	0.8	1.4	3.3	8.9	9.1	7.8	9.3
Minimum	3	6.3	8.3	60	63	67	67
Median	4.1	8.4	10.5	71	74	76	77
Maximum	5	10	16.6	84.8	89	89	90.7

All times (min) are recorded from administration of dart.

significance was set at $P < 0.05$. Statistical analyses were performed using STATA 12.0 (Stata Corporation, College Station, Texas 77840, USA).

RESULTS

The time distribution for induction and recovery behaviors and duration of recumbency from six rhinoceros with complete injection are shown in Table 1. No significant differences in induction parameters were observed between rhinoceros receiving oral diazepam and those that did not. Time to intubation took a median of 18.0 min from darting in these six rhinoceros. Spontaneous breathing ranged from 2 to 20 breaths/min prior to intubation. An increase in median values for pHa and PaO_2 and decrease in median $PaCO_2$ values were observed following endotracheal intubation and ventilation ($P = 0.068$, $P < 0.001$, and $P = 0.003$, respectively; Table 2; Fig. 2). The PaO_2 improved from a median value of 58 mm Hg prior to ventilation to a median value of 123 mm Hg after ventilation, whereas the $PaCO_2$ decreased from a median value of 63.1 mm Hg to a median value of 52 mm Hg. Bicarbonate values also decreased significantly ($P = 0.038$) after intubation. Blood lactate ranged from 0.32 to 3.36 mmol/L, with most recorded values being less than 2 mmol/L. Aside from an elevation in creatine kinase in one rhinoceros (1,166 mg/dl), all hematology and serum biochemistry values were within reference ranges.[23]

Heart rate and direct arterial blood pressure values over 10-min intervals during recumbency are presented in Table 3. An overall decrease in heart rate of 1.4 (95% CI, 0.4–2.4) beats/10 min was observed over time ($P = 0.002$) during recumbency. A decrease in direct arterial blood pressure values was also noted ($P < 0.0001$) with systolic, diastolic, and mean arterial blood pressures decreasing an average of 22.9, 16.8, and 15.7 mm Hg/10 min (95% CI, 1.8–3.0, 12.9–20.6, and 11.3–20.1 mm Hg), respectively.

The median duration of recumbency was 71 min (Table 1). The time to spontaneous breathing was not specifically recorded but observed shortly after administration of reversal agents and before extubation in all animals. Recovery was timely (Table 1), calm, and uneventful. The animal that appeared resedated a few hours after recovering from anesthesia exhibited typical behaviors within 4.5 min of repeated atipamezole administration.

DISCUSSION

This report demonstrates the clinical benefits of intubation and mechanical ventilation in rhinoceros anesthetized with injectable medications. Although FiO_2 was not measured in all rhinoceros, evaluation of the mega-vertebrate ventilator under similar circumstances of use supports the manufacturer claim of a FiO_2 of 40%. This ventilator, which has the advantage of portability and simplicity over other anesthetic ventilators, works by creating a venturi with driving gas (oxygen), allowing air to be entrained to provide the volume necessary to expand the chest over the duration (2–3 s) of the manually triggered breath. The built-in manometer allows the individual providing breaths to measure and limit airway pressure. As shown in Table 2 and Figure 2, A–C, a statistically significant reduction in $PaCO_2$ with a corresponding increase in pHa and clinically important and statistically significant increase in PaO_2 values was observed in these rhinoceros after initiation of ventilation. Presumably, this effect is due to multiple factors including breathing a higher FiO_2, improved ventilation, and recruitment of alveoli.

Compared with values from spontaneously breathing white rhinoceros receiving similar doses of etorphine followed by butorphanol for a similar duration of recumbency, it is clear that ventilation with an increased FiO_2 is beneficial.[8] Although it is possible that the co- (vs consequent) administration of butorphanol with etor-

Table 2. Summary of cardiovascular and blood gas measurements in seven white rhinoceros (*C. simum*) before and after intubation and ventilation.

Intubation status	Heart rate (beats/min)	Systolic (mm Hg)	Mean (mm Hg)	Diastolic (mm Hg)	pH (units)	$PaCO_2$ (mm Hg)	PaO_2 (mm Hg)	BE (mEq/L)	HCO_3 (mEq/L)	Lactate (mmol/L)
Not intubated										
Mean	42	NA	NA	NA	7.31	64.7	56.2	6.3	32.4	1.2
SD	NA	NA	NA	NA	0	6.2	9.8	2.3	2.2	1.2
Minimum	42	NA	NA	NA	7.25	55.3	38	4	29.9	0.36
Q1	42	NA	NA	NA	7.29	60.9	55	4	30	0.39
Median	42	NA	NA	NA	7.33	63.1	58	7	32.6	0.62
Q3	42	NA	NA	NA	7.33	71.4	61	9	34.7	1.78
Maximum	42	NA	NA	NA	7.34	73.2	67	9	35.5	3.36
n	1	0	0	0	7	7	7	7	7	7
Intubated										
Mean	36.2	214.8	143.9	172.7	7.37	53	117.1	5.1	30.3	0.9
SD	8.6	45	32.1	34.3	0.1	9.1	28.7	3	2.9	0.5
Minimum	23	118	71	102	7.24	30.2	42	−6	20.4	0.32
Q1	31	177	121	144	7.34	48.9	99	5	29.7	0.5
Median	34	213	140	174.5	7.37	52	123	5	30.8	0.8
Q3	44	252	164	198	7.40	57.8	132.5	7	32	1.2
Maximum	75	295	233	260	7.58	75.2	184	9	34.5	2.4
n	116	85	85	86	29	29	28	29	29	28

n, number of measurements summarized; NA, not available for that period.

phine in the current study may have had some influence, median PaO_2 values at 50 and 60 min of recumbency in the prior report[8] were 57 and 61 mm Hg, respectively, compared with a median PaO_2 value of 120 mm Hg for the same period (50–<60 min; Table 3) in the current report. The median $PaCO_2$ summarized for all time points after mechanical ventilation for rhinoceros in this report (Table 2; Fig. 2B) also compares favorably with those from spontaneously breathing animals in the same prior study: 52 compared with 68.5 mm Hg, respectively.

Current blood gas results also differ from previous reports with intratracheal oxygen supplementation where PaO_2 increased, but $PaCO_2$ remained high or increased further and pHa remained low.[5,14] When compared to awake values,[9] rhinoceros consistently exhibit hypercapnia and hypoxemia during drug induced recumbency in the absence of intervention. Hypercapnia in the anesthetized rhinoceros is presumably related to drug and accompanying recumbency-induced hypoventilation and hypoxemia secondary to hypoventilation and ventilation–perfusion abnormalities. Recent reports suggest that hypoxemia also results from increased oxygen consumption in etorphine-immobilized white rhinoceros.[6,12] Hypoxemia is reported in recumbent horses (*Equus caballus*) (also Perissodactyla) anesthetized with injectable anesthetics,[19,27] where changes are attributed to pulmonary atelectasis and vascular shunting resulting in ventilation–perfusion abnormalities.[18] Although pulse oximeter values for oxygen saturation were not consistently available for this report, a PaO_2 of 60 mm Hg corresponds to a saturation of approximately 90% (if one assumes a human oxygen hemoglobin dissociation curve).[17] Although the impact relative to anesthetic management is still to be fully determined, there are reports indicating that the oxygen hemoglobin curve for rhinoceros is shifted to the left (lower p50) compared with that of humans.[2,15] This may offer a protective effect.

The ideal alveolar partial pressure of oxygen (P_A) may be calculated from the following equation: $(P_A = [BP - H_2O_{\text{vapor pressure = 47 mm Hg}} \times FiO_2] - PaCO_2/RQ)$, where RQ = respiratory quotient of 0.8.[32] A 20% alveolar to arterial gradient is considered acceptable over a broad range of FiO_2 values, or said differently, the A-a gradient normally increases from 10–20 to 50–100 mm Hg as FiO_2 increases from 0.21 to 1.0.[32] For rhinoceros breathing a FiO_2 of 40% at the study elevation (barometric pressure, 745 mm Hg) with an average $PaCO_2$ of 52 mm Hg, a P_A value of 214 mm Hg was calculated. Considering this value, the PaO_2 should be no less than 171 mm Hg in the ideally functioning lung. Although values were not available from all rhinoceros for each 10-min interval, data (Table 3) suggest that this was attained only in a few rhinoceros and that the improvement was gradual. Therefore, although

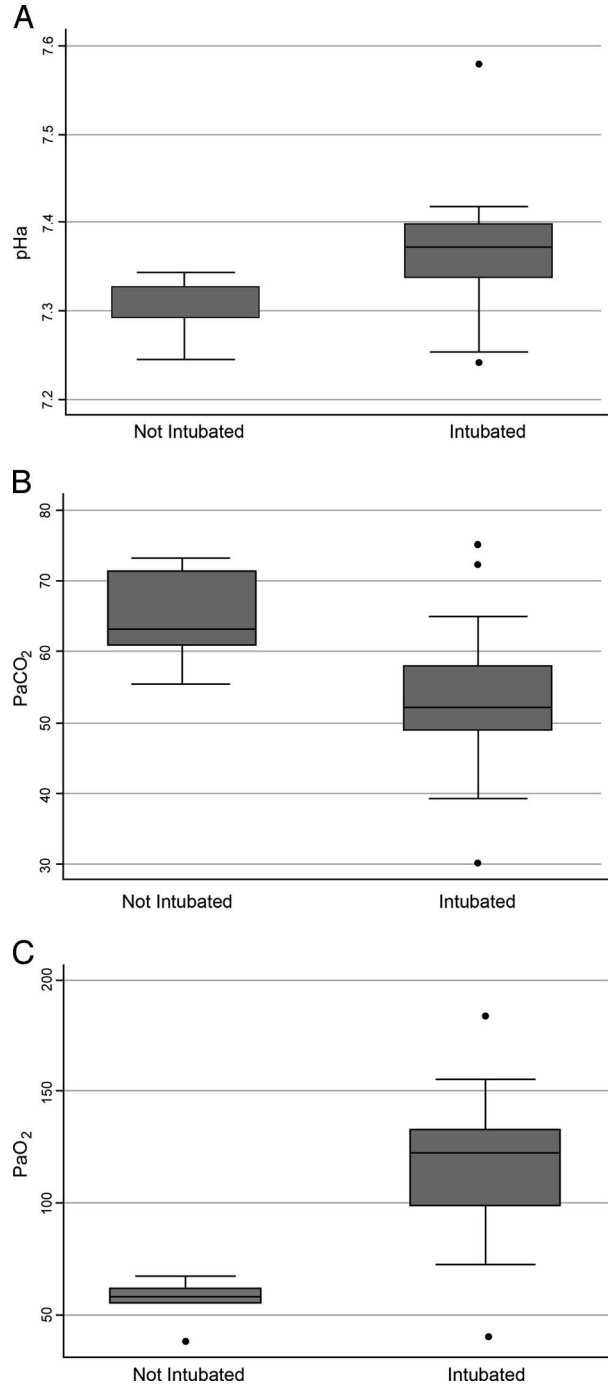

Figure 2. A–C. Median values for pHa (**A**), $PaCO_2$ (**B**), and PaO_2 (**C**) for seven white rhinoceros (*C. simum*) prior to and after intubation and ventilation. Minimum, maximum, and first (Q1) and third (Q3) quartile values are shown in addition to median values. Outlier points are measurements that are distant from the other observations.

Table 3. Summary of cardiovascular and blood gas measurements over 10-min intervals in seven white rhinoceros (*C. simum*).

Time interval from initial dart (min)	Heart rate (beats/ min)	Systolic (mm Hg)	Mean (mm Hg)	Diastolic (mm Hg)	pHa (units)	$PaCO_2$ (mm Hg)	PaO_2 (mm Hg)	BE (mEq/L)	HCO_3 (mEq/L)
10 to <20									
Mean	40.7	NA	NA	NA	7.31	63.5	56.3	5.6	31.7
SD	3.2	NA	NA	NA	0.04	6	12.6	2.3	2.1
Minimum	37	NA	NA	NA	7.25	55.3	38	4	29.9
Q1	37	NA	NA	NA	7.30	60.9	48.5	4	30
Median	42	NA	NA	NA	7.33	63.1	60	4	30.9
Q3	43	NA	NA	NA	7.33	66.6	64	7	33
Maximum	43	NA	NA	NA	7.34	71.4	67	9	34.7
20 to <30									
n	3	0	0	0	5	5	5	5	5
Mean	41.3	271	197.4	182.3	7.33	61.7	86	6.5	32.3
SD	5.2	14.4	21.8	11.6	0.06	10.8	40.7	2.7	2.7
Minimum	35	250	160	174	7.24	49.7	42	2	27.6
Q1	36	262.5	200	174.5	7.29	51.1	55	5	31.7
Median	42	275.5	205	178	7.34	60.5	76.5	7	32.5
Q3	45	279.5	205	190	7.37	73.2	131	9	34.1
Maximum	49	283	217	199	7.4	75.2	135	9	35.5
n	15	4	5	4	6	6	6	6	6
30 to <40									
Mean	36.7	253.2	202.9	175.2	7.38	47.9	115.8	3	28.2
SD	8.2	43.6	36.1	35.7	0.03	5.2	21	5.1	4.4
Minimum	26	152	127	98	7.32	39.4	79	−6	20.4
Q1	31.5	254	198	167	7.37	47.6	118	4	29
Median	33.5	259	205	174	7.38	48.9	125	5	30.2
Q3	45	279	232	204	7.39	49.9	127	6	30.3
Maximum	50	292	242	222	7.41	53.6	130	6	31
n	20	13	13	13	5	5	5	5	5
40 to <50									
Mean	34.9	239.8	190	158.5	7.39	51.3	132.3	4.8	29.9
SD	7.8	32.6	26.9	26.3	0.11	13.6	40.9	1.7	2.0
Minimum	25	179	142	120	7.25	30.2	77	2	27
Q1	29	223	177	145	7.36	45.6	91	4	28.3
Median	33	245	188	156	7.37	52.7	143.5	5	30.1
Q3	43	259	204	168	7.38	54.1	155	6	31.8
Maximum	49	295	260	233	7.58	72.3	184	7	32
n	27	21	21	21	6	6	6	6	6
50 to <60									
Mean	36.3	199.8	162.2	133.5	7.35	55.4	115	4.9	30.5
SD	10.5	26.2	19.3	14.9	0.03	8.4	24.2	3.1	3.2
Minimum	24	155	123	104	7.32	39.4	72	−1	24.3
Q1	29	179.5	148	123.5	7.32	51.2	97	4	30
Median	34	202.5	166	136.5	7.34	57.8	120	5	30.5
Q3	43	221.5	176.5	144	7.38	61.5	136	7	33.1
Maximum	75	246	192	163	7.40	64.9	141	9	34.5
n	29	24	24	24	7	7	7	7	7
60 to <70									
Mean	33.9	172.9	148.7	119.5	7.40	51.2	113	6.6	31.4
SD	8.3	33.8	31.4	19.5	0.03	4.4	12.6	1.3	1.3
Minimum	23	118	109	94	7.34	47.2	101	5	29.7
Q1	27	140	122	101	7.40	47.6	103	6	30.7
Median	34	163	138	117	7.41	50.1	111	6	31.4
Q3	35	196	172	136	7.42	53.4	123	8	32.4
Maximum	47	235	215	154	7.42	57.8	128	8	32.8
n	17	15	15	15	5	5	5	5	5

Table 3. Continued.

Time interval from initial dart (min)	Heart rate (beats/ min)	Systolic (mm Hg)	Mean (mm Hg)	Diastolic (mm Hg)	pHa (units)	$PaCO_2$ (mm Hg)	PaO_2 (mm Hg)	BE (mEq/L)	HCO_3 (mEq/L)
70 to <80									
Mean	31.7	181.9	139.1	111.9	7.37	55.4	123	6.5	31.8
SD	8	33.8	25.1	22	0.05	6.9	1.4	0.71	0.28
Minimum	23	137	102	71	7.33	50.5	122	6	31.6
Q1	24	154	120	99.5	7.33	50.5	122	6	31.6
Median	32	182	138.5	114	7.37	55.4	123	6.5	31.8
Q3	34	210	162	130.5	7.40	60.2	124	7	32
Maximum	45	226	170	136	7.40	60.2	124	7	32
n	6	8	8	8	2	2	2	2	2

n, number of measurements summarized during a given 10-min period; NA, not available for that period.

the addition of mechanical ventilation with a FiO_2 of approximately 40% improved PaO_2 (and $PaCO_2$) to more closely approximate or exceed normal values in standing, air-breathing rhinoceros at sea level, ideal values were not consistently attained.[9] Additionally, there were differences in individual animal responses as is seen in horses.[1]

One possible reason for differences in individual responses could relate to animal size and its influence on the relationship of ventilation to perfusion. A prior report in white rhinoceros notes hypoxemia to be worse in subadults and adults than in calves during anesthesia.[33] Although the correlation of oxygenation to body size was not assessed given the limited number of animals, the differences in animal mass (rhinoceros in this study ranged in weight from 1,252 to 2,000 kg) may have contributed. It is also possible that chest wall rigidity or increased muscle activity following etorphine contributed to poor thoracic compliance as is reported after potent opioids in people.[10] This may help explain the consistently low PaO_2 values during early recumbency from rhinoceros in numerous studies[5,8,13,14,16,20,24,33] and slight improvements observed in the absence of respiratory supportive measures[5] seen after presumed absorption of concurrently administered medications (azaperone, medetomidine), which may serve to partially counter muscle rigidity or respiratory depression caused by etorphine.[8,14,33] The dose of etorphine and other concurrent drugs such as butorphanol may also play a role. As mentioned previously, an increase in oxygen consumption caused by etorphine-related muscle activity can contribute to hypoxemia; a recent report suggests butorphanol given after recumbency may help partially mitigate this.[6]

In this report, anesthetic induction was accomplished using etorphine, medetomidine, butorphanol, and midazolam. Etorphine, a potent mu agonist, is considered the primary anesthetizing drug, but due to significant muscle rigidity observed when administered alone, medetomidine and midazolam were included for muscle relaxation, with medetomidine providing the additional benefit of analgesia.[22] Butorphanol was used in an effort to alleviate the respiratory depression associated with etorphine.[8,31,33] As mentioned previously and consistent with other studies, a ratio of 10 mg butorphanol to 1 mg of etorphine was maintained.[8,31]

Prior reports suggest tachycardia is a feature of rhinoceros anesthetized with etorphine combinations,[8,20] as in horses,[3,11,29] and is related to sympathetic stimulation. Tachycardia was not observed in this study, and in fact, heart rates in these anesthetized rhinoceros were similar to those previously reported in unrestrained, standing animals,[9] with decreasing values recorded over time. This may have been due to the α-2 agent medetomidine and possibly that these captive rhinoceros were less physiologically stressed at the time of anesthetic drug administration. Butorphanol given after etorphine-induced recumbency has also been shown to reduce heart rate in one recent study.[7] It is also possible that normalization of arterial blood gas values played a role.

Conversely, compared with indirect blood pressure measurements from healthy, unrestrained, nonmedicated white rhinoceros,[9] and direct blood pressure measurements from unmedicated horses,[22] the rhinoceros in this report where blood pressure was directly measured exhibited hypertension, albeit values did decrease over time. This has been previously reported using both direct and indirect measurements[13,16,21] in rhinoceros as for horses receiving potent opioids.[11,29] The cause for hypertension remains largely unknown, but the literature suggests that it is likely at least in

part to be the result of sympathetic stimulation,[21] as measured levels of norepinephrine are increased in horses and rhinoceros receiving etorphine.[3,12] Medetomidine, which has potent vasoconstrictive effects in other species, may have also contributed to the elevations in blood pressure observed during anesthesia in these rhinoceros.[4,25,34] The added influence of propofol on cardiovascular variables is possible, but as all animals received propofol, it is difficult to ascertain.

All animals had a calm and rapid rise to standing once reversal agents were administered. One rhinoceros displayed signs of sedation 5 hr after recovery, and although she was one of the animals that received oral diazepam (0.21 mg/kg p.o.), the sedative effects were completely reversed with repeat administration of atipamezole, supporting medetomidine administration as the cause of this effect. Resedation has been anecdotally reported with α-2 agonist use despite reversal in other nondomestic species, but the reasons are not fully known. It is possible that the dosing of the reversal agent atipamezole was not adequate or that uptake of the same from the i.m. injection site was incomplete.

In summary, this retrospective report in southern white rhinoceros describes the benefits of intubation and mechanical ventilation using a FiO_2 of approximately 40%. Clinically relevant and statistically significant improvements in oxygenation and ventilation were observed during anesthesia drug–induced recumbency.

Acknowledgments: The authors thank Dr. Jack Allen, Ms. Barbara Kurtz, and Ms. Angie Hoyt for facilitating data collection and the Harter hospital staff, mammal curators, animal managers, and keepers at the San Diego Zoo Safari Park for invaluable assistance during the procedures. The authors also thank Drs. Matt Johnston, Melinda Frye, and Mark Stetter at Colorado State University for support of this collaborative effort.

LITERATURE CITED

1. Auckburally A, Nyman G. Review of hypoxaemia in anaesthetized horses: predisposing factors, consequences and management. Vet Anaesth Analg. 2017; 44(3):397–408.

2. Baumann R, Mazur G, Braunitizer G. Oxygen binding properties of hemoglobin from the white rhinoceros (beta 2-GLU) and the tapir. Respir Physiol. 1984;56(1):1–9.

3. Bogan JA, MacKenzie G, Snow DH. An evaluation of tranquillisers for use with etorphine as neuroleptanalgesic agents in the horse. Vet Rec. 1978;103: 471–472.

4. Bueno AC, Cornick-Seahorn J, Seahorn TL, Hosgood G, Moore RM. Cardiopulmonary and sedative effects of intravenous administration of low doses of medetomidine and xylazine to adult horses. Am J Vet Res. 1999;60(11):1371–1376.

5. Bush M, Raath JP, Grobler D, Klein L. Severe hypoxemia in field-anaesthetised white rhinoceros (*Ceratotherium simum*) and effects of using tracheal insufflation of oxygen. J S Afr. Vet Assoc. 2004;75(2): 79–84.

6. Buss P, Miller M, Fuller A, Haw A, Stout E, Olea-Popelka F, Meyer L. Postinduction butorphanol administration alters oxygen consumption to improve blood gases in etorphine-immobilized white rhinoceros. Vet Anaesth Analg. 2017. In press. doi: 10.1016/ j. vaa.2017.03.008.

7. Buss P, Miller M, Fuller A, Haw A, Wanty R, Olea-Popelka F, Meyer L. Cardiovascular effects of etorphine, azaperone, and butorphanol combinations in chemically immobilized captive white rhinoceros (*Ceratotherium simum*). J Zoo Wildl Med. 2016;47(3): 834–843.

8. Buss P, Olea-Popelka F, Meyer L, Hofmeyr J, Mathebula N, Kruger M, Brüns A, Martin L, Miller M. Evaluation of cardiorespiratory, blood gas, and lactate values during extended immobilization of white rhinoceros (*Ceratotherium simum*). J Zoo Wildl Med. 2015; 46(2):224–233.

9. Citino SB, Bush MR. Reference cardiopulmonary physiologic parameters for standing, unrestrained white rhinoceroses (*Ceratotherium simum*). J Zoo Wildl Med. 2007;38(3):375–379.

10. Coruh B, Tonelli MR, Park DR. Fentanyl-induced chest wall rigidity. Chest. 2013;143(4):1145–1146.

11. Daniel M, Ling CM. The effect of an etorphine/acepromazine mixture on the heart rate and blood pressure of the horse. Vet Rec. 1972;90(12):336–339.

12. De Lange SS, Fuller A, Haw A, Hofmeyr M, Buss P, Miller M, Meyer L. Tremors in white rhinoceroses (*Ceratotherium simum*) during etorphine-azaperone immobilisation. J S Afr. Vet Assoc. 2017;88(1):1–10.

13. Hattingh J, Knox CM, Raath JP. Arterial blood pressure and blood gas composition of white rhinoceros under etorphine anaesthesia. S Afr J Wildl. Res. 1994;24(1–2):12–14.

14. Haw A, Hofmeyr M, Fuller A, Buss P, Miller M, Fleming G, Myer L. Butorphanol with oxygen insufflation corrects etorphine-induced hypoxaemia in chemically immbolized white rhinoceros (*Ceratotherium simum*). BMC Vet Res. 2014;10:253.

15. Haymerle A, Knauer F, Walzer C. Two methods to adapt the human haemoglobin-oxygen dissociation algorithm to the blood of white rhinoceros (*Ceratotherium simum*) and to determine the accuracy of pulse oximetry. Vet Anaesth Analg. 2016;43:566–570.

16. Heard DJ, Olsen JH, and Stover J. Cardiopulmonary changes associated with chemical immobilization and recumbency in a white rhinoceros (*Ceratotherium simum*). J Zoo Wildl. Med. 1992;23(2): 197–200.

17. Hubbell JA, Muir WW. Monitoring anesthesia. In: Muir WW, Hubbell JA (eds.). Equine anesthesia: monitoring and emergency therapy. 2nd ed., St. Louis (MO): Elsevier; 2009. p. 156–157.

18. Kerr CL, McDonell WN. Oxygen supplementation and ventilatory support. In: Muir WW, Hubbell JA (eds.). Equine anesthesia: monitoring and emergency therapy. 2nd ed., St. Louis (MO): Elsevier; 2009. p. 333.

19. Kerr CL, McDonell WN, Young SS. A comparison of romifidine and xylazine when used with diazepam/ketamine for short duration anesthesia in the horse. Can Vet J. 1996;37(10):601–609.

20. Kock MD, Morkel P, Atkinson M, Foggin CM. Chemical immobilization of free-ranging white rhinoceros (*Ceratotherium simum simum*) in Hwange and Matobo National Parks, Zimbabwe, using combinations of etorphine (M99), fentanyl, xylazine, and detomidine. J Zoo Wildl Med. 1995;26(2):207–219.

21. LeBlanc PH, Eicker SW, Curtis M, Beehler B. Hypertension following etorphine anesthesia in a rhinoceros (*Diceros simus*). J Zoo An Med. 1987;18(4): 141–143.

22. Magdesian KG. Monitoring the critically ill equine patient. Vet Clin North Am Equine Pract. 2004;20:11–39.

23. Mathebula N, Miller M, Buss P, Joubert J, Martin L, Kruger M, Hofmeyr M, Olea-Popelka F. Biochemical values in free-ranging white rhinoceros (*Ceratotherium simum*) in Kruger National Park, South Africa. J Zoo Wildl Med. 2012;43(3):530–538.

24. Miller ER. Rhinoceridae (rhinoceroses). In: Miller RE, Fowler ME (eds.). Zoo and wild animal medicine. 7th ed., St. Louis (MO): Elsevier; 2015. p. 538–546.

25. Pypendop BH, Verstegen JP. Hemodynamic effects of medetomidine in the dog: a dose titration study. Vet Surg. 1998;27:612–622.

26. Radcliffe RW, Ferrell ST, Childs SE. Butorphanol and azaperone as a safe alternative for repeated chemical restraint in captive white rhinoceros. J Zoo Wildl Med. 2000;31(2):196–200.

27. Rezende ML, Boscan P, Stanley SD, Mama KR, Steffey EP. Evaluation of cardiovascular, respiratory and biochemical effects, and anesthetic induction and recovery behavior in horses anesthetized with a 5% micellar microemulsion propofol formulation. Vet Anaesth Analg. 2010;37(5):440–450.

28. Saragusty J, Diecke S, Drukker M, Durrant B, Ben-Nun IF, Galli C, Göritz F, Hayashi K, Hermes R, Holtze S, Johnson S, Lazzari G, Loi P, Loring JF, Okita K, Renfree MB, Seet S, Voracek T, Stejskal J, Ryder OA, Hildebrandt TB. Rewinding the process of mammalian extinction. Zoo Biol. 2016;9999:1–13.

29. Schlarmann B, Görlitz BD, Wintzer HJ, Frey HH. Clinical pharmacology of an etorphine-acepromazine preparation: experiments in dogs and horses. Am J Vet Res. 1973;34(3):411–415.

30. Valverde A, Crawshaw GJ, Cribb N, Bellei M, Gianotti G, Arroyo L. Koenig J, Kummrow M, Costa MC. Anesthetic management of a white rhinoceros (*Ceratotherium simum*) undergoing an emergency exploratory celiotomy for colic. Vet Anaesth and Analg. 2010;37(3):280–285.

31. van Zijill Langhout M, Caraguel CG, Raath JP, Boardman WS. Evaluation of etorphine and midazolam anesthesia, and the effect of intravenous butorphanol on cardiopulmonary parameters in game-ranched white rhinoceroses (*Ceratotherium simum*). J Zoo Wildl Med. 2016;47(3):827–833.

32. Wilson WC, Benumof JL. Respiratory physiology and respiratory function during anesthesia. In: Miller RD (ed.). Miller's anesthesia. 6th ed., Philadelphia (PA): Elsevier Churchill Livingstone; 2005. p. 679–722.

33. Wenger S, Boardman W, Buss P, Govender D, Foggin C. The cardiopulmonary effects of etorphine, azaperone, detomidine, and butorphanol in field-anesthetized white rhinoceroses (*Ceratotherium simum*). J Zoo Wildl Med. 2007;38(3):380–387.

34. Yamashita K, Tsubakishita S, Futaok S, Ueda I, Hamaguchi H, Seno T, Katoh S, Izumisawa Y, Kotani T, Muir WW. Cardiovascular effects of medetomidine, detomidine and xylazine in horses. J Vet Med Sci. 2000; 62(10):1025–1032.

35. Zeiler GE, Stegmann GF. Anaesthetic management of a 10-month-old white rhinoceros (*Ceratotherium simum*) calf for emergency exploratory celiotomy. J S Afr Vet Assoc. 2012;83(1):939–943.

Accepted for publication 22 July 2017