

## RESEARCH ARTICLE

# Intranasal oxygen reverses hypoxaemia in immobilised free-ranging capybaras (*Hydrochoerus hydrochaeris*)

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## Abstract

Capybara (*Hydrochoerus hydrochaeris*) is the main host of tick-borne pathogens causing Brazilian spotted fever; therefore, controlling its population is essential, and this may require chemical restraint. We assessed the impact of chemical restraint protocols on the partial pressure of arterial oxygen (PaO<sub>2</sub>) and other blood variables in 36 capybaras and the effect of different flows of nasal oxygen (O<sub>2</sub>) supplementation. The capybaras were hand-injected with dexmedetomidine (5 µg/kg) and midazolam (0.1 mg/kg) and butorphanol (0.2 mg/kg) (DMB, n = 18) or methadone (0.1 mg/kg) (DMM, n = 18). One-third of the animals were maintained in ambient air throughout the procedure, and one-third were administered intranasal 2 L/min O<sub>2</sub> after 30 min whereas the other third were administered 5 L/min O<sub>2</sub>. Arterial blood gases, acid-base status, and electrolytes were assessed 30 and 60 min after drug injection. The DMB and DMM groups did not vary based on any of the evaluated variables. All animals developed hypoxaemia (PaO<sub>2</sub> 44 [30; 73] mmHg, SaO<sub>2</sub> 81 [62; 93] %) 30 min before O<sub>2</sub> supplementation. Intranasal O<sub>2</sub> at 2 L/min improved PaO<sub>2</sub> (63 [49; 97] mmHg and SaO<sub>2</sub> [92 [85; 98] %), but 9 of 12 capybaras remained hypoxaemic. A higher O<sub>2</sub> flow of 5 L/min was efficient in treating hypoxaemia (PaO<sub>2</sub> 188 [146; 414] mmHg, SaO<sub>2</sub> 100 [99; 100] %) in all the 12 animals that received it. Both drug protocols induced hypoxaemia, which could be treated with intranasal oxygen supplementation.

## Introduction

The capybara (*Hydrochoerus hydrochaeris*) is the world's largest rodent, and its population can grow exponentially with a large food supply and in the absence of natural predators [1]. In Brazil, the capybara is an important host for the transmission cycle of Brazilian spotted fever [2]. Seven hundred and thirty-six human cases of the disease have been confirmed only in São Paulo state from 2011 to 2020, with a mortality rate of 63.5% [3]. It is, therefore, imperative to control the capybara population by removing individuals [4] or using contraceptive measures [5]; these are strategies that may require capture procedures [5–8].

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Several anaesthetic protocols for captive or free-ranging capybaras have been previously described [6–12], but no study has assessed the impact of these protocols on the arterial partial pressure of oxygen (PaO<sub>2</sub>). Hypoxaemia is a concern during the chemical restraint of wild animals [13] as it can lead to myopathy and myocardial hypoxia [14, 15]. Thus, oxygen (O<sub>2</sub>) supplementation has been used to prevent or treat hypoxaemia during the immobilisation of wild animals [13, 16–19]. Furthermore, chemical restraint protocols in capybaras have been based on dissociative anaesthesia (ketamine or tiletamine) in combination with other drugs (xylazine, romifidine, midazolam, zolazepam, levomepromazine, medetomidine, or dexmedetomidine) [7–12], and may be associated with muscle spasticity, nystagmus, disorientation, increased heart rate, and blood pressure [9]. In general, if the state of ‘dissociation’ persists during recovery, it can cause disorientation, anxiety, stress, myoclonus, catalepsy, and abnormal behaviour in the targeted animal [20].

Reversible chemical restraint combination protocols have been used in free-ranging animals, seeking to avoid the side effects observed with dissociative anaesthesia [18, 19, 21, 22]; the advantages of their use include animals returning to their normal pattern of activities quicker and safer, preventing them from becoming vulnerable to predators or accidents due to the disorientation related to anaesthetic recovery. Similarly, they can be given drug reversal agents if a dose higher than the recommended dose is administered or if the animal experiences unwanted side effects.

The objectives of this study were to assess the impact of fully reversible chemical restraint protocols on free-ranging capybaras and the effects of different O<sub>2</sub> supplementation flows. Based on the studies carried out with other species [18, 19, 23] as well as the authors’ experience, we hypothesised that nasal oxygen flows of either 2 or 5 L/min would reverse hypoxaemia in chemically restrained capybaras.

## Materials and methods

The study was approved by the Chico Mendes Institute for Biodiversity Conservation (protocol 58028) and the Animal Ethics Committee of the Faculty of Animal Science and Food Engineering, University of São Paulo (protocol 9796180717). The animals were captured between May 2018 and October 2019 in southeast Brazil (21°59′46″S; 47°25′33″W) at 627 m above sea level during rainless nights with an average temperature of 21.8 ± 3.5°C.

To capture the capybaras, two portable corral-style traps (4 and 25 m<sup>2</sup>, respectively) with an iron fence or metal mesh walls were used and baited with corn or sugarcane in automatic closing platforms. If more than one animal was caught at once, only one animal was immobilised, and the others were released. Capybaras were excluded if they were very wet, weighed less than 20 kg, had severe injuries, or did not allow manipulation after 20 min after the drug injection. Thirty-six of 49 capybaras that were captured were included in the study; these included 30 females and 6 males weighing 48.9 ± 17.8 kg (actual body weight).

After the capybaras were caught in the corral-style trap, they were physically restrained with a one-metre diameter net for drug administration. They were given one of two drug combinations by intramuscular hand injection in the lateral side of the hind limb using a syringe and a 20 G needle. The drug combinations used were 5 µg/kg dexmedetomidine (Dexdomitor<sup>®</sup> 0.5 mg/mL, Zoetis, São Paulo, SP, Brazil) + 0.1 mg/kg midazolam (Dormire<sup>®</sup> 5 mg/mL, Cristalia, Itapira, SP, Brazil) + 0.2 mg/kg butorphanol (Torbugesic<sup>®</sup> 10 mg/mL, Fort Dodge Animal Health, Fort Dodge, IA, USA) (DMB, n = 18) or 5 µg/kg dexmedetomidine + 0.1 mg/kg midazolam + 0.1 mg/kg methadone (Mytedom<sup>®</sup> 10 mg/mL, Cristalia, Itapira, SP, Brazil) (DMM, n = 18). The doses were calculated based on the estimated body weights. The animals were weighed during immobilisation, after which they were kept in right lateral recumbency.

Six animals from each drug protocol group were maintained in breathing air (21% O<sub>2</sub>) (DMB-Air and DMM-Air) throughout the procedure, whereas six animals received O<sub>2</sub> supplementation at 2 L/min (DMB-2L and DMM-2L) and six others received O<sub>2</sub> supplementation at 5 L/min (DMB-5L and DMM-5L) for 30 min after the initial drug injection. This design was proposed to understand which treatment might reverse a possible hypoxaemia condition, when PaO<sub>2</sub> < 80 mmHg. Oxygen was provided from a 5-L portable cylinder connected to a number 16 bladder probe (outer diameter 5.3 mm) lubricated with 2% lidocaine (Xylestesin jelly 20 mg/mL, Cristalia, Itapira, SP, Brazil) and introduced into one of the nostrils up to the medial canthus of the eye. Oxygen supplementation was provided for 30 min and discontinued 60 min after the drug injection. Afterward, the immobilisation was reversed with an intramuscular injection of 2 µg/kg flumazenil (Flumazenil 0.1 mg/mL, Cristalia, Itapira, SP, Brazil) + 5 µg/kg atipamezole (Antisedan 5 mg/mL, Zoetis, São Paulo, SP, Brazil) + 4 µg/kg naloxone (Narcan 0.4 mg/mL, Cristalia, Itapira, SP, Brazil), mixed in the same syringe, and the animals were released from the traps 30 min later. The treatment order was assigned as a block randomisation design, using a website ([www.sorteador.com.br](http://www.sorteador.com.br)).

Respiratory rate (RR) was monitored by observing chest movements, and heart rate (HR) was measured by auscultation of the heart. Arterial blood samples were withdrawn from a branch of the femoral artery with a heparinised 1-mL syringe and a 22 G needle for blood gas analysis and the analysis of other blood variables. The first sample was withdrawn 30 min after the injection, when all the animals were breathing air, and the second sample was withdrawn 60 min after the injection. The samples were immediately processed with a portable blood gas analyser (I-Stat<sup>®</sup> 1 and CG8+ Cartridges, Abbott Point of Care, IL, USA). pH, PaO<sub>2</sub>, partial pressure of arterial CO<sub>2</sub> (PaCO<sub>2</sub>), plasma ionised calcium (Ca<sup>2+</sup>), potassium (K<sup>+</sup>), sodium (Na<sup>+</sup>), and glucose concentrations were measured, and the bicarbonate (HCO<sub>3</sub><sup>-</sup>) and haemoglobin oxygen saturation (SaO<sub>2</sub>) were calculated. The results were corrected for the rectal temperature of the animal. The ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub>) was also calculated.

Plasma lactate was measured with another handheld device (Accutrend<sup>®</sup> Plus—Roche Diagnostics, Mannheim, Germany). The device had a lower limit of detection of 0.8 mmol/L, and values below that were considered rounded to 0.7 mmol/L for statistical comparison.

The alveolar-arterial O<sub>2</sub> gradient [P(A-a)O<sub>2</sub>], PaO<sub>2</sub>, and partial pressure of inspired O<sub>2</sub> (PiO<sub>2</sub>) were estimated at a standard temperature of 37°C, respiratory coefficient (RQ) of 1, barometric pressure (P<sub>B</sub>) of 707.5 mmHg, fraction of inspired O<sub>2</sub> (F<sub>i</sub>O<sub>2</sub>) of 0.21, and saturated water vapour pressure (P<sub>H<sub>2</sub>O</sub>) of 47 mmHg.

$$[P(A-a)O_2] = PAO_2 - PaO_2$$

$$PAO_2 = P_iO_2 - (PaCO_2/RQ)$$

$$P_iO_2 = F_iO_2 \times (P_B - P_{H_2O})$$

Based on the principle that [P(A-a)O<sub>2</sub>] < 10 mmHg, the minimum expected normal value for PaO<sub>2</sub> was calculated for animals breathing ambient air.

$$PaO_2 \text{ minimum expected} > PAO_2 - 10$$

The statistical analysis was performed using GraphPad Prism Software (San Diego, CA, USA). The variables (mean ± standard deviation) were considered parametric if they were normally distributed according to the Shapiro–Wilk test and had a coefficient of variation of less than 0.2; otherwise, they were considered nonparametric data (median [interquartile range]). For parametric data, a one-tailed unpaired t-test was used for comparison of values at 30 and 60 min, and analysis of variance (ANOVA) with Tukey's post-test was performed for

comparing data among the treatments. For non-parametric data, Wilcoxon test and Kruskal–Wallis test with Dunn’s post-test were used. Pearson’s correlation analysis was used to assess the correlation between the impact of O<sub>2</sub> supplementation and blood gas variables at 60 min while comparing the animals of the Air group with those of the 2 L/min and 5 L/min groups. Differences were considered statistically significant at  $p < 0.05$ .

## Results

The capybaras remained quiet after they were caught in the trap. Both DMM ( $9.2 \pm 3.0$  min) and DMB ( $10.5 \pm 3.7$  min) produced an equally fast induction, and there were no deaths during the study. No statistically significant differences were observed between the DMB and DMM groups. Thus, the animals from the DMB and DMM were grouped together for a more robust data analysis.

HR was approximately 70–80 beats/min and RR was about 26–36 breaths/min throughout the procedure. There was no statistical difference in these variables among the treatments. The same was observed in the arterial blood pH, over time. All animals that were breathing air only developed hypoxaemia at 30 min after drug injection, and remained hypoxaemic at 60 min. PaO<sub>2</sub> was lower than the PaO<sub>2minimum expected</sub>, i.e., higher than  $83 \pm 4$  mmHg while breathing air, resulting in a P(A-a)O<sub>2</sub> of 49 [16; 65] mmHg and PaO<sub>2</sub>/FiO<sub>2</sub> ratio of 209 [190; 228]. After O<sub>2</sub> supplementation at a flow rate of 2 L/min, there was an increase in SaO<sub>2</sub> and PaO<sub>2</sub> compared with that at 30 min when breathing only air ( $p < 0.0001$ ;  $p = 0.0002$ , respectively), but 9 of the 12 capybaras remained hypoxaemic, and there was no significant difference in both variables compared with the air group at 60 min (Table 1). A flow rate of 5 L/min reversed the hypoxaemia in all 12 animals (PaO<sub>2</sub>,  $p < 0.0001$ ) (Table 1).

The PaCO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup>, and plasma glucose levels increased significantly over time (from 30 min pre-O<sub>2</sub> to 60 min) in the 5 L/min group ( $p = <0.0001$ ) (Table 1). There was difference in plasma lactate over time only in the 5 L/min group ( $p = 0.0365$ ). Values above 2 mmol/L were measured in six animals in the Air group, four animals in the 2 L/min group, and none in the 5 L/min group. Rectal temperature decreased over time in the 5 L/min group ( $p < 0.0001$ ) (Table 1). Regarding electrolytes, ionised Ca<sup>2+</sup> concentration slightly decreased in the Air group between 30 and 60 min ( $p = 0.0449$ ) and increased in the 5L/min group ( $p = 0.030$ ), K<sup>+</sup> concentration increased in the 2L/min group ( $p = 0.0161$ ), while Na<sup>+</sup> did not vary over time in any group (Table 1).

Comparing the data from the capybaras belonging to the Air and 2 L/min groups at 60 min, positive correlations were found between increased flow and SaO<sub>2</sub> and PaO<sub>2</sub>. Comparing the air and 5 L/min groups at 60 min, positive correlations were observed between the flow and SaO<sub>2</sub>, PaO<sub>2</sub>, PaCO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup>, Ca<sup>2+</sup>, and glucose. The increase in the O<sub>2</sub> flow rate was negatively correlated with lactate (Fig 1).

## Discussion

The chemical restraint of the free-ranging capybaras is an important step in population management, and optimal maintenance of respiratory capacity is indispensable in choosing the anaesthetic protocol. Thus, we assessed the changes in the respiratory variables and electrolytes in the capybaras after the administration of two different drug combinations, based on a benzodiazepine, an alpha<sub>2</sub> adrenergic agonist, and an opioid. We also assessed the effectiveness of two O<sub>2</sub> supplementation flows and the factors involved in this process.

Although blood gas analysers use algorithms based on human haemoglobin, these values have commonly been used in species for which results validation studies have not been carried

**Table 1. Heart rate, respiratory rate, blood gas analysis, rectal temperature, glucose, lactate, plasma ionised calcium (Ca<sup>2+</sup>), sodium (Na<sup>+</sup>) and potassium (K<sup>+</sup>) plasma concentrations in free-ranging capybaras (*Hydrochoerus hydrochaeris*) chemically restrained with dexmedetomidine and midazolam, and either butorphanol (DMB) or methadone (DMM)<sup>§</sup>. All animals (n = 36) were breathing air when the 30-min sample was collected (pre-treatment) and supplemented nasally or not with oxygen after that until the 60-min sample was collected. Values expressed as mean ± standard deviation or median [interquartile range].**

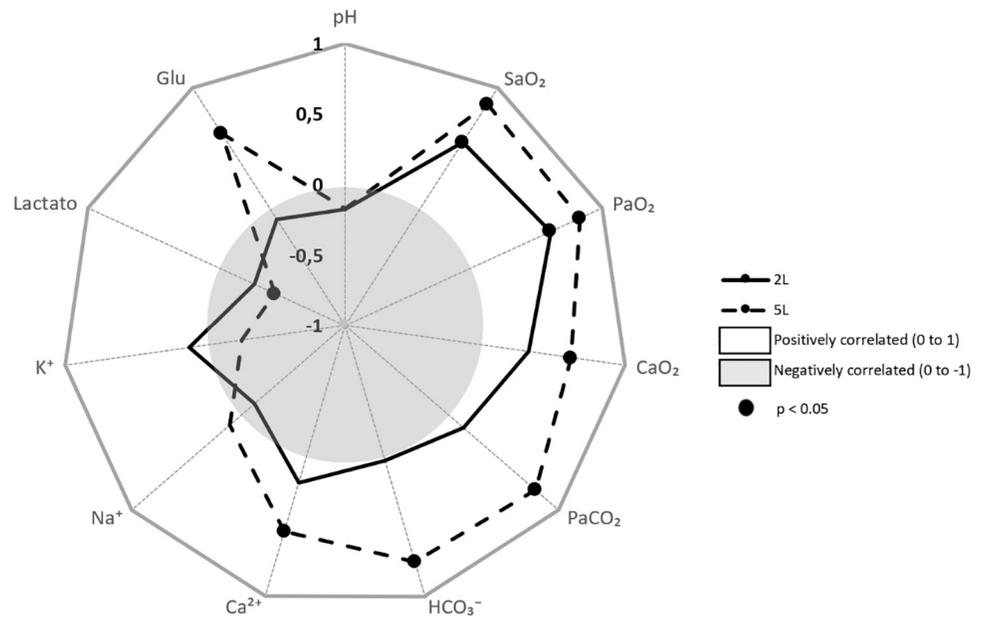
Variable	Pre-treatment	30 min	Treatment	60 min
HR	Air (n = 36)	79 ± 8.8	Air (n = 12)	76 ± 5.8
			2L (n = 12)	74 ± 10.9
			5L (n = 12)	73 ± 4.5
RR	Air (n = 36)	36 [20; 55]	Air (n = 12)	30 [25; 38]
			2L (n = 12)	34 [25; 47]
			5L (n = 12)	26 [21; 32]
pH	Air (n = 36)	7.40 ± 0.04	Air (n = 12)	7.42 ± 0.04
			2L (n = 12)	7.40 ± 0.04
			5L (n = 12)	7.40 ± 0.02
PaO <sub>2</sub> (mmHg)	Air (n = 36)	44 [40; 47]	Air (n = 12)	51 [45; 56] <sup>A</sup>
			2L (n = 12)	63 [56; 86] <sup>*A</sup>
			5L (n = 12)	188 [171; 286] <sup>*B</sup>
SaO <sub>2</sub> (%)	Air (n = 36)	81.6 ± 6.1	Air (n = 12)	85.7 ± 6.0 <sup>A</sup>
			2L (n = 12)	92.4 ± 4.2 <sup>*A</sup>
			5L (n = 12)	99.8 ± 0.4 <sup>*B</sup>
PaCO <sub>2</sub> (mmHg)	Air (n = 36)	45 ± 4	Air (n = 12)	45 ± 4 <sup>A</sup>
			2L (n = 12)	46 ± 7 <sup>A</sup>
			5L (n = 12)	54 ± 4 <sup>*B</sup>
HCO <sub>3</sub> <sup>-</sup> (mEq/L)	Air (n = 36)	29 [28; 31]	Air (n = 12)	30 [26; 32] <sup>A</sup>
			2L (n = 12)	29 [26; 31] <sup>A</sup>
			5L (n = 12)	35 [34; 36] <sup>*B</sup>
Rectal temp.	Air (n = 36)	36.5 [35.7; 36.8]	Air (n = 12)	36.6 [36.2; 37.2] <sup>A</sup>
			2L (n = 12)	36.2 [35.6; 36.8] <sup>A</sup>
			5L (n = 12)	35.2 [35.0; 35.7] <sup>*B</sup>
Glucose (mg/dL)	Air (n = 36)	197 [169; 214]	Air (n = 12)	206 [162; 224] <sup>A</sup>
			2L (n = 12)	188 [180; 191] <sup>A</sup>
			5L (n = 12)	273 [245; 301] <sup>*B</sup>
Lactate (mmol/L)	Air (n = 36)	0.75 [0.70; 2.07]	Air (n = 12)	2.10 [0.70; 3.65]
			2L (n = 12)	0.85 [0.70; 2.58]
			5L (n = 12)	0.70 [0.70; 0.77] <sup>*</sup>
Ca <sup>2+</sup> (mEq/L)	Air (n = 36)	0.95 [0.86; 1.09]	Air (n = 12)	0.85 [0.65; 0.96] <sup>*A</sup>
			2L (n = 12)	0.91 [0.70; 1.06] <sup>AB</sup>
			5L (n = 12)	1.15 [0.95; 1.19] <sup>*B</sup>
Na <sup>+</sup> (mEq/L)	Air (n = 36)	135.5 ± 1.96	Air (n = 12)	135.92 ± 1.38
			2L (n = 12)	135.22 ± 3.16
			5L (n = 12)	136.17 ± 1.75
K <sup>+</sup> (mEq/L)	Air (n = 36)	3.9 ± 0.43	Air (n = 12)	4.18 ± 0.60
			2L (n = 12)	4.33 ± 0.61 <sup>*</sup>
			5L (n = 12)	3.93 ± 0.36

HR, heart rate; RR, respiratory rate; pH, potential hydrogen; PaO<sub>2</sub>, partial pressure of arterial of oxygen; SaO<sub>2</sub>, haemoglobin oxygen saturation; PaCO<sub>2</sub>, partial pressure of arterial of carbon dioxide; HCO<sub>3</sub><sup>-</sup>, bicarbonate; Ca<sup>2+</sup>, plasma ionised calcium; K<sup>+</sup>, plasma potassium; Na<sup>+</sup>, plasma sodium; mmHg, millimetres of mercury; mEq/L, milliequivalents per litre; mmol/L, millimoles per litre; mg/dL, milligrams per decilitre; Air, animals without oxygen supplementation; 2L, animals which received 2L/min oxygen supplementation after 30 min; 5L, animals which received 5L/min oxygen supplementation after 30 min.

\* indicates a significant difference between the times (30 and 60 min), and different superscript letters indicate differences between the treatments ( $p < 0.05$ ). pH, PaO<sub>2</sub> and PaCO<sub>2</sub> values were corrected to the rectal temperature of the animal.

<sup>§</sup> The animals from the DMB and DMM were grouped together for a more robust data analysis since there were no statistical differences between the groups.

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**Fig 1. Pearson's correlation coefficient ( $r$ ) and significance ( $p$ ) of blood variables with different O<sub>2</sub> flows during immobilisation of free-ranging capybaras (*Hydrochoerus hydrochaeris*).** pH, potential hydrogen; SaO<sub>2</sub>, haemoglobin oxygen saturation; PaO<sub>2</sub>, partial pressure of arterial of oxygen; PaCO<sub>2</sub>, partial pressure of arterial of carbon dioxide; HCO<sub>3</sub><sup>-</sup>, bicarbonate; Ca<sup>2+</sup>, plasma ionised calcium; Na<sup>+</sup>, plasma sodium; K<sup>+</sup>, plasma potassium; Glu, glucose; 2L, animals which received 2L/min oxygen supplementation after 30 min until 60 min; 5L, animals which received 5L/min oxygen supplementation after 30 min until 60 min. Vertical axis represents  $r$  values. In the bright area, the closer to the edge, the greater the positive correlation. In the dark area, the closer to the centre, the greater the negative correlation. Markers represent a significant correlation ( $p < 0.05$ ).

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out [17–19, 24]. Thus, the data obtained here for capybaras can help in interpreting the results and variations observed due to the change in oxygen flow.

Arterial blood gases did not differ when methadone or butorphanol was included in the drug protocol. Due to the agonist function of methadone at the  $\mu$ -opioid receptors, it was expected that methadone would induce greater respiratory depression than butorphanol, since the latter acts as an antagonist at the  $\mu$ -opioid receptors [25]. However, our results are consistent with those of another study that reported no difference in sheep sedated with a combination of dexmedetomidine and butorphanol or methadone [26].

Blood gas analysis is crucial for detecting hypoxaemia in capybaras. All animals developed hypoxaemia at 30 min, even in the absence of evident clinical signs. Although the portable blood gas analyser used was based on human-determined algorithms, it was and is, together with the co-oximetre, one of the available tools for measuring oxygen levels for field conditions [27]. In addition to the parameters of an ordinary blood gas analysis, there are also easy-to-calculate indices that allow a better understanding of respiratory dynamics and provide clinically useful prognostic information. It was found that the values of  $[P(A-a)O_2]$  were higher than 10 mmHg and the PaO<sub>2</sub>/F<sub>1</sub>O<sub>2</sub> ratio was less than 300 in animals breathing air. This was also observed during the chemical restraint of other wild animals, indicating that changes may have occurred in the integrity of the alveolar capillary, causing hypoxaemia due to intrapulmonary factors, such as the formation of shunts and ventilation/perfusion imbalance [17, 28, 29].

Although the intranasal flow of 2 L/min O<sub>2</sub> improved the PaO<sub>2</sub> in all animals, nine animals remained hypoxaemic. In comparison, the low flow rate of 2 L/min O<sub>2</sub> was adequate to

prevent hypoxaemia in cheetahs (*Acinonyx jubatus*) sedated with dexmedetomidine, butorphanol, and midazolam [18] and revert hypoxaemia in brown bears (*Ursus arctos*) immobilised with the medetomidine/tiletamine-zolazepam combination [23].

Hypercapnia (PaCO<sub>2</sub> > 45 mmHg) was observed in six animals that were breathing air, six in the 2 L/min group, and all the 12 in the 5 L/min group at 60 min. Hypercapnia may have occurred due to poor ventilation, but its increase in the 5 L/min group may be due to the inhibition of hypoxic pulmonary vasoconstriction. This compensatory mechanism is activated in response to low P<sub>A</sub>O<sub>2</sub> and diverts blood flow to better-ventilated areas of the lung [30–32]. Thus, the CO<sub>2</sub> produced goes through the functional alveoli before it is eliminated. When hypoxaemia was reversed with O<sub>2</sub> supplementation, hypoxic pulmonary vasoconstriction was inhibited, leading to impaired CO<sub>2</sub> elimination.

The Haldane effect can also be involved in this process, as higher levels of O<sub>2</sub> acidify haemoglobin, which impairs the binding of CO<sub>2</sub> and increases PaCO<sub>2</sub> [33]. Although the F<sub>I</sub>O<sub>2</sub> of animals was not measured in this study, it is known that high F<sub>I</sub>O<sub>2</sub> rates are associated with the appearance of atelectasis, and if they are provided to individuals with low ventilation/perfusion ratio, the lungs may collapse because alveolar gas passes into the blood at a higher flow rate than that at which it is inspired [34].

High values of plasma glucose were expected because glycogenolysis occurs to provide energy to meet the increased energy demand during the increase in cardiac frequency during stressful conditions, such as capture [35]. In addition, dexmedetomidine decreases the levels of insulin [36], which may lead to an increase in plasma glucose within a few minutes after drug administration [37]. However, plasma glucose increased over time only in the 5 L/min group. Anaerobic glycolysis was probably present in some animals in the air and 2 L/min groups due to low O<sub>2</sub> levels. Despite the highest level of lactate (9.9 mmol/L) recorded in a capybara that was breathing air at 60 min, lactic acidosis was not observed.

## Conclusion

Both drug protocols quickly induced chemical immobilisation in the capybaras, but they also caused hypoxaemia, regardless of the opioid used. Furthermore, oxygen supplementation should be provided to prevent hypoxaemia during chemical restraint, when these drug combinations are used. Based on the results of this study, a flow rate of 5 L/min is recommended because the lower evaluated flow rate of 2 L/min did not correct the hypoxaemia in all the animals. However, further studies are needed to determine if 3 or 4 L/min is adequate.

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## References

1. Heard D. Rodents. In: West G, Heard D, Caulkett N, editors. Zoo animal and wildlife immobilization and anesthesia. 2nd ed. Ames, Iowa: Wiley Blackwell; 2014. p. 893–903.
2. Labruna MB. Ecology of rickettsia in South America. *Ann N Y Acad Sci.* 2009; 166:156–66. <https://doi.org/10.1111/j.1749-6632.2009.04516.x> PMID: 19538276
3. State SP. Casos autóctonos confirmados de febre maculosa brasileira no estado de São Paulo de 1985 a 2019\* por ano de início dos sintomas e letalidade [Internet]. 2019. Available from: [http://www.saude.sp.gov.br/resources/cve-centro-de-vigilancia-epidemiologica/areas-de-vigilancia/doencas-de-transmissao-por-vetores-e-zoonoses/dados/fmaculosa/fmb8519\\_cautoctone\\_ano\\_obito.pdf](http://www.saude.sp.gov.br/resources/cve-centro-de-vigilancia-epidemiologica/areas-de-vigilancia/doencas-de-transmissao-por-vetores-e-zoonoses/dados/fmaculosa/fmb8519_cautoctone_ano_obito.pdf)
4. Nunes FBP, Silva SC da, Cieto AD, Labruna MB. The dynamics of ticks and capybaras in a residential park area in southeastern Brazil: Implications for the risk of *Rickettsia rickettsii* infection. *Vector-borne zoonotic Dis.* 2019;3–8. <https://doi.org/10.1089/vbz.2017.2257> PMID: 30256745
5. Rosenfield DA, Pizzutto CS. On the importance of alpha behavior integrity in male capybara *Hydrochoerus hydrochaeris* (Mammalia: Rodentia: Caviidae) following immuno-contraceptive treatment. *J Threat Taxa.* 2019; 11(8):13967–76.
6. Szabuniewicz M, Sanchez L, Sosa A, Gil B, De Gomez M, Perez T, et al. The electrocardiogram of the capybara (*Hydrochoerus hydrochaeris*, Linné). *Zentralblatt für Vet R A.* 1978; 25:162–71. <https://doi.org/10.1111/j.1439-0442.1978.tb00915.x> PMID: 417533
7. Cruz ML, Luna SPL, Moura CA, Castro GB, Teixeira Neto FJ, Nishida SM. Anaesthetic techniques in capybaras (*Hydrochoerus hydrochaeris*, Linné). *Ciência Rural.* 1998; 28(3):411–5.
8. Salas V, Pannier E, Galíndez-silva C, Gols-ripoll A, Herrera EA, Salas V, et al. Methods for capturing and marking wild capybaras in Venezuela. *Wildl Soc Bull.* 2004; 32(1):202–8.
9. Nishiyama SM, Pompermayer LG, Lavor MSL de, Mata LBSC. Ketamine-xylazine, tiletamine-zolazepam and tiletamine-zolazepam-levomepromazine combinations in capybara (*Hydrochoerus hydrochaeris*). *Ceres.* 2006; 53(307):406–12.
10. King JD, Congdon E, Tosta C. Evaluation of three immobilization combinations in the capybara (*Hydrochoerus hydrochaeris*). *Zoo Biol.* 2010; 29:59–67. <https://doi.org/10.1002/zoo.20269> PMID: 19645047
11. Monsalve-Buritica S, Rojano-Bolaño C, Carrascal-Velásquez JC. Comparación de dos protocolos anestésicos en chigüiros (*Hydrochaerus hydrochaeris*) silvestres en el departamento de Córdoba, Colombia. *Vet y Zootecnia.* 2013; 7(1):90–9.
12. Rosenfield D, Ferraro MA, Souza CI, Cortopassi RSG, Pizzutto CS. Chemical immobilization of free-living capybaras (*Hydrochoerus hydrochaeris*) using ketamine-dexmedetomidine combination and a remote drug delivery system. *Brazilian J Vet Med.* 2020; 42:1–12.
13. Fahlman Å, Arnemo JM, Neuhaus P, Ruckstuhl KE. Efficacy of a portable oxygen concentrator with pulsed delivery for treatment of hypoxemia during anesthesia of wildlife. *J Zoo Wildl Med.* 2012; 43(1):67–76. <https://doi.org/10.1638/2011-0064.1> PMID: 22448511
14. Read MR. A review of alpha 2 adrenoreceptor agonists and the development of hypoxemia in domestic and wild ruminants a review of alpha 2 adrenoreceptor agonists and the development of hypoxemia in domestic and wild ruminants. *J Zoo Wildl Med.* 2003; 34(2):134–8. [https://doi.org/10.1638/1042-7260\(2003\)034\[0134:AROAAA\]2.0.CO;2](https://doi.org/10.1638/1042-7260(2003)034[0134:AROAAA]2.0.CO;2) PMID: 12885129
15. Spraker TR. Stress and capture myopathy in artiodactylids. In: Fowler ME, editor. *Zoo and wild animal medicine—Current therapy 3.* Philadelphia: W. B. Saunders; 1993. p. 481–8. <https://doi.org/10.1103/physrevc.48.r5> PMID: 9968855
16. Fahlman Å, Arnemo JM, Pringle J, Nyman G. Oxygen supplementation in anesthetized brown bears (*Ursus arctos*)—How low can you go? *J Wildl Dis.* 2014; 50(3):574–81. <https://doi.org/10.7589/2013-06-148> PMID: 24807187

17. Fahlman Å, Edner A, Wenger S, Foggin C, Nyman G. Pulmonary gas exchange and acid–base status during immobilisation of black rhinoceroses (*Diceros bicornis*) in Zimbabwe. *J S Afr Vet Assoc.* 2016; 87(1):1–9.
18. Colburn AMW, Murray S, Hayek LC, Marker L, Sanchez CR. Cardiorespiratory effects of dexmedetomidine-butorphanol-midazolam (dbm): a fully reversible anesthetic protocol in captive and semi–freeranging cheetahs (*Acinonyx jubatus*). *J Zoo Wildl Med.* 2016; 48(1):40–7.
19. Lian M, Bjorck S, Arnemo JM, Esteruelas NF, Angel M, Minsaas SC, et al. Severe hypoxemia in musk-oxen (*Ovibos moschatus*) immobilized with etorphine and xylazine corrected with supplemental nasal oxygen. *J Wildl Dis.* 2017; 53(2):000–000. <https://doi.org/10.7589/2016-04-085> PMID: 28051570
20. Berry S. Injectable anesthetics. In: Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA, editors. *Lumb & Jones Veterinary Anesthesia and Analgesia.* 5th ed. Iowa: Blackwell Pub; 2015. p. 277–96.
21. Fiorello C V, Rapoport GS, Rivera S, Clauss TM, Brainard BM. Comparison of anesthesia with fully reversible dexmedetomidine-butorphanol-midazolam versus ketamine-midazolam in captive Asian small-clawed otters (*Aonyx cinereus*). *JAVMA.* 2014; 244(1):107–14. <https://doi.org/10.2460/javma.244.1.107> PMID: 24344859
22. Wenger S, Buss P, Joubert J, Steenkamp J, Shikwambana P, Hatt J-M. Evaluation of butorphanol, medetomidine and midazolam as a reversible narcotic combination in free-ranging African lions (*Panthera leo*). *Vet Anaesth Analg.* 2010; 37,491–500. <https://doi.org/10.1111/j.1467-2995.2010.00569.x> PMID: 21040373
23. Fahlman Å, Pringle J, Arnemo JM, Swenson J, Brunberg S, Nyman G. Treatment of hypoxemia during anesthesia of brown bears (*Ursus arctos*). *J Zoo Wildl Med.* 2010; 41(1):161–4. <https://doi.org/10.1638/2009-0036.1> PMID: 20722273
24. Fahlman Å, Bosi EJ, Phil M, Nymand G. Reversible anesthesia of southeast asian primates with medetomidine, zolazepam and tiletamine. *J Zoo Wildl Med.* 2006; 37(4):558–61. <https://doi.org/10.1638/05-044.1> PMID: 17315446
25. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology.* 2010; 112:226–38. <https://doi.org/10.1097/ALN.0b013e3181c38c25> PMID: 20010421
26. Borges LPB, Nishimura LT, Carvalho LL, Cerejo SA, Auckburally A, Mattos-Junior E. Behavioral and cardiopulmonary effects of dexmedetomidine alone and in combination with butorphanol, methadone, morphine or tramadol in conscious sheep. *Vet Anaesth Analg.* 2016; 43(5):1–12. <https://doi.org/10.1111/vaa.12409> PMID: 27374608
27. Zoff A, Dugdale AHA, Scarabelli S, Rioja E. Evaluation of pulse co-oximetry to determine haemoglobin saturation with oxygen and haemoglobin concentration in anaesthetized horses: a retrospective study. *Vet Anaesth Analg.* 2019; 46(4):452–7. <https://doi.org/10.1016/j.vaa.2019.02.005> PMID: 31196749
28. Zeiler GE, Stegmann GF, Fosfogate G, Buck RK, Kästner SBR, Kummrow M, et al. Etorphine–ketamine–medetomidine total intravenous anesthesia in wild impala (*Aepyceros melampus*) of 120-minute duration. *J Zoo Wildl Med.* 2015; 46(4):755–66. <https://doi.org/10.1638/2015-0052.1> PMID: 26667531
29. Meyer LCR, Hetem RS, Fick LG, Mitchell D, Fuller A. Effects of serotonin agonists and doxapram on respiratory depression and hypoxemia in etorphine-immobilized impala (*Aepyceros melampus*). *J Wildl Dis.* 2010; 46(2):514–24. <https://doi.org/10.7589/0090-3558-46.2.514> PMID: 20688644
30. Sylvester JT, Shimoda LA, Aaronson PI, Ward JPT, Jt S, La S, et al. Hypoxic pulmonary vasoconstriction. *Physiol Rev.* 2012; 92:367–520. <https://doi.org/10.1152/physrev.00041.2010> PMID: 22298659
31. Marshall BE, Marshall C, Frasch F, Hanson CW. Intensive care medicine role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. *Intensive Care Med.* 1994; 20:291–7. <https://doi.org/10.1007/BF01708968> PMID: 8046124
32. Moudgil R, Michelakis ED, Archer SL, Michelakis ED, Hypoxic SLA. Hypoxic pulmonary vasoconstriction. *J Appl Physiol.* 2005; 98(123):390–403. <https://doi.org/10.1152/jappphysiol.00733.2004> PMID: 15591309
33. Siggaard-Andersen O, Garby L. The bohr effect and the haldane effect. *Scand J Clin Lab Invest.* 1973; 31(1):1–8. <https://doi.org/10.3109/00365517309082411> PMID: 4687773
34. Duggan M, Kavanagh B. Pulmonary atelectasis. A pathogenic perioperative entity. *Anesthesiology.* 2005; 102:838–54. <https://doi.org/10.1097/0000542-200504000-00021> PMID: 15791115
35. Reeder DM, Kramer KM. Stress in free-ranging mammals: Integrating physiology, ecology, and natural history. *J Mammal.* 2005; 86(2):225–35.
36. Restitutti F, Raekallio M, Vainionpää M, Kuusela E, Vainio O. Plasma glucose, insulin, free fatty acids, lactate and cortisol concentrations in dexmedetomidine-sedated dogs with or without MK-467: A

peripheral  $\alpha$ -2 adrenoceptor antagonist. *Vet J.* 2012; 193(2):481–5. <https://doi.org/10.1016/j.tvjl.2011.12.010> PMID: 22277719

37. Vaughan KL, Szarowicz MD, Herbert RL, Mattison JA. Comparison of anesthesia protocols for intravenous glucose tolerance testing in rhesus monkeys. *J Med Primatol.* 2014; 43:162–8. <https://doi.org/10.1111/jmp.12104> PMID: 24697511