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Dead space volumes in cats and dogs with small body mass ventilated with a fixed tidal volume

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Abstract

Objective To compare the portion of tidal volume (V_T) ventilating dead space volumes in nonbrachycephalic cats and dogs with small body mass receiving volume-controlled ventilation (VCV) with a fixed V_T.

Study design Prospective, experimental study.

Animals A group of eight healthy adult cats and dogs [ideal body weight (IBW): 3.0 ± 0.5 and 3.8 ± 1.1 kg, respectively].

Methods Anesthetized cats and dogs received VCV with a 12 mL kg^{-1} V_T (inspiratory pause ≥ 0.5 seconds). Respiratory rate (f_R) was adjusted to maintain normocapnia. Airway dead space (V_{Daw}) and alveolar tidal volume (V_{Talv}) were measured by volumetric capnography. Physiological dead space (V_{Dphys}) and V_{Dphys}/V_T ratio were calculated using the Bohr–Enghoff method. Data recorded before surgery were compared by an unpaired *t*-test or Mann–Whitney *U* test ($p < 0.05$ considered significant).

Results The IBW ($p = 0.07$), $PaCO_2$ ($p = 0.40$) and expired V_T [$V_{T(exp)}$] ($p = 0.77$) did not differ significantly between species. The V_{Daw} (mL kg^{-1}) was lower in cats (3.7 ± 0.4) than in dogs (7.7 ± 0.9) ($p < 0.0001$). The V_{Talv} (mL kg^{-1}) was larger in cats (8.3 ± 0.7) than in dogs (4.3 ± 0.7) ($p < 0.0001$). Cats presented a smaller V_{Dphys}/V_T ratio (0.33 ± 0.03) and V_{Dphys} (4.0 ± 0.3 mL kg^{-1}) than dogs (V_{Dphys}/V_T: 0.60 ± 0.09; V_{Dphys}: 7.2 ± 1.4 mL kg^{-1}) ($p < 0.0001$). The f_R and minute ventilation ($V_{T(exp)} \times f_R$) were lower in cats than in dogs ($p = 0.048$ and $p = 0.038$, respectively).

Conclusions and clinical relevance A fixed V_T results in more effective ventilation in cats than in dogs with small body mass because of species-specific differences in and V_{Daw} and V_{Dphys}. Because of the smaller V_{Daw} and V_{Dphys} in cats than in dogs, a lower f_R is required to maintain normocapnia in cats.

Keywords airway dead space, cats, physiological dead space, volumetric capnography.

Introduction

Mechanical ventilatory support is frequently required during general anesthesia in veterinary patients to prevent hypercapnia and respiratory acidosis, increase arterial oxygen partial pressure (PaO_2) and to reduce the work of breathing. Although a wide range of tidal volume (V_T) settings (10–20 mL kg^{-1}) have been historically adopted for mechanical ventilation in small animal anesthesia (Mosley 2015), there is a lack of scientific evidence to guide initial V_T adjustments in different animal species. Dead space volumes are important factors to consider when adjusting the V_T delivered by the ventilator. The V_T should be large enough to surpass the airway dead space volume (V_{Daw}) and ventilate perfused alveoli. The total dead space, referred to as physiologic dead space volume (V_{Dphys}), is the sum of V_{Daw} and alveolar dead space volume (V_{Dalv}) (Tusman et al. 2012; Petersson & Glenny 2014; Suarez-Sipmann et al. 2014).

Although increasing the V_T is an efficient means of increasing alveolar ventilation and preventing hypercapnia, a supraphysiological V_T may cause greater decreases in cardiac output associated with greater swings in stroke volume/arterial pulse pressure with each tidal breath (Andersen & Kuchiba 1967; Michard 2005). A relatively large V_T may also result in excessive compression of pulmonary capillaries, increasing total dead space volume (V_{Dphys}) owing to an increase in ventilated lung areas with poorly perfused or nonperfused alveoli (V_{Dalv}) (Baker & Burki 1987). Alveolar overstretching

caused by an excessively large V_T has also been associated with ventilator-induced lung injury (VILI) and an increase in the rate of postanesthetic respiratory complications in anesthetized humans without preexisting lung disease (Wolthuis et al. 2008; Futier et al. 2013). Although there is currently a lack of evidence of VILI in healthy dogs and cats receiving routine, short-duration ventilatory support, prevention of alveolar overdistension is generally considered a desirable goal considering the evidence of VILI associated with high V_T delivery in other species (Dreyfuss et al. 1988).

Extrapolation of V_Ts recommended for anesthesia in humans without lung disease [6−8 mL kg^{-1} of ideal body weight (IBW)] to animal species is questionable because of species-related differences in the portion of V_T that fills the V_{Daw} and in V_{Dphys} (Tusman et al. 2013; Bumbacher et al. 2017; Young et al. 2019). Currently there is a lack of evidence to substantiate initial V_T settings during routine mechanical ventilation in cats. The use of the same V_T in dogs and cats may be inappropriate if there are differences in V_{Daw} and V_{Dphys} between species. Compared to dogs of similar body mass, cats are usually intubated with smaller size endotracheal tubes, suggesting that V_{Daw} is smaller in this species. Knowledge of species-specific differences in dead space ventilation may provide important information to guide mechanical ventilation adjustments with the objective of optimizing gas exchange at the cost of causing the least alveolar distension/stress. This study aimed to determine if there are differences in dead space volumes between cats and dogs with small body mass receiving mechanical ventilation with the same V_T (12 mL kg^{-1}), with the goal of providing evidence to guide initial ventilator settings in these species.

Materials and methods

Animals

The study was conducted considering the CONSORT guidelines after approval by the Ethics Committee on Animal Use of São Paulo State University, Brazil (protocol CEUA 0488/2023). This was an exploratory study and an initial sample size of eight animals per group was chosen to test the main study hypothesis (dead space volumes differ between cats and dogs of similar body mass). After obtaining informed owner consent, eight cats (three client-owned and five university-owned) and eight (client-owned) dogs were enrolled.

The inclusion criteria were nonbrachycephalic healthy animals with body mass < 5.5 kg, between 1 and 3 years of age and scheduled for elective ovariohysterectomy or orchiectomy. Animals were assessed as healthy based on physical examination and results of venous blood gas analysis and plasma electrolytes (ABL 80 Flex Basic; Radiometer Medical, Denmark). Animals with hemodynamic instability/hypotension [mean arterial pressure (MAP) < 60 mmHg] at the time of data collection were excluded from the study.

Anesthesia, instrumentation and mechanical ventilation

Food was withheld for 12 hours before the study, with free access to water until 1 hour before premedication. To minimize the dead space resulting from the portion of the endotracheal tube protruding outside the mouth on total V_{Daw}, the endotracheal tubes (Cuffed ET tube; Bio Med Healthcare Products, India) were shortened from their original length. To achieve this goal, with animals positioned in sternal recumbency, the endotracheal tubes were placed in a lateral view in relation to the body with their tips at the level of the thoracic inlet (first rib), and the portion of the tubes that extended beyond the incisors were cut to allow only the endotracheal tube connector to protrude outside the oral cavity.

Premedication and intravenous induction agents were chosen by a single anesthesiologist (C.H.G.) based on clinical judgment. After an adequate level of sedation/chemical restraint was achieved, a 22 gauge catheter (Safelet; Nipro Medical Ltda, SP, Brazil) was aseptically placed in the cephalic vein and animals were prepared for surgery. Anesthesia was induced 30 minutes after premedication. Upon the loss of laryngeal reflex, orotracheal intubation was performed with the assistance of a laryngoscope. In cats, orotracheal intubation was performed after 0.1 mL of 2% lidocaine was sprayed into the larynx.

After visual inspection of the entrance to the larynx, an endotracheal tube with the largest possible internal diameter (ID) was chosen by a single experienced anesthesiologist (C.H.G.) who performed intubation. Animals were positioned in left lateral recumbency after intubation, and the endotracheal tube was connected to the flow/carbon dioxide (CO_2) sensor of the volumetric capnography monitor (Respironics NM3; Philips Healthcare, The Netherlands) and to a pediatric circle breathing circuit (9100c NXT; GE Healthcare, SP, Brazil). To maintain anesthesia, isoflurane was carried with oxygen and air and the flow rate of each gas adjusted to achieve an inspired oxygen fraction (F_IO_2) of 0.4 (acceptable range 0.39−0.41). Heart rate (HR), electrocardiography (lead II) and pulse oximetry were monitored throughout anesthesia using a multiparameter monitor (B40 monitor; GE Healthcare). The end-expired isoflurane concentration (F_E'Iso) was measured by an anesthetic agent analyzer (N-CAIO Airway Gas Module; GE Healthcare), with the gas sampling line attached to the Y piece. The gas analyzer was calibrated at the beginning and at the end of the study with a standard gas mixture provided by the manufacturer (Quick Calibration Gas 755583-HEL; GE Healthcare). Fluid therapy with lactated Ringer's solution (3 mL kg^{-1} $hour^{-1}$ for cats and 5 mL kg^{-1} $hour^{-1}$ for dogs) was

administered intravenously (Digipump LP8x; Digicare Animal Health, FL, USA) and a forced air warming device was used to maintain esophageal temperature between 36.5 °C and 38.0 °C (Bair Hugger; Arizant Healthcare, MN, USA).

An ascending bellows ventilator (9100c NXT; GE Healthcare) was set in volume-controlled ventilation (VCV) mode with an end-inspiratory pause of 40% of total inspiratory time. The V_T delivered by the ventilator was adjusted to maintain expired V_T ($V_{T(exp)}$) values, monitored by the volumetric capnography monitor, at 12 mL kg^{-1} of IBW (acceptable range < 13 mL kg^{-1} and > 11 mL kg^{-1}). While the $V_{T(exp)}$ was held constant, the respiratory frequency (f_R) set on the ventilator was adjusted to maintain end-expired carbon dioxide partial pressure ($P_E'CO_2$) between 33 and 40 mmHg (4.4−5.3 kPa). A body condition score (BCS, scale range 1−9) was used to predict IBW in cats and dogs by a single experienced anesthesiologist (C.H.G.), with a score of 5 representing IBW. With each increase in the score above 5 (overweight range: 6, 7, 8 and 9), IBW is predicted by decreasing the actual body weight by 10%, 20%, 30% and 40%, respectively. For each decrease in the score below 5 (underweight range: 4, 2, 3 and 1), IBW is predicted by increasing the actual body weight by 10%, 20%, 30% and 40%, respectively (German et al. 2006; Becvarova 2011).

The ratio of inspiratory-to-expiratory time was initially set at 1:2. If the end-inspiratory pause was < 0.5 seconds as a result of high f_R settings (≥17 breaths minute^{-1}), the ratio of inspiratory-to-expiratory time was adjusted to 1:1.5 to maintain the end-inspiratory pause ≥ 0.5 seconds. The bellows-type ventilator used in this study resulted in an intrinsic (non-adjustable) positive end-expiratory pressure of 2 cmH_2O. Respiratory mechanics variables provided by the volumetric capnography monitor [peak inspiratory pressure (P_{peak}), total airway resistance (R_{aw}) and dynamic compliance of the respiratory system (C_{dyn})] were recorded for analysis.

A 24 gauge catheter (Safelet; Nipro Medical Ltda) was placed in a dorsal pedal artery for direct blood pressure monitoring (B40; GE Healthcare). While the skin was being aseptically prepared for catheter insertion, systolic arterial blood pressure was measured by a Doppler ultrasound device (Model 811-B; Parks Medical Inc., OR, USA). If necessary, intravenous dopamine (5−20 μg kg^{-1} minute^{-1}) (Dopacris; Cristália Produtos Químicos e Farmacêuticos Ltda, SP, Brazil) was administered using a syringe pump (BeneFusion SP3; Mindray Animal Care, Shenzhen, China) to maintain systolic arterial pressure above 90 mmHg. Upon completion of catheterization, the arterial catheter was connected to a fluid-filled blood pressure transducer system (Tru-Wave PX260; Edwards Lifesciences Corp., CA, USA), with the reference level (0 mmHg) set at the level of the mid-sternum. After direct blood pressure monitoring was initiated, dopamine infusion was adjusted to maintain MAP ≥ 60 mmHg. Bradycardia (HR < 100 beats minute^{-1} in cats and < 70 beats minute^{-1} in dogs) with concurrent hypotension (MAP < 60 mmHg) was treated with 0.02 mg kg^{-1} of atropine intravenously (Pasmodex; Halex Istar Indústria Farmacêutica S.A., CE, Brazil) intravenously.

Arterial oxygenation variables

Arterial blood samples were drawn from the dorsal pedal artery for measurement of temperature-corrected arterial blood gases (ABL 80 Flex Basic; Radiometer Medical).

The average barometric pressure at the location where the study was conducted [690 mmHg (92 kPa) in Botucatu, located 800 m above sea level] was used to calculate the partial pressure of oxygen in alveoli (PAO_2) according to the formula below. The difference between partial pressures of oxygen in the alveoli and in arterial blood [$P(A-a)O_2$] was calculated by subtracting PaO_2 from PAO_2:

$$PAO_2 = [FiO_2 \times (\text{barometric pressure} - 47\ \text{mmHg})] - PaCO_2/0.8$$

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

Volumetric capnography monitoring

The zero CO_2 level of the mainstream CO_2 sensor (Capnostat 5, Philips-Respironics, PA, USA) of the volumetric capnography monitor was adjusted with room air before each experiment and displayed CO_2 values were corrected for inspired gas composition (FiO_2 and percent inspired isoflurane). Before and after completion of the study, the accuracy of $V_{T(exp)}$ measured by the neonatal and pediatric fixed orifice flow sensor (flow/CO_2 sensor; Philips-Respironics) was verified over the range of predicted V_Ts (30−60 mL) using a spirometer tester (Spirometry tester 844202; Datex-Ohmeda, Finland). The $V_{T(exp)}$ displayed by the monitor differed by < 10% from the volume displayed by the spirometry tester. The V_{Daw} and the alveolar tidal volume (V_{Talv}), which corresponds to the portion of the V_T that ventilates the alveoli, were measured from the volumetric capnography waveform (plotting of CO_2 and expired gas volume) on a breath-by-breath basis (Bartels et al. 1954; Tusman et al. 2012; Suarez-Sipmann et al. 2014).

As per manufacturer's recommendations, the size of the flow/CO_2 sensor was chosen based on the endotracheal tube ID: for animals where the endotracheal tube ID was ≤ 4.0 mm, a human neonatal flow/CO_2 sensor was used (dead space < 1 mL); for animals where endotracheal tube ID ranged 4.5−6 mm, a human pediatric flow/CO_2 sensor was used (dead space < 4 mL) (Bhalla et al. 2015).

Dead space volumes and ventilatory variables

The apparatus dead space volume was measured as the volume of water necessary to fill the portions of equipment protruding

outside the mouth where there is bidirectional flow (endotracheal tube connector, flow/CO_2 sensor and the patient end of the Y piece of the breathing circuit) (Fig. S1). The apparatus dead space volume was divided by IBW for comparison between groups. $V_{T(exp)}$, V_{Daw} and V_{Talv} were averaged from three sequential volumetric capnograms. The volume of CO_2 eliminated per minute ($\dot{V}CO_2$), calculated from the area under the volumetric capnography curve, was also recorded. The V_{Dphys}/V_T ratio was calculated according to the Enghoff modification of the Bohr method, where $PaCO_2$ is used as a surrogate of mean alveolar CO_2 partial pressure, while the partial pressure of CO_2 in mixed expired gas ($P\bar{E}CO_2$) was measured from the volumetric capnogram (average of three capnograms). The V_{Dphys} and V_{Dalv} were calculated as follows (Tusman et al. 2012):

$$V_{Dphys}/V_T \text{ (Bohr–Enghoff)} = (PaCO_2 - P\bar{E}CO_2)/PaCO_2$$

$$V_{Dphys} \text{ (mL)} = V_{Dphys}/V_T \times V_{T(exp)}$$

$$V_{Dalv} = V_{Dphys} - V_{Daw}$$

Calculated ventilatory variables included: minute ventilation ($\dot{V}_E = V_{T(exp)} \times f_R$) and effective alveolar ventilation [$\dot{V}_A = (V_{T(exp)} - V_{Dphys}) \times f_R$)] (Tusman et al. 2012; Petersson & Glenny 2014; Suarez-Sipmann et al. 2014). All dead space volumes and ventilatory variables were indexed to the IBW where applicable.

Upon completion of instrumentation, variables of interest were recorded after a 10 minute period of steady state anesthesia, defined as absence of patient–ventilator asynchrony and stable hemodynamic function (absence of bradycardia and MAP > 60 mmHg). After the end of the experimental phase, animals were repositioned in dorsal recumbency and prepared for surgery. Anesthesia and analgesia protocols were subsequently adjusted at the discretion of the primary anesthetist.

Statistical analysis

Data were analyzed using commercial software (GraphPad Prism Version 10.0.2; GraphPad, CA, USA). Dead space volumes (V_{Daw} and V_{Dphys}) were the primary outcome variables. Secondary outcome variables were V_{Dphys}/V_T ratio, f_R, $\dot{V}_E$ and $\dot{V}_A$. The Shapiro–Wilk test was conducted to assess normality of data distribution. For symmetrically distributed data (presented as mean ± standard deviation), an unpaired two-tailed Student's *t*-test compared variables recorded in cats and dogs. For data with asymmetrical distribution (presented as median and interquartile range), the Mann–Whitney *U* test compared variables between cats and dogs. Fisher's exact test compared the number of cats and dogs requiring dopamine to prevent hypotension at the time of data sampling. The significance level was set at $p < 0.05$.

Results

A total of eight cats and eight dogs were enrolled (four males and four females of each species). The actual body weight of cats and dogs (3.0 ± 0.5 kg and 3.9 ± 1.3 kg, respectively) did not differ significantly ($p = 0.09$). All cats were of mixed breed with a BCS of 5 (actual body weight equal to IBW). Dogs enrolled in the study included three German Spitz, two Miniature Pinscher, two mixed breed and one Yorkshire Terrier. The BCS deviated from ideal in five dogs (score 7 in two dogs, score 4 in two dogs, score 3 in one dog). The IBW of dogs (3.8 ± 1.1 kg) did not differ significantly from the IBW of cats ($p = 0.07$).

Three cats were premedicated with intramuscular dexmedetomidine (5 μg kg^{-1}) (Dexdomitor; Zoetis LTDA, SP, Brazil) and methadone (0.2 mg kg^{-1}) (Mytedom; Cristália Produtos Químicos e Farmacêuticos Ltda). One cat receiving this combination also required intramuscular ketamine (7 mg kg^{-1}) (Cetamin; Syntec do Brasil, SP, Brazil). The remaining five cats were administered intramuscular premedication with methadone (0.2 mg kg^{-1}) combined with midazolam (0.2 mg kg^{-1}) (Dormire; Cristália Produtos Químicos e Farmacêuticos Ltda) and ketamine (12 mg kg^{-1}). All dogs were premedicated with morphine (0.5 mg kg^{-1}, intramuscularly) (Dimorf; Cristália Produtos Químicos e Farmacêuticos Ltda). Induction of anesthesia was achieved by intravenous injection of propofol (Propovan, Dimorf; Cristália Produtos Químicos e Farmacêuticos Ltda) alone (six cats) or in combination with ketamine (1 mg kg^{-1}) (two cats and eight dogs). The total dose of propofol required for induction of anesthesia [cats: 5.0 (3.4–7.3) mg kg^{-1}; dogs: 4.0 (3.9–5) mg kg^{-1}] and the time from induction of anesthesia until recording variables of interest (cats: 37 ± 15 minutes; dogs: 39 ± 13 minutes) did not differ significantly between species ($p = 0.57$ and $p = 0.73$, respectively).

During maintenance of anesthesia with isoflurane, dopamine (5–20 μg kg^{-1} $minute^{-1}$) was required to maintain MAP ≥ 60 mmHg in all cats at the time of data sampling. Dopamine (7.5 μg kg^{-1} $minute^{-1}$) was necessary to achieve MAP ≥ 60 mmHg at the time of data collection in two dogs. The number of animals requiring dopamine for hemodynamic stabilization was significantly higher in cats than in dogs ($p = 0.007$). Atropine (0.02 mg kg^{-1} intravenously) was administered to treat bradycardia and hypotension 15 and 25 minutes before respiratory data collection in two dogs, respectively, and 20 minutes before respiratory data collection in one cat. These animals were included in the analysis as HR and MAP increased to normal levels. The $F\bar{E}$Iso and physiologic variables recorded during volumetric capnography measurements are presented in Table 1.

A 4 mm ID endotracheal tube was used in seven cats (IBW range: 2.5–3.7 kg) and a 3.5 mm tube in one cat (IBW: 2.4

Table 1 End-expired isoflurane concentration ($F_E'Iso$) and physiologic variables recorded during volumetric capnography measurements in cats ($n = 8$) and dogs presenting small body mass ($n = 8$) anesthetized with isoflurane receiving volume-controlled ventilation (tidal volume 12 mL kg^{-1} and 40% of end-inspiratory pause) with an inspired oxygen fraction of 0.4. Data are presented as mean ± standard deviation or median (interquartile range). HR, heart rate; MAP, mean arterial pressure.

Variable	Species		*p* value
	Cat	Dog	
$F_E'Iso$ (%)	1.40 ± 0.27	1.28 ± 0.20	0.32
HR (beats minute^{-1})	125 ± 21	84 ± 17	0.0008
MAP (mmHg)	66 (61–74)	65 (62–67)	0.70
Esophageal temperature (°C)	37.0 ± 0.6	37.0 ± 0.8	0.86

kg). Endotracheal tubes with ID ranging 5–6 mm were placed in dogs (IBW: 2.16–5.2 kg). There were no significant differences in arterial oxygenation and respiratory mechanics variables between dogs and cats, except for a significantly lower P_{peak} and a significantly higher R_{aw} in cats compared to dogs (Table 2).

Ventilatory variables are presented in Table 3. The $PaCO_2$, $P_E'CO_2$ and $PaCO_2 - P_E'CO_2$ gradient did not differ significantly between species, whereas the CO_2 in mixed expired gas ($P\bar{E}CO_2$) was significantly higher in cats than in dogs. A negative $PaCO_2 - P_E'CO_2$ gradient was observed in one cat (−0.1 mmHg) and four dogs (−0.5 to −2.3 mmHg). The f_R and $\dot{V}_E$ adjusted to maintain normocapnia during VCV were significantly lower in cats than in dogs. The $\dot{V}_A$ and $\dot{V}CO_2$ were significantly higher in cats than in dogs.

Table 2 Arterial oxygenation variables and respiratory mechanics recorded in cats ($n = 8$) and dogs presenting small body mass ($n = 8$) anesthetized with isoflurane receiving volume-controlled ventilation (tidal volume 12 mL kg^{-1} and 40% of end-inspiratory pause) with an inspired oxygen fraction of 0.4. Data are presented as mean ± standard deviation or median (interquartile range). PaO_2, arterial partial pressure of oxygen; PaO_2:F_IO_2, ratio of arterial partial pressure of oxygen and fraction of inspired oxygen; $P(A-a)O_2$, alveolar to arterial oxygen partial pressure difference; P_{peak}, peak inspiratory pressure; C_{dyn}, dynamic compliance of the respiratory system; R_{aw}, airway resistance.

Variable	Species		*p* value
	Cat	Dog	
PaO_2 mmHg (kPa)	198 ± 19 (26.4 ± 2.5)	198 ± 15 (26.4 ± 2.0)	0.95
PaO_2:F_IO_2 mmHg (kPa)	483 ± 39 (64.4 ± 5.2)	494 ± 34 (65.9 ± 4.5)	0.55
$P(A-a)O_2$ mmHg (kPa)	21 ± 6 (2.8 ± 0.8)	14 ± 7 (1.9 ± 0.9)	0.07
P_{peak} (cmH_2O)*	9 (8–9)	10 (9–12)	0.03
C_{dyn} (mL cmH_2O^{-1} kg^{-1})	1.87 ± 0.25	1.93 ± 0.32	0.69
R_{aw} (cmH_2O L^{-1}second^{-1})	31 ± 6	17 ± 3	< 0.0001

Based on endotracheal tube IDs, a neonatal flow/CO_2 sensor was used in all cats and a pediatric flow/CO_2 sensor was used for volumetric capnography measurements in dogs. The apparatus dead space volume/IBW was significantly larger in dogs than in cats (3.1 ± 0.8 and 2.0 ± 0.3 mL kg^{-1}, respectively; $p = 0.004$) and represented a significantly larger percentage of the $V_{T(exp)}$ in dogs (25.5 ± 6.5%) than in cats (16.5 ± 2.9%) ($p = 0.003$).

Expired V_T measured by volumetric capnography did not differ significantly between cats and dogs (Fig. 1a). Compared to dogs, cats presented significantly smaller V_{Daw} (Fig. 1b) and significantly larger V_{Talv} (Fig. 1c). The Bohr–Enghoff V_{Dphys}/V_T ratio and V_{Dphys} were significantly smaller in cats than in dogs (Fig. 1d and e). In one cat and four dogs, V_{Dalv} values were negative, which coincided with negative $PaCO_2 - P_E'CO_2$ gradients. Negative V_{Dalv} values were considered as 0. The V_{Dalv} was significantly higher in cats than in dogs (Fig. 1f).

After data collection, the surgery was performed without complications. Intraoperative analgesia protocols used for cats and dogs are reported in Appendix SA. All animals recovered uneventfully from anesthesia, and no complications were reported 1 week after surgery (Appendix SA).

Discussion

This study showed that the portion of a fixed V_T that ventilates the V_{Daw} is significantly smaller in cats than in dogs with small body mass. Because of differences in V_{Daw}, a larger percentage of the V_T ventilated the alveoli (V_{Talv}) in cats in comparison to dogs. The V_{Daw} was the major determinant of V_{Dphys} in both species. The smaller V_{Daw} and V_{Dphys} in cats resulted in a more effective alveolar ventilation per tidal breath, explaining why cats required a lower f_R to maintain normocapnia in comparison to dogs. The lower f_R resulted in smaller $\dot{V}_E$ in cats in comparison to dogs. However, to maintain normocapnia, the effective ventilation per minute ($\dot{V}_A$), which better corresponds to CO_2 removal than $\dot{V}_E$, was higher in cats because of the higher $\dot{V}CO_2$ compared to that in dogs of similar mass (Suarez-Sipmann et al. 2014; Kremeier et al. 2020).

In neonatal/pediatric human patients and in animals with a small body mass, the use of airway adapters or an excessively long portion of the endotracheal tube protruding outside the mouth (apparatus dead space) can significantly increase total V_{Daw}, negatively impacting $\dot{V}_A$ (King & Feldman 2017). The effect of apparatus dead space on total V_{Daw} was relatively small in cats because the neonatal flow/CO_2 sensor used in this species added a relatively small dead space. By contrast, in dogs, the dead space of the pediatric flow/CO_2 sensor used for volumetric capnography measurements had a larger impact

Table 3 Ventilatory variables in cats ($n = 8$) and dogs with small body mass ($n = 8$) anesthetized with isoflurane receiving volume-controlled ventilation (tidal volume 12 mL kg^{-1} and 40% of end-inspiratory pause) with an inspired oxygen fraction of 0.4. Data are presented as mean ± standard deviation or median (interquartile range). f_R, respiratory rate; $PaCO_2$, arterial partial pressure of carbon dioxide; $PaCO_2 - P_{E'}CO_2$, arterial to end-expired partial pressure of carbon dioxide gradient; $P_{E'}CO_2$, end-expired partial pressure of carbon dioxide; $P_{\bar{E}}CO_2$, carbon dioxide partial pressure in mixed expired gas; $\dot{V}_A$, effective alveolar ventilation; $\dot{V}CO_2$, carbon dioxide elimination per minute; $\dot{V}_E$, minute ventilation.

Variable	Species		*p* value
	Cat	Dog	
$PaCO_2$ mmHg (kPa)	39.4 ± 3.1 (5.3 ± 0.4)	37.1 ± 5.5 (4.9 ± 0.7)	0.40
$P_{E'}CO_2$ mmHg (kPa)	36.6 ± 2.9 (4.9 ± 0.4)	36.5 ± 3.1 (4.9 ± 0.4)	0.93
$PaCO_2 - P_{E'}CO_2$ mmHg (kPa)	2.8 ± 2.0 (0.4 ± 0.3)	1 ± 2.9 (0.1 ± 0.4)	0.17
$P_{\bar{E}}CO_2$ mmHg (kPa)	26.3 ± 2.0	14.6 ± 2.7	< 0.0001
f_R (breaths minute^{-1})	10 (10–16)	17 (13–18)	0.048
$\dot{V}_E$ (mL minute^{-1} kg^{-1})	127 (118–195)	188 (162–222)	0.038
$\dot{V}_A$ (mL minute^{-1} kg^{-1})	88 (78–129)	75 (60–82)	0.038
$\dot{V}CO_2$ (mL minute^{-1} kg^{-1})	4.5 ± 1.2	3.2 ± 0.6	0.02

on total V_{Daw}. The V_{Daw} recorded in dogs with small body mass (7.7 mL kg^{-1}) was slightly higher than V_{Daw} values (6.83 mL kg^{-1}) reported by a previous study performed in larger dogs (28.3 ± 11.0 kg) mechanically ventilated with a 12 mL kg^{-1} V_T, where the adult flow/CO_2 sensor (< 8.5 mL of added dead space) used for volumetric capnography measurements probably had a smaller effect on total V_{Daw} (Bumbacher et al. 2017).

The Bohr–Enghoff V_{Dphys}/V_T and V_{Dphys} values observed in the dogs with small body mass approached the V_{Dphys}/V_T and V_{Dphys} values obtained by the same method in medium to large size dogs (19–56 kg) receiving mechanical ventilation with

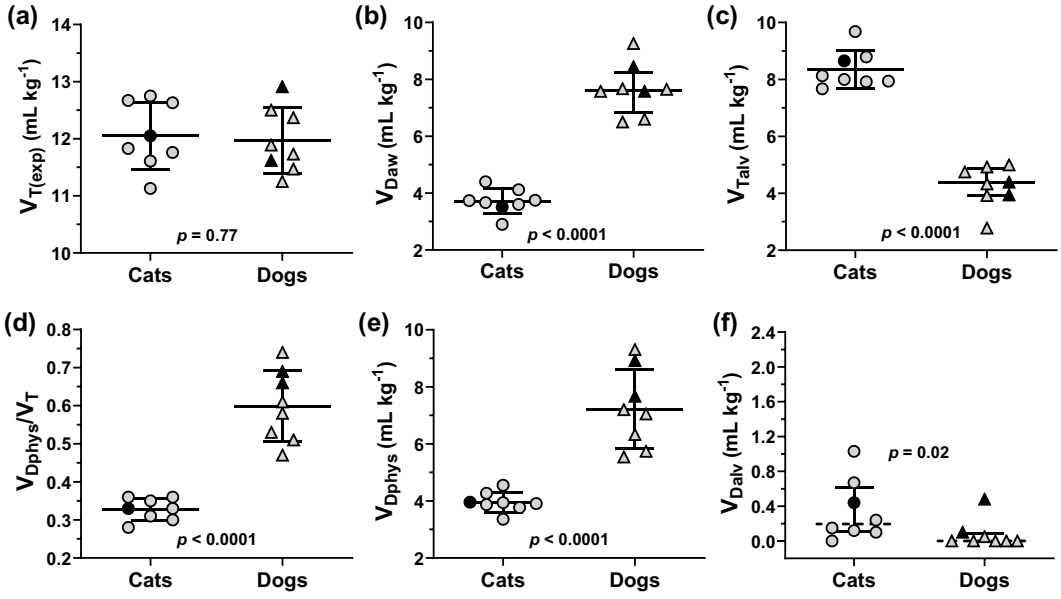

Figure 1 Volumetric capnography derived variables recorded in cats ($n = 8$) and dogs with small body mass ($n = 8$) anesthetized with isoflurane receiving volume-controlled ventilation (tidal volume 12 mL kg^{-1} and 40% of end-inspiratory pause) with an inspired oxygen fraction of 0.4. Data are presented as mean ± standard deviation or median (dashed lines) and interquartile range. Individual data are shown by circles (cats) and triangles (dogs). The one cat and two dogs that were administered atropine to treat bradycardia and hypotension 15–20 minutes prior to measurements are shown by the black circle and triangles, respectively. V_{Dalv}, alveolar dead space volume; V_{Daw}, airway dead space volume; V_{Dphys}, physiological dead space volume; V_{Dphys}/V_T, physiological dead space to tidal volume ratio; V_{Talv}, alveolar tidal volume; $V_{T(exp)}$, expired tidal volume.

the same V_T (12 mL kg^{-1}) (Mosing et al. 2010). Considering that the V_{Dphys} in the dogs of the present report (7.2 ± 1.4 mL kg^{-1}) is substantially larger than the V_{Dphys} measured by the same method in healthy anesthetized humans (approximately 2 mL kg^{-1} for individuals weighing 75 kg), extrapolation of a V_T within the range recommended for humans (8 mL kg^{-1}) will likely result in less efficient ventilation (hypercapnia/respiratory acidosis) despite the use of high respiratory rates in canine species (>30 breaths $minute^{-1}$) (Tusman et al. 2013; Bumbacher et al. 2017; De Monte et al. 2018). By contrast, because of the smaller V_{Dphys} in cats, a V_T within the range recommended for mechanical ventilation in humans (8 mL kg^{-1}) might result in more effective control of $PaCO_2$ levels in cats than in dogs.

$\dot{V}_E$ carries a linear correlation with $PaCO_2$ and conditions of normocapnia were maintained at a cost of a lower $\dot{V}_E$ in cats than in dogs. As both species were ventilated with the same V_T, lower f_R settings were necessary to decrease $\dot{V}_E$ and maintain normocapnia in cats. However, the important factor that determines gas exchange/$PaCO_2$ levels is not the V_T per se but rather the portion of V_T that expands alveoli that are ventilated and perfused, calculated by subtracting the V_{Dphys} from each mechanical breath (Tusman et al. 2012; Petersson & Glenny 2014). $\dot{V}_A$ better correlates with $PaCO_2$ than $\dot{V}_E$ because $\dot{V}_A$ reflects the ventilation per minute of lung areas that participate in gas exchange. In the present report, despite the lower $\dot{V}_E$ in cats compared to dogs, a higher $\dot{V}_A$ was necessary to maintain normocapnia in cats because the CO_2 production by aerobic metabolic activity ($\dot{V}CO_2$ measured during constant ventilation and hemodynamic stability) was higher in cats than in dogs (Suarez-Sipmann et al. 2014; Kremeier et al. 2020) (discussion of differences in $\dot{V}CO_2$ between dogs and cats presented in the Appendix SA).

The Enghoff modification of the Bohr formula simplifies V_{Dphys}/V_T measurements by using $PaCO_2$ as a surrogate measure of the mean alveolar CO_2 partial pressure (Tusman et al. 2012; Suarez-Sipmann et al. 2013, 2014). The Bohr–Enghoff method will overestimate true V_{Dphys} if there is an increase in mixed venous admixture (percentage of mixed venous blood bypassing ventilated lung areas) leading to increased $PaCO_2$ levels (Tusman et al. 2012; Suarez-Sipmann et al. 2013, 2014). However, with the mechanical ventilation protocol used in the present study, the CO_2-rich mixed venous admixture was relatively small because PaO_2 approached theoretical alveolar oxygen levels (PAO_2) in both species [$P(A-a)O_2$ values < 25 mmHg]. Therefore, the near-optimal oxygen exchange across the alveolar–capillary barrier/minimal mixed venous admixture suggests that the Bohr–Enghoff V_{Dphys}/V_T measurements did not substantially overestimate true V_{Dphys}/V_T.

The $PaCO_2 - P_E'CO_2$ values were paradoxically negative in some animals. Negative $PaCO_2 - P_E'CO_2$ values [mean $PaCO_2 - P_E'CO_2$: −0.18 kPa (−1.4 mmHg)] are commonly reported in anesthetized children (Onodi et al. 2017). Under most circumstances, the $P_E'CO_2$, which corresponds to emptying of alveoli with the longest expiratory time constant (highest value at the end of the volumetric capnogram), is lower than $PaCO_2$ because of mixing of expired gas from alveoli devoid of CO_2 (V_{Dalv}), or with low CO_2 (high ventilation-to-perfusion ratio), with the expired gas from ventilated and well-perfused alveoli, which contain higher CO_2 partial pressures (Petersson & Glenny 2014; Suarez-Sipmann et al. 2014). However, when the V_{Dalv} is near 0, slightly negative $PaCO_2 - P_E'CO_2$ values are possible because of intrinsic error/inaccuracies of the methods used to measure $PaCO_2$ and $P_E'CO_2$. According to the manufacturer, the mainstream CO_2 sensor used in the present study has an accuracy (difference from the 'real' value) of ± 2 mmHg at CO_2 values ranging from 0 to 40 mmHg. Intrinsic error/inaccuracies in displayed $P_E'CO_2$ could have been corrected by evaluating the correlation between the CO_2 provided by the monitor and at least three reference gas mixtures containing different CO_2 concentrations. The blood gas analyzer used in this present report corrects the partial pressure of CO_2 and oxygen for actual body temperature using an algorithm developed for human blood, which may also account for some of the inaccuracies observed in the present study.

Animals with negative $PaCO_2 - P_E'CO_2$ also presented negative V_{Dalv} values because the V_{Daw} obtained from the volumetric capnogram was paradoxically higher than the Bohr–Enghoff V_{Dphys}. These results can also be related to inaccuracies related to the equipment used to measure dead space volumes when true V_{Dalv} is 0 or near 0. For this reason, the V_{Dalv} was taken as 0 when calculated V_{Dalv} ($V_{Dphys} - V_{Daw}$) yielded negative values. The contribution of V_{Dalv} to total V_{Dphys} was very small or nonexistent in the dogs of the present study, whereas the V_{Dalv} in cats was significantly larger than the V_{Dalv} in dogs. The larger V_{Talv} observed in cats could have contributed to an increase in V_{Dalv} through a greater compression of pulmonary capillaries secondary to a greater increase in alveolar volume.

The use of atropine to treat vagally mediated bradycardia and hypotension in one cat and two dogs might have been a potential confounder because this drug can induce bronchodilation and increase the V_{Daw}. However, these animals were not excluded from the analysis because the V_{Daw} did not change after atropine administration and, when data were recorded under conditions of hemodynamic stability, the V_{Daw} of these animals were close to values observed in the remaining population. Atropine induces bronchodilation and may increase V_{Daw} in animals with small airway disease (e.g. asthma in horses) or with drug-induced bronchoconstriction (Murphy et al. 1980; Brown et al. 1993). However, atropine is likely to have minimal effects on V_{Daw} of healthy animals, especially if the bronchomotor tone is already decreased by drugs with

bronchodilatory properties, such as isoflurane (Brown et al. 1993; Dikmen et al. 2003; Mondoñedo et al. 2015).

The use of ketamine as premedication in cats and as part of the induction regimen in dogs and cats might have altered dead space volumes because this drug has been reported to cause airway relaxation (decreased R_{aw}) in humans with asthma/bronchopulmonary disease (Huber et al. 1972; Tiwari et al. 2016). However, it is unlikely that ketamine altered dead space volumes under the conditions of the present study because this drug does not alter the resting bronchomotor tone (i.e. the bronchomotor tone in the absence of bronchoconstriction) (Gateau et al. 1989). Even if ketamine had decreased bronchomotor tone, this effect would likely be minimal because of isoflurane-induced bronchodilation at the time of data sampling.

In conclusion, a standard 12 mL kg^{-1} V_T results in different degrees of alveolar ventilation in nonbrachycephalic cats and dogs presenting small body mass because the portion of V_T that ventilates the V_{Daw} and V_{Dphys} differs significantly between these two animal populations. The smaller V_{Daw} and V_{Dphys} in cats compared to dogs increased the efficacy of ventilation and decreased f_R adjusted to maintain normocapnia during VCV with a fixed V_T in cats. Considering that mechanical ventilation should optimize gas exchange without causing excessive alveolar distension, the smaller V_{Dphys} in cats suggests that $\dot{V}_A$ and normocapnia can be maintained with lower V_Ts and higher f_Rs in cats. Future studies are recommended to evaluate the effects of mechanical ventilation with smaller V_Ts on dead space volumes and on arterial blood gases in cats.

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Authors' contributions

CHG and DAOA: study design, execution of the study protocol, manuscript preparation. FJTN: study conception and design, execution of the study protocol, statistical analysis, manuscript preparation. PVAV: execution of the study protocol, manuscript preparation. ARCM: study design, manuscript preparation. CK: study conception and design, manuscript preparation. All authors read and approved the final version of the manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

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Supporting Information

Additional supporting information may be found in the online version of this article: https://doi.org/10.1016/j.vaa.2024.06.009.

Figure S1. Measurement of apparatus dead space using the neonatal and pediatric flow/CO_2 sensors in dogs and cats, respectively.

Appendix SA. Analgesia protocols, recovery from anesthesia/postanesthetic period and discussion of $\dot{V}CO_2$ differences between cats and dogs.

