Monitoring of the respiratory system is an essential component of modern anesthesia. It is particularly important in equine species, as their body mass predisposes to atelectasis and ventilation-perfusion imbalances.1–3 Initially described and calculated in 1891 by the Bohr equation, and later in 1938 by the Enghoff modification of the Bohr equation, dead space ventilation (V_d) represents the portion of tidal volume (V_t) that does not contribute to gas exchange. The Enghoff modification substitutes the more easily measured arterial partial pressure of carbon dioxide (PaCO_2) for the partial pressure of mixed alveolar carbon dioxide (PaCO_2).4,5 Variables that contribute to calculated V_d include anatomical dead space of conducting airways (V_danat), alveolar dead space (V_dalv), areas of pure shunt, and disturbances of ventilation-perfusion matching (V/Q mismatch). Physiologic dead space fraction

OBJECTIVE
To evaluate the agreement between the Tafonius large animal ventilator-integrated volumetric capnography (vCap) software and the Respironics NICO noninvasive cardiac output monitor reference system.

ANIMALS
Data were collected from 56 healthy adult horses undergoing general anesthesia.

METHODS
Animals were placed under general anesthesia and connected to the Tafonius large animal ventilator circle system. A flow partitioning device with CO_2 and flow sensors was utilized to couple the endotracheal tube to the NICO monitor. Tafonius CO_2 and flow sensors are incorporated into the Y-piece of the breathing circuit. Arterial blood samples were collected to determine the partial pressure of arterial carbon dioxide (PaCO_2) immediately before data collection. The PaCO_2 was input into the Tafonius and NICO monitor, and dead space ventilation (%V_d), end-tidal CO_2 partial pressure (ETCO_2), mixed-expired CO_2 partial pressure (Peco_2), and expired tidal volume (V_t) were calculated over a single breath. Multiple measurements were completed for each patient, with a total of 200 paired data points collected for analysis. Data were assessed for normality, and Bland-Altman analysis was performed. Bias and 95% limits of agreement were calculated.

RESULTS
The limits of agreement for %V_d of the ventilator-derived measurements fell within ± 10% of the NICO monitor reference method.

CLINICAL RELEVANCE
Our results indicate that, when compared to the NICO monitor method, the Tafonius-integrated vCap software provides clinically acceptable values of P eco_2, V_t, and %V_d in healthy adult horses.

Keywords: respiratory physiology, equine anesthesia, volumetric capnography, dead space, large animal ventilator
(Vd/Vt) is defined as the sum of Vdanat and Vdalg divided by Vt, and this value can also be expressed as a percentage (%Vd).\textsuperscript{4,6-8}

Volumetric capnography (vCap) analyzes the kinetics of CO₂ elimination on a breath-by-breath basis.\textsuperscript{5} The volume-based capnogram plots expired CO₂ concentration against exhaled volume and consists of 3 phases, which correspond to expired CO₂ from sequential lung compartments.\textsuperscript{5,9} The volumetric capnogram is useful in assessing a patient’s ventilatory status, including CO₂ elimination, Vdanat, and Vdalg. Changes in CO₂ concentration can reflect disturbances in metabolism, cardiac output, or pulmonary ventilation/perfusion (V/Q).\textsuperscript{5-11} Clinically, vCap analysis can be used to improve the efficacy and quality of ventilation of intubated patients.

In humans and small animals, commercially available flow sensors exist for monitoring ventilation parameters. Until recently, the use of these devices in equine patients was limited by the size of the flow sensor. Traditionally produced to fit a standard 15-mm connection, these flow sensors are too small to adapt to a large animal endotracheal tube and would generate a high airway resistance during respiration. In 2014, Ambrisko et al\textsuperscript{12} described and validated a universal flow-partitioning device (FPD) for use in adult horses, which allows the use of any standard, commercially available human spirometry sensor. The addition of a flow sensor with mainstream CO₂ to this system makes vCap monitoring possible in large veterinary species when coupled to an appropriate monitor.\textsuperscript{12,13}

The Respironics NICO noninvasive cardiac output monitor provides a respiratory profile based on capnography, flow, and pressure. As a stand-alone monitor, the NICO monitor can be coupled to the breathing circuit and utilized with any mechanical ventilator and is compatible with the FPD developed by Ambrisko et al.\textsuperscript{12,13} Generated values include CO₂ elimination (VCO₂), airway dead space (Vdalg), and expired Vt/Vr, and expired Vt. Several equine studies\textsuperscript{3,10,12-16} have employed vCap capabilities of the NICO monitor. The accuracy of Vt measurements derived by the NICO monitor in conjunction with the FPD has been verified and reported in an in vivo experiment in anesthetized, mechanically ventilated horses using the Tafonius large animal ventilator (Hallowell EMC).\textsuperscript{15} Kobler et al\textsuperscript{15} determined that the addition of the NICO monitor resulted in a change in accuracy of only 0.36% in the volume measurement of the Tafonius ventilator. Of note, this group also determined that the Tafonius ventilator measures Vt on average 20% lower than a reference volume provided by a calibration syringe at Vt between 0.5 L and 7 L.\textsuperscript{15}

The Tafonius large animal ventilator combines a precision-controlled piston-driven ventilator with a fully integrated monitoring system.\textsuperscript{17} The integrated computer of the Tafonius workstation allows for adjusting, adding, and updating existing software. Recently developed vCap software for this workstation enables breath-by-breath Vol analysis in the anesthetized patient. Integrated vCap software eliminates the need for additional monitors and allows data to be viewed, correlated, and recorded within 1 patient file, creating a more complete picture of the anesthetic event.

The aim of this study was to evaluate the agreement between Tafonius-integrated vCap software and the NICO monitor with the hypothesis that the limits of agreement (LOA) for %Vd of the tested method would fall within 10% of the reference method.

**Methods**

This study was approved by the Institutional Animal Care and Use Committee (protocol No. 806775) of the University of Pennsylvania. Owner consent was obtained for all privately owned horses that participated in this study.

Data were collected from 56 healthy adult horses: 45 horses undergoing general anesthesia for elective surgical procedures (37 arthroscopic surgeries, 8 castrations) and 11 research animals enrolled in an unrelated surgical study. The animals were between 3 and 19 years of age with weights ranging from 375 to 640 kg. All horses were systemically healthy based on preanesthetic physical examination and routine bloodwork, including packed cell volume, total solids, fibrinogen, and a standard hematologic profile. Patients were held off feed for a minimum of 6 hours before undergoing anesthesia with unlimited access to water.

On the day of surgery, a 14-gauge catheter was placed into the left or right jugular vein. Animals were premedicated with xylazine, and general anesthesia was induced with intravenous ketamine and midazolam. Patients were intubated with an appropriately sized endotracheal tube and subsequently hoisted and positioned on the surgical table in either lateral or dorsal recumbency. They were connected to a large animal anesthetic circle system and fitted with standard anesthesia monitoring equipment. Monitoring included electrocardiography, invasive blood pressure, pulse oximetry, heart rate, respiratory rate, end-tidal CO₂ (ETCO₂), and end-tidal inhalant. Anesthesia was maintained with desflurane in oxygen, and dobutamine constant rate infusions were administered as necessary to maintain adequate blood pressure (mean arterial pressure > 70 mm Hg). Intravenous crystalloid solutions were infused at a rate of 3 to 4 ml/kg/h.

All horses were mechanically ventilated immediately using a volume-controlled mode. Ventilation was adjusted to deliver a Vt of 12 to 15 mL/kg at an inspiratory to expiratory ratio of 1:2 to 1:3 and a rate sufficient to ensure ETCO₂ in the range of 35 to 55 mm Hg. At the end of the surgery, horses were disconnected from the anesthetic circuit and placed into a recovery stall. During the recovery period, the endotracheal tube was replaced with a nasotracheal tube used to insufflate oxygen at a rate of 15 L/min and all horses received intravenous xylazine or dexmedetomidine sedation. Recovery was assisted using head and tail ropes.

For gas sampling and analysis, as well as for respiratory pressure monitoring by the Tafonius

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**AJVR**
workstation, lines and pressure sensors were incorporated into the Y-piece of the breathing circuit. The FPD was placed between the Y-piece and the endotracheal tube as described by Ambrosio et al.2 and paired to the NICO monitor using a standard human mainstream capnography sensor (Capnostat) connected to an adult-size NICO monitor CO2/flow sensor. The placement of the devices in series allowed for coupled analysis of the ventilator-derived (vCap) and NICO monitor-derived measurements over the same breath.

Determination of physiological and alveolar dead space volumes via the Tafonius workstation was performed using software that uses a combination of the Bohr-Enghoff equation and Fowler’s method. In brief, the Bohr-Enghoff equation relates the ratio of dead space and tidal volume (Vd/Vt) to the partial pressures of carbon dioxide in the arterial blood (PaCO2) and in the mixed exhaled gases (PECO2):

\[ \frac{V_d}{V_t} = \frac{(PaCO_2 - PECO_2)}{PaCO_2}. \]

The Tafonius accurately monitors and records all piston movements, so the exhaled Vt is measured and known at all times. In addition, every 100 ms the flow value is calculated, providing continuous gas flow information during the breathing cycle.

The PECO2 is calculated by constant measurement of the exhaled gas. Tafonius uses a sidestream CO2 monitoring system with a known time delay between sampling at the Y-piece and data arrival at the computer analysis unit. Using this known delay, the exhalation of CO2 can be brought back into line with the volume or flow data. Once the 2 data streams are synchronized, the volume of CO2 exhaled can be calculated, and the true CO2 fraction of the full exhaled breath determined. This provides similar results as the traditional method of collecting the entire exhaled breath in a Douglas bag and then determining the resultant CO2 fraction. The PaCO2 value that is obtained from a blood gas analyzer can be entered into the “Volume Capnography” dialog box for use by the PC. During exhalation, Tafonius plots the CO2 content versus the exhaled volume to produce the classical volumetric capnography trace.

The data are analyzed and processed to produce linear regression lines that delineate phase III and phase I. From these, the start of phase II and start of phase III can be determined. Using these 2 points of reference, the midpoint of the rising phase II is found by implementing a digital version of Fowler’s method, whereby the point on the slope that gives equal volumes on either side of that point but bound by the regression lines of phase III and phase I is determined. This central point provides the airway dead space volume. Using the physiological dead space volume, the alveolar dead space volume can then be calculated by VD_alv = Vt – VD aw. The method therefore uses the modified Bohr equation to calculate the physiological dead space, and an implementation of Fowler’s method to determine the VD aw. From these, VD_alv is calculated.

Before data collection in each patient, the ventilator was tested through an automated leak and compliance check and the vCap mode was enabled on the Tafonius workstation. The NICO monitor CO2 and flow sensors were initialized and calibrated, and a warmup period of 10 minutes was used as a stabilization period before the first measurement.

Arterial catheters were placed in all patients. The PaCO2 values were derived from serial arterial blood gas analyses and input before each calculation of Vd/Vt in both machines. A breath-by-breath curve of ETCO2 versus Vt was generated by the integrated vCap software and displayed on the Tafonius workstation screen. All horses were maintained under controlled ventilation. After the initial stabilization period and when minimal breath-to-breath variation was noted, measurements were collected and analyzed over a single breath. From this information, Vt, PECO2, PAO2, and Vd/Vt were calculated and displayed. Directly compared variables in this study were %Vd, ETCO2, PECO2, and Vt. Due to differences in procedure duration, the total number of analyzed breaths per horse ranged from 2 to 7, with a minimum of 15 minutes between measurements.

Statistical analysis

Data were analyzed using the statistical software GraphPad Prism Version 7 (GraphPad Software, Inc.). Visual assessment of qq-plots and the Shapiro-Wilk test were used to confirm normal distribution of model residuals of dependent variables, and they are presented as mean difference (95% LOA) for normally distributed data. The Tafonius-derived measurements of %Vd, ETCO2, PECO2, and Vt were compared to NICO monitor measurements. Volume measurements derived from the FPD-NICO monitor system were calculated with a correction factor of 4, assuming equal flow partitioning throughout the device.12 The degree of agreement between the 2 techniques was determined by Bland-Altman analysis.10 Bias is defined as the mean difference between the 2 methods of measurement calculated for each set of paired data points and 95% LOA as bias ± 1.96 X SD. Positive and negative biases signify overestimation and underestimation of the reference system values, respectively. There is no published standard for measuring the accuracy of spirometry sensors in anesthetized subjects. Based on clinical judgement, Tafonius %Vd values were considered acceptable if the LOA fell within ± 10% of the measurements obtained by the reference FPD-NICO monitor system.12,19,20

Results

A total of 200 paired data points were collected for analysis. All data were normally distributed. The results of Bland-Altman analysis are presented (Table 1) and briefly described below.

Bias (95% LOA) for ETCO2 and PECO2 was 3.80 mm Hg (−1.09 to 8.68 mm Hg) and −1.54 mm Hg (−5.93 to 2.86 mm Hg), respectively. Bias (95% LOA) of Vt for the Tafonius versus NICO monitor methods was 0.35 L (−0.90 to 1.60 L). Bias (95% LOA) of %Vd for the Tafonius versus NICO monitor methods was 0.58% (−6.79 to 7.97%).
therefore, %Vt increases as PECO2 decreases. Perhaps, the tendency for the Tafonius vCap software to slightly overestimate %Vt may be partially explained by its underestimation of PECO2 observed in this study. Mainstream PECO2 has been shown to provide a more accurate estimation of PeCO2 than sidestream PECO2 measurement. A potential source of PECO2 underestimation by the Tafonius side-stream capnograph is gas mixing. Sidestream analyzers may register low PECO2 values due to dilution of the sample, particularly at high fresh gas flow rates. Dilution occurs during aspiration into the CO2 sensor, wherein the sample becomes mixed with fresh gas originating from the anesthetic circuit.22,33

Expired Vt showed a linear correlation between the NICO monitor-derived data and the Tafonius. The Tafonius vCap system tends to slightly underestimate the PECO2 and slightly overestimate %Vt. When calculating Vt/Vr using the Enghoff modification of the Bohr equation, %Vt increases as PECO2 decreases. Perhaps, the tendency for the Tafonius vCap software to slightly overestimate %Vt may be partially explained by its underestimation of PECO2 observed in this study. Mainstream PECO2 has been shown to provide a more accurate estimation of PeCO2 than sidestream PECO2 measurement. A potential source of PECO2 underestimation by the Tafonius side-stream capnograph is gas mixing. Sidestream analyzers may register low PECO2 values due to dilution of the sample, particularly at high fresh gas flow rates. Dilution occurs during aspiration into the CO2 sensor, wherein the sample becomes mixed with fresh gas originating from the anesthetic circuit.22,33

Expanding examination of the Bland-Altman plot of Vt demonstrates divergence, such that increasing magnitudes of Vt correlated to a greater variance of the differences between the methods. As average Vt increases, the values remain distributed about the same bias implying that the source of the generated error does not systematically favor an over- or underestimation of the true value. This implies

Table 1—Statistical results of percent dead space ventilation (%Vd), end-tidal CO2 partial pressure (ETCO2), mixed-expired CO2 partial pressure (PECO2), and expired tidal volume (Vt) analyzed by Bland-Altman method when comparing the Tafonius large animal ventilator-integrated volumetric capnography software to the NICO noninvasive cardiac output monitor.

<table>
<thead>
<tr>
<th></th>
<th>%Vd</th>
<th>ETCO2 (mm Hg)</th>
<th>PECO2 (mm Hg)</th>
<th>Vt (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bland-Altman</td>
<td>0.59</td>
<td>3.80</td>
<td>-1.54</td>
<td>346</td>
</tr>
<tr>
<td>95% LOA</td>
<td>-6.79 to 7.97</td>
<td>-1.09 to 8.68</td>
<td>-5.93 to 2.86</td>
<td>-904 to 1,597</td>
</tr>
</tbody>
</table>

LOA, limits of agreement.

Discussion

Results of this study show that the integrated Tafonius vCap software can measure PECO2, Vt, and, therefore, %Vt within clinically acceptable values without the use of a separate analyzer and flow partitioning device. These results have several important clinical applications.

During general anesthesia, functional residual capacity (FRC) in the lung is reduced by approximately 20% and even further in patients with concurrent airway disease or those with particularly large body mass. The primary mechanism is likely the loss of inspiratory muscle tone, with gas trapping as an additional mechanism. Reduction of FRC results in decreased lung compliance and increased airway resistance. Further, reduction in FRC leads to increases in intrapulmonary physiologic shunt and creating regions of low V/Q matching.21 These physiologic alterations result in the collapse of small airways, particularly those in dependent lung regions.30 Impairment of gas exchange and increasing physiologic Vd/Vt contribute to both intra- and postoperative hypoxemia.21 Addition of continuous positive airway pressure in spontaneously breathing patients, has been shown to increase FRC, decrease intrapulmonary physiologic shunt, and improve PaO2.22,23 In a clinical setting, monitoring Vd/Vt may assist in determining the best continuous positive airway pressure/positive end-expiratory pressure (PEEP), the level which maximizes PaO2 without compromising hemodynamics or increasing Vd/Vt.5,22 Further, vCap has provided clinically useful information in both clinical cases and experimental models of lung injury. In human patients, elevated physiologic dead space in the context of acute respiratory distress syndrome has been identified as a strong predictor of mortality.24,25 Vd/Vt has also been evaluated as a predictor of successful extubation.26-28 Hubble et al27 found that Vd/Vt ≤ 0.50 reliably predicted extubation success with 75% sensitivity and 92% specificity, while a Vd/Vt > 0.65 identified patients at risk for failure. In a porcine lung injury model, Tusman et al29 showed that vCap-derived values are sensitive and specific indicators of gas exchange efficiency during recruitment maneuver and PEEP titration. Using the same porcine model, vCap measurements were compared to the multiple inert gas elimination technique (MIGET), which demonstrated that reduction in Vd/Vt and decreased slope of the phase III alveolar plateau were associated with successful alveolar recruitment and improved V/Q matching.30 As demonstrated by the literature, utilization of vCap in intubated patients has conceivable applications as an indicator for recruitment, estimator of best PEEP, and measure of therapeutic efficacy, as well as a predictor of survival or odds of successful extubation in the postoperative intensive care setting.

The Tafonius vCap system tends to slightly underestimate the PECO2 and slightly overestimate %Vt. When calculating Vd/Vt using the Enghoff modification of the Bohr equation, %Vt increases as PECO2 decreases. Perhaps, the tendency for the Tafonius vCap software to slightly overestimate %Vt may be partially explained by its underestimation of PECO2 observed in this study. Mainstream PECO2 has been shown to provide a more accurate estimation of PeCO2 than sidestream PECO2 measurement.31 A potential source of PECO2 underestimation by the Tafonius side-stream capnograph is gas mixing. Sidestream analyzers may register low PECO2 values due to dilution of the sample, particularly at high fresh gas flow rates. Dilution occurs during aspiration into the CO2 sensor, wherein the sample becomes mixed with fresh gas originating from the anesthetic circuit.32,33

Expanding examination of the Bland-Altman plot of Vt demonstrates divergence, such that increasing magnitudes of Vt correlated to a greater variance of the differences between the methods. As average Vt increases, the values remain distributed about the same bias implying that the source of the generated error does not systematically favor an over- or underestimation of the true value. This implies
that measurement error from one or both methods is likely increasing proportionally with increasing \( V_t \), such that \( V_o/V_t \) may become less reliable at a very large \( V_t \).

Bland-Altman analysis of \( \%V_o \) showed that the Tafonius system only marginally overestimated \( \%V_o \), with a bias of 0.6% for calculated physiologic dead space values with LOA between -6.8 and 8.0% (Figure 1). These results confirm the accuracy of \( \%V_o \) generated by the Tafonius vCap system, falling within the preselected, clinically acceptable cut-off of ± 10% of reference values. Based on these data, the Tafonius-derived \( \%V_o \) varies negligibly from the reference FPD-NICO monitor system, such that the 2 methods may be used interchangeably in a clinical setting. The ability to obtain accurate vCap data without the use of a separate analyzer is clinically important. The main advantages of an integrated vCap system are twofold: (1) ease of use and (2) reduction of error. Firstly, monitoring vCap-derived ventilatory parameters becomes substantially less technically challenging when less equipment is required. The Tafonius vCap software provides an intuitive, ventilator-integrated means of evaluating pulmonary mechanics in intubated patients. Further, the need for additional, cumbersome monitoring equipment is eliminated. The utilization of a separate monitoring system connected to the anesthetic circuit increases the risk of perpetuating error, both in clinical and research settings.

One limitation of the current study is the working assumption that the NICO monitor method provides accurate dead space analysis. The gold standard for calculating Bohr dead space is MIGET. This approach allows quantification of all the pulmonary and extrapulmonary determinants of arterial oxygenation. However, this technique is time consuming and technically challenging and is therefore not useful in clinical practice and rarely used in clinical studies. Another limitation is that this study utilizes mainstream and sidestream capnography sensors in series. However, a prior bench study determined that there is no position-related bias with the distal or proximal placement of multiple CO\(_2\) sensors. Another potential source of error arises from the inherent differences in response time between mainstream and sidestream capnometers. Response time is the delay caused by transit time (the time taken for the sample to reach the analyzer) and rise time (the time it takes for the analyzer to respond to the change in CO\(_2\) concentration from 10% to 90% of the final value).

Transit time is negligible in mainstream capnometers and is influenced by sampling line diameter, length, and suction flow rate in sidestream models. The transit time delay between the Y-piece and gas analyzer is known and corrected for in the ventilator-integrated system. Rise time is more rapid in mainstream capnometer sensors, at less than 125 ms, compared to sidestream models at approximately 200 ms to 400 ms. These delays associated with sidestream capnometry may contribute to error and skew vCap data, creating a "lag time" in the resultant vCap curve (Figure 2). This effect may be magnified in smaller animals with more rapid respiratory rates but does not seem to have greatly influenced agreement for the larger and slower breathing equine species. However, the breath-by-breath trends over time may still prove useful.

Additionally, our data were collected from a cohort of systemically healthy, adult horses. Further investigation is warranted to assess the accuracy of the Tafonius vCap method in very young or systemically compromised patients as well as from horses ventilated over a wide range of \( V_t \). Nevertheless, in this study, the expiratory volumes analyzed ranged from 2 L to 10 L with acceptable trending at these values.

The present study investigated only mechanically ventilated patients. Applications of vCap in spontaneously breathing patients have been proposed in the human medical field. Examples include using it as a screening tool for pulmonary embolism in patients presenting through the emergency department and identification and monitoring of broncho-pulmonary dysplasia or disease in infants. These applications require reference values, which would...
require further studies to develop as they do not currently exist for any veterinary species.

Finally, the LOA of ± 10% were chosen based on clinical judgment. Ambrisco et al.\(^2\) utilized the same 10% cut-off limit when analyzing the accuracy of their large animal spirometry device with CO\(_2\) sensors manufactured for human use, citing that the accuracy of anesthetic equipment is commonly tested against similar values.\(^9\)

In conclusion, this study confirms that in systemically healthy, mechanically ventilated, adult horses %\(\text{VCO}_2\) and %\(\text{PeCO}_2\) can be calculated using vCap measurements from the Tafonius workstation. The excellent agreement, within 10%, between %\(\text{VCO}_2\) calculated by the Tafonius workstation vCap software and the previously accepted FPD-NICO monitor system indicates that these 2 methods can be used interchangeably in a clinical setting. This information supports the use of the Tafonius-integrated vCap system as a sole means of acquiring \(\text{VCO}_2\) data in mechanically ventilated patients, negating the need for a separate volumetric \(\text{CO}_2\) monitor. Further studies are required to evaluate the accuracy of the Tafonius vCap software for physiologic dead space analysis in foals as well as systemically compromised adult patients.

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None reported.

**Disclosures**

The authors have nothing to disclose. No AI-assisted technologies were used in the generation of this manuscript.

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