End-Tidal and Arterial Carbon Dioxide Measurements Correlate Across All Levels of Physiologic Dead Space

S David McSwain MD, Donna S Hamel RRT FAARC, P Brian Smith MD, Michael A Gentile RRT FAARC, Saumini Srinivasan MD, Jon N Meliones MD, and Ira M Cheifetz MD FAARC

BACKGROUND: End-tidal carbon dioxide (PETCO\textsubscript{2}) is a surrogate, noninvasive measurement of arterial carbon dioxide (PaCO\textsubscript{2}), but the clinical applicability of PETCO\textsubscript{2} in the intensive care unit remains unclear. Available research on the relationship between PETCO\textsubscript{2} and PaCO\textsubscript{2} has not taken a detailed assessment of physiologic dead space into consideration. We hypothesized that PETCO\textsubscript{2} would reliably predict PaCO\textsubscript{2} across all levels of physiologic dead space, provided that the expected PETCO\textsubscript{2}-PaCO\textsubscript{2} difference is considered. METHODS: Fifty-six mechanically ventilated pediatric patients (0–17 y old, mean weight 19.5 ± 24.5 kg) were monitored with volumetric capnography. For every arterial blood gas measurement during routine care, we measured PETCO\textsubscript{2} and calculated the ratio of dead space to tidal volume (VD/VT). We assessed the PETCO\textsubscript{2}-PaCO\textsubscript{2} relationship with Pearson’s correlation coefficient, in 4 VD/VT ranges. RESULTS: VD/VT was < 0.40 for 125 measurements (25%), 0.41–0.55 for 160 measurements (32%), 0.56–0.70 for 154 measurements (31%), and > 0.7 for 54 measurements (11%). The correlation coefficients between PETCO\textsubscript{2} and PaCO\textsubscript{2} were 0.95 (mean difference 0.3 ± 2.1 mm Hg) for VD/VT < 0.40, 0.88 (mean difference 5.9 ± 4.3 mm Hg) for VD/VT 0.41–0.55, 0.86 (mean difference 13.6 ± 5.2 mm Hg) for VD/VT 0.56–0.70, and 0.78 (mean difference 17.8 ± 6.7 mm Hg) for VD/VT > 0.7. CONCLUSIONS: There were strong correlations between PETCO\textsubscript{2} and PaCO\textsubscript{2} in all the VD/VT ranges. The PETCO\textsubscript{2}-PaCO\textsubscript{2} difference increased predictably with increasing VD/VT. Key words: capnography; artificial respiration; blood gas analysis; pediatric; infant; mechanical ventilation; carbon dioxide. [Respir Care 2010;55(3):288–293. © 2010 Daedalus Enterprises]

Introduction

Capnography is a useful monitoring tool during mechanical ventilation and is the standard of care for confirming endotracheal tube placement\textsuperscript{1-5} and monitoring in the operating room setting.\textsuperscript{6-8} Capnography is also useful for monitoring the integrity of the ventilator circuit for early detection of mishaps such as inadvertent extubation.\textsuperscript{9-11}

There is less agreement about the utility of continuous capnography for ventilated intensive care unit (ICU) patients.\textsuperscript{12} Advocates of capnography believe that end-tidal
carbon dioxide \( (P_{\text{ETCO}_2}) \) may be used as a surrogate for arterial carbon dioxide \( (P_{\text{aCO}_2}) \), which would provide a quick and noninvasive assessment of the adequacy of ventilation. Critics of capnography reference multiple studies that conclude that \( P_{\text{ETCO}_2} \) and \( P_{\text{aCO}_2} \) do not reliably correlate in some clinical situations.\(^{13-19}\) However, many of these clinical situations involve patients with substantially elevated physiologic dead space. The analyses used in those studies differed markedly and failed to consider physiologic dead space and/or its effect on the relationship (ie, expected gradient) between \( P_{\text{aCO}_2} \) and \( P_{\text{ETCO}_2} \) as dead space increases.

Physiologic dead-space ventilation is the sum of anatomical dead space from the conducting airways and alveolar dead space from disease processes and/or therapies. The difference between \( P_{\text{ETCO}_2} \) and \( P_{\text{aCO}_2} \) is directly proportional to the degree of physiologic dead space.\(^{20-22}\) Although the alveolar CO\(_2\) concentration is typically slightly greater than that of arterial blood, \( P_{\text{ETCO}_2} \) is normally 2–5 mm Hg lower than \( P_{\text{aCO}_2} \),\(^{23}\) due to mixing of CO\(_2\)-containing alveolar gas with exhaled gas devoid of carbon dioxide from the anatomical dead space. In a patient with lung disease the addition of alveolar dead space further dilutes \( P_{\text{ETCO}_2} \) relative to \( P_{\text{aCO}_2} \). The normal ratio of physiologic dead space to tidal volume \( (V_d/V_T) \) is 0.20–0.35.\(^{24}\) The \( V_d/V_T \) in adult patients with acute lung injury is generally 0.40–0.55, and in patients with acute respiratory distress syndrome a substantially elevated \( V_d/V_T \) is associated with higher mortality.\(^{25}\)

The objective of this physiology-based study was to evaluate the relationship between \( P_{\text{ETCO}_2} \) and \( P_{\text{aCO}_2} \) across a wide range of \( V_d/V_T \) values. We hypothesized that \( P_{\text{ETCO}_2} \) reliably predicts \( P_{\text{aCO}_2} \) across all levels of physiologic dead space, as long as the increased \( P_{\text{ETCO}_2} - P_{\text{aCO}_2} \) difference predicted by a high physiologic dead space is considered. Despite the fact that multiple earlier studies have compared \( P_{\text{ETCO}_2} \) and \( P_{\text{aCO}_2} \) to our knowledge no previous study has examined the effect of changes in physiologic dead space on the \( P_{\text{ETCO}_2} \) and \( P_{\text{aCO}_2} \) relationship across a wide range of \( V_d/V_T \) ratios (from minimal to severe lung disease) in a diverse group of mechanically ventilated pediatric patients.

**Methods**

**Subjects**

This study is a retrospective cross-sectional analysis of data from a previous study at this institution (Donna S Hamel RRT FAARC and Ira M Cheifetz MD FAARC, personal communication, 2009). In the parent study, all children (ie, < 18 years of age) admitted to the pediatric ICU at Duke Children’s Hospital with an anticipated need for mechanical ventilation of at least 24 hours and a functional indwelling arterial catheter were eligible for enrollment (Table 1). Enrollment occurred between November 2001 and June 2005. The study was approved by the Duke Medical Center institutional review board. Written informed consent was obtained from at least one parent or legal guardian prior to enrollment. Exclusion criteria included tracheostomy, need for high-frequency ventilation or extracorporeal life support, limitations on life support, baseline long-term invasive or noninvasive respiratory support, and intubation for known upper-airway obstruction.

**Ventilator Management**

The mechanical ventilators (Avea, Viasys Healthcare, Yorba Linda, California, or Servo 300, Siemens, Solna, Sweden) were equipped with basic airway graphic monitors and were calibrated as per the manufacturer’s recommendations. Ventilator management was directed by a standard pediatric ICU protocol. Of note, specific capnography parameters were not incorporated into the ventilator management protocol. Arterial blood gas analysis and chest radiographs were obtained and pharmacologic sedation administered as per standard clinical practice. A heterogeneous group of mechanically ventilated pediatric ICU patients was monitored with volumetric capnography (NICO Monitor, Philips-Respironics, Wallingford, Connecticut) from the initiation of mechanical ventilation in our pediatric ICU until extubation.

**Data Collection**

For every arterial blood gas obtained during routine medical care, \( P_{\text{ETCO}_2} \) and mixed exhaled carbon dioxide \( (P_{\text{SECO}_2}) \) values were electronically collected at the proximal end of the endotracheal tube. The data acquisition rate of the NICO monitor is 100 Hz. The monitor continuously

**Table 1. Subjects**

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>( n = 56 )</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>1–6</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>≥ 7</td>
<td>17</td>
<td>30</td>
</tr>
</tbody>
</table>

**Primary Reason for Admission**

- Pulmonary: 11 (20%)
- Cardiac: 21 (38%)
- Bone marrow transplantation: 4 (7%)
- Non-cardiac postoperative: 7 (13%)
- Neurologic: 9 (16%)
- Other: 4 (7%)

\( ^\dagger \) Percentages do not sum to 100 because of rounding.
checks factory calibration values to assure accuracy and alerts the clinician if there is a calibration error. $V_d/V_T$ was calculated with the Enghoff modification\(^26\) of the Bohr equation:

$$V_d/V_T = (P_{a\text{CO}_2} - P_{\text{CO}_2})/P_{a\text{CO}_2}$$

Corresponding arterial blood gas values were recorded.

**Statistical Analysis**

The relationship between $P_{\text{ETCO}_2}$ and $P_{a\text{CO}_2}$ within 4 $V_d/V_T$ ranges ($\leq 0.40$, $0.41–0.55$, $0.56–0.70$, and $> 0.7$) was assessed with Pearson’s correlation coefficient. We also calculated the mean $P_{\text{ETCO}_2}-P_{a\text{CO}_2}$ difference within each $V_d/V_T$ range. We used multivariable linear regression models to explore the relationships between all the dependent and independent variables and created Bland-Altman plots for each $V_d/V_T$ range to further evaluate the agreement between $P_{\text{ETCO}_2}$ and $P_{a\text{CO}_2}$. Analyses were done with statistics software (Stata 9, StataCorp, College Station, Texas).

**Results**

From a heterogeneous group of 56 mechanically ventilated pediatric patients (age range 0–17 y, mean weight $19.5 \pm 24.5$ kg), we obtained 493 data points for analysis. $V_d/V_T$ was $\leq 0.40$ in 125 measurements (25%), $0.41–0.55$ in 160 measurements (32%), $0.56–0.70$ in 154 measurements (31%), and $> 0.7$ in 54 measurements (11%).

For $V_d/V_T \leq 0.40$ the correlation coefficient between $P_{\text{ETCO}_2}$ and $P_{a\text{CO}_2}$ was 0.95 and the mean $P_{\text{ETCO}_2}-P_{a\text{CO}_2}$ difference was $0.3 \pm 2.1$ mm Hg. For $V_d/V_T 0.41–0.55$ the correlation coefficient was 0.88 and the mean $P_{\text{ETCO}_2}-P_{a\text{CO}_2}$ difference was $5.9 \pm 4.3$ mm Hg. For $V_d/V_T 0.56–0.70$ the correlation coefficient was 0.86 and the mean $P_{\text{ETCO}_2}-P_{a\text{CO}_2}$ difference was $13.6 \pm 5.2$ mm Hg. For $V_d/V_T > 0.7$ the correlation coefficient was 0.78 and the mean $P_{\text{ETCO}_2}-P_{a\text{CO}_2}$ difference was $17.8 \pm 6.7$ mm Hg (Table 2).

<table>
<thead>
<tr>
<th>Vd/VT Range</th>
<th>Data points</th>
<th>Percent of total*</th>
<th>Correlation coefficient ($\rho$)</th>
<th>PETCO2-Paco2 difference (mean ± SD mm Hg)</th>
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<tr>
<td>$\leq 0.40$</td>
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**Discussion**

Capnography is accepted by some as an indispensable tool for mechanical ventilation to reduce the frequency of blood gas measurements in many clinical situations. However, there remains substantial debate as to whether capnography is useful as a continuous monitoring technique for mechanically ventilated patients. The goal of this study was to provide physiologic data to help clarify the relationship between $P_{\text{ETCO}_2}$ and $P_{a\text{CO}_2}$ in a heterogeneous pediatric ICU population.

There are potential benefits to the continuous monitoring of exhaled CO\(_2\) in an ICU. Not only can continuous assessment of the patient’s ventilatory status allow for early warning in case of a loss of integrity of the ventilator circuit or inadvertent extubation, it may help to optimize mechanical ventilation and shorten weaning time.\(^{26}\) In addition, capnography can be a useful early indicator of changes in cardiopulmonary status due to alterations in pulmonary blood flow, respiratory effort, effective minute ventilation, and/or respiratory compliance.\(^ {27}\)

Previous reports suggest that $P_{\text{ETCO}_2}$ may not be a reliable surrogate for measured arterial CO\(_2\), which may cast doubt on the utility of capnography as a continuous monitor.\(^ {13}–^{19}\) However, those studies generally did not include a comprehensive statistical analysis accounting for differences in physiologic dead-space ventilation and the resulting difference between $P_{\text{ETCO}_2}$ and $P_{a\text{CO}_2}$. For example, the pediatric study by McDonald et al\(^ {19}\) in 2002 found an overall moderately strong correlation ($r^2 = 0.716$) between $P_{a\text{CO}_2}$ and $P_{\text{ETCO}_2}$ for all included patients, but that substantial lung disease (ie, ratio of $P_{a\text{CO}_2}$ to fraction of inspired oxygen < 200 mm Hg) negatively affected the correlation.

However, the degree of physiologic dead space was not included in the analysis, which makes the results difficult to apply in the clinical setting. In contrast, our study incorporates the effect of physiologic dead space in patients with substantial lung disease.

Increased physiologic dead space lowers $P_{\text{ETCO}_2}$ relative to $P_{a\text{CO}_2}$ because of the mixing of gas from poorly perfused lung regions (devoid of CO\(_2\)) with that from well perfused areas, thus resulting in a larger difference between the 2 measurements. In this study we provide evidence that physiologic dead-space ventilation is a major factor in determining the relationship between $P_{\text{ETCO}_2}$ and $P_{a\text{CO}_2}$. In patients with a $V_d/V_T \leq 0.40$ there was an excellent

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**Table 2. Correlation of P\(_{\text{ETCO}_2}\) and P\(_{a\text{CO}_2}\)**

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correlation \((\rho = 0.95)\) between \(P_{ETCO_2}\) and \(P_{aCO_2}\). Though the strength of the association diminishes slightly as \(V_D/V_T\) increases, the correlation remains strong \((\rho = 0.86)\) even at \(V_D/V_T\) of 0.56–0.70, and moderately strong \((\rho = 0.78)\) at \(V_D/V_T > 0.7\). Thus, \(P_{ETCO_2}\) appears to be a useful indicator of \(P_{aCO_2}\), even in patients with substantial lung disease, provided that the expected increase in the \(P_{ETCO_2} - P_{aCO_2}\) difference (from an average of 0.3 mm Hg at low \(V_D/V_T\) to an average of 18 mm Hg at high \(V_D/V_T\)) is taken into consideration (see Fig. 1).

For the purposes of the clinical application of our results, it is important to note that correlation is not the same as equality. Physiologically, as described above, the difference between \(P_{ETCO_2}\) and \(P_{aCO_2}\) is expected to increase at higher \(V_D/V_T\). The decrease in the correlation coefficient between \(P_{ETCO_2}\) and \(P_{aCO_2}\) at high \(V_D/V_T\) is not due to that increased difference, but rather to the slightly increased variability of that difference at higher \(V_D/V_T\). This is an important distinction, because the moderately strong correlation coefficient at high \(V_D/V_T\) values indicates that the expected larger difference between \(P_{ETCO_2}\) and \(P_{aCO_2}\) remains fairly predictable, despite the increased dead-space ventilation.

This distinction is very important in interpreting the Bland-Altman plots in Figure 2. Bland-Altman plots are a visual assessment of agreement between 2 methods of measurement, and demonstrate “good agreement” only when the difference between the 2 methods is consistent across all measurements. In a situation in which the difference between the 2 measurements is expected to change based on a third variable (in this case, \(V_D/V_T\)), the Bland-Altman plots lose importance. These plots do not take into account the expected change in the \(P_{ETCO_2} - P_{aCO_2}\) difference seen with increasing physiologic dead space, except insofar as we have divided the data set into 4 specific \(V_D/V_T\) ranges. Thus, it is impossible to tell whether the variation seen in these plots is due to variation in physiologic dead space within each subset or to unreliability of \(P_{ETCO_2}\) as a surrogate measure. We have included these plots for completeness, but they should be interpreted with an understanding of their shortcomings with regard to these data.

From a purely statistical standpoint, the best method to compare \(P_{ETCO_2}\) and \(P_{aCO_2}\) is a multiple linear regression equation using \(P_{ETCO_2}\) and \(V_D/V_T\) to predict \(P_{aCO_2}\). From a clinical standpoint, however, we feel that this would not be practical. It is for that reason that we have grouped our
data into $V_d/V_T$ ranges corresponding to normal, mildly elevated, moderately elevated, and severely elevated physiologic dead space. At the bedside it is easier to consider into what category of physiologic dead space a patient falls than it is to calculate a predicted $P_{aCO_2}$ value using a derived equation.

Continuous $P_{ETCO_2}$ monitoring in the pediatric ICU may help clinicians to more closely monitor mechanically ventilated infants and children. Our data support the view that $P_{ETCO_2}$ does closely trend with $P_{aCO_2}$, potentially allowing for a reduction in the number of arterial blood gas analyses. At low dead-space values, $P_{ETCO_2}$ closely matches $P_{aCO_2}$. As dead space increases, the trend between $P_{ETCO_2}$ and $P_{aCO_2}$ remains reliable in most patients; however, the difference between these values does increase, as physiology predicts.

**Limitations**

A key limitation of our study is the assumption that $V_d/V_T$ is stable between blood gas analyses over time for an individual patient. Data on the stability of $V_d/V_T$ and the $P_{aCO_2}-P_{ETCO_2}$ difference over time in individual patients were not available for this study. As clinical status changes, dead space may change as well, and the relationship between $P_{aCO_2}$ and $P_{ETCO_2}$ becomes less predictable. Thus, the clinician should obtain periodic blood gas analyses, especially if there are important changes in the patient’s overall pulmonary status, to reassess the correlation between $P_{aCO_2}$ and $P_{ETCO_2}$.

The increased variation in the $P_{aCO_2}-P_{ETCO_2}$ difference at highly elevated physiologic dead space must be noted. The data analysis does not allow us to determine whether the variation in the relationship at severely elevated physiologic dead space is present in individual patients. We expect there is less variation in the $P_{aCO_2}-P_{ETCO_2}$ difference in individual patients, even at severely elevated $V_d/V_T$, and, thus, the increased variability of the $P_{aCO_2}-P_{ETCO_2}$ difference in our data set is at least partly a function of combining data from different patients. Additionally, some of the variation in the highest $V_d/V_T$ subgroup might be due to the slightly wider distribution of $V_d/V_T$ (ie, the
largest grouping beyond the normal range). Since the $P_{acO_2}$ - $P_{ETCO_2}$ difference should increase as VD/V T increases, a larger range of differences is expected given the larger VD/V T range. Despite these caveats, it is likely that $P_{ETCO_2}$ does lose some capacity to predict $P_{acO_2}$ in patients with the most severe lung disease and, thus, the most severely elevated physiologic dead space—a fact that must be taken into consideration clinically.

Application of these results in the clinical setting may require additional clinician training and equipment. The capnography monitor we use automatically calculates VD/V T when blood gas data are entered, which obviates calculation by the clinician. In addition, the capnography sensors measure both gas flow and CO 2 concentration, so that only one endotracheal tube attachment is required.

The results of this study should, theoretically, allow fewer blood gas analyses per patient and enable more efficient management of the mechanical ventilator via continuous capnography. However, proof of this speculation is beyond the scope of this physiology-based study.

Conclusions

We found moderate to strong positive linear correlation coefficients between $P_{ETCO_2}$ and $P_{acO_2}$ for all 4 VD/V T ranges, although the strength of the correlation decreased slightly as VD/V T increased. As expected physiologically, the absolute difference between $P_{ETCO_2}$ and $P_{acO_2}$ consistently increased with increasing VD/V T.

REFERENCES