Monitoring Exhaled Carbon Dioxide

Mark S Siobal RRT-ACCS FAARC

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In the past few decades, assessment of exhaled CO₂ in both intubated and non-intubated patients has evolved into an essential component in many aspects of patient monitoring. Besides the basic assessment of ventilation, exhaled CO₂ monitoring can provide valuable patient safety information and critical physiologic data in regard to the ventilation and perfusion matching in the lungs, cardiac output, and metabolic rate. Despite these important clinical monitoring benefits and widespread availability, exhaled CO₂ monitoring is often underutilized. The purpose of this paper is to review the importance and present the extensive body of knowledge to support the use of exhaled CO₂ monitoring in various areas of clinical practice. Advanced application concepts and the future development of exhaled CO₂ monitoring will also be discussed. Key words: end-tidal CO₂; capnometry; capnography; capnogram; volumetric capnography; physiologic dead space; resting energy expenditure. [Respir Care 0;0(0):1–]. © 0 Daedalus Enterprises]
MONITORING EXHALED CARBON DIOXIDE

Introduction

The measurement of CO₂ in air was first developed around 1918 and performed to analyze gas concentrations in mines.¹ This process of analysis was painstakingly tedious, using an intricate apparatus that involved measuring quantities of CO₂ and other gases that were chemically absorbed from a known gas volume. The volume of absorbed CO₂ was then compared with the total gas volume, which yielded the fraction or percentage of CO₂ present. A decade later, a technique was developed to analyze exhaled CO₂ from a single breath during vigorous exercise.² This process entailed capturing exhaled gas using a system the size of a telephone booth consisting of a series of electro-mechanically controlled valves, which directed sequential portions of expired air into 6 small rubber bags. The collected CO₂ in each bag was then analyzed multiple times to yield the average CO₂, which was plotted over time, thus resulting in the first exhaled capnogram. By the 1970s, exhaled CO₂ was monitored in ICUs using mass spectrometry systems that aspirated exhaled gas through long lengths of capillary tubing to a central monitoring location.³,⁴ Periodic measurements of the partial pressure of end-tidal CO₂ (PₑTCO₂) occurred on a timed schedule or in a sequential loop as the sampling cycle rotated between a number of monitored beds.⁵ With the introduction of the smaller infrared sensor, portable exhaled CO₂ monitors came to the bedside in the 1980s.⁶ Miniature CO₂ monitors that can fit into the palm of the hand and are capable of displaying an exhaled CO₂ capnogram are currently available.⁶,⁷

The technological advancement of exhaled CO₂ monitoring has coincided with the progression of use and importance in clinical practice. The significance of exhaled CO₂ monitoring extends well beyond the very basic utilization of monitoring the adequacy of ventilation. Detection of exhaled CO₂ has proven to be an invaluable mechanism for confirming tracheal intubation, recognizing accidental esophageal intubations, and other critical patient safety benefits. The patient protection enhancements provided by CO₂ monitoring also include: the detection of invasive airway disconnection, dislodgement, or obstruction and monitoring for respiratory depression postoperatively, during procedural sedation, and during patient-controlled analgesia. Of critical significance is the use of PₑTCO₂ to gauge the effectiveness of cardiopulmonary resuscitation (CPR), to predict outcome, and to guide the continuation of resuscitation efforts.⁸ Exhaled CO₂ can also be described as the “vital sign for ventilation and perfusion” because the volume of CO₂ excreted by the cardiorespiratory system is a sensitive indicator not only of ventilation efficiency but also of pulmonary perfusion and cardiac output. The volume of exhaled CO₂ per minute (V.CO₂) can also be used to estimate the metabolic rate and nutritional requirements of the critically ill patient.⁹

The recognition and importance of monitoring exhaled CO₂ in many areas of patient care has led to the expanding recommendation for its use by regulatory agencies and inclusion in the standards and practice guidelines of many professional organizations, such as the American Society for Anesthesia (ASA), the American Heart Association, the American Association for Respiratory Care, the Joint Commission, and the Centers for Medicare and Medicaid Services. Despite this heightened level of awareness and the regulatory and organizational guidance, exhaled CO₂ monitoring is often underutilized.⁸,¹⁰-¹⁶

The reasons for this disparity between knowledge and practice may be due in part to the cost burden of acquiring the technology; the clinician time required for set-up, maintenance, and troubleshooting; and the lack of awareness of the best practices for optimal utilization. Universally accepted standards of care mandating the use of CO₂ monitoring in specific circumstances or patient categories yielding the highest potential to impact patient safety and influence outcomes are also lacking.

The purpose of this review is to increase the awareness and understanding of health-care providers of the importance of exhaled CO₂ monitoring and its application in clinical practice. An appraisal of the different technologies will be followed by a review of the recognized indications for monitoring and an assessment of the potential for further advancements in exhaled CO₂ monitoring.

Classification and Types of Exhaled CO₂ Monitoring

Understanding available technologies and how they function can provide important insights into their appropriate application, potential limitations, and problems associated with use. The following is a brief review of the classification and types of exhaled CO₂ monitoring commonly utilized.

Colorimetric CO₂ Detectors

Colorimetric CO₂ detectors provide continuous qualitative and semi-quantitative exhaled CO₂ monitoring. Col-
orimetric CO₂ detectors are the simplest form of CO₂ monitors. They are portable, disposable, inexpensive, single-use devices that can rapidly detect and confirm tracheal intubation and estimate the amount of CO₂ in exhaled gas. Colorimetric detectors contain chemically treated material that is pH-sensitive and colorimetrically reflects CO₂ concentrations in expired gas.¹⁷ Limitations of colorimetric CO₂ detectors include false positive readings when the detection medium is contaminated with gastric acid or acidic solutions instilled through an endotracheal tube.¹⁷,¹⁸

Mainstream CO₂ Monitoring

Mainstream CO₂ monitoring devices utilize a small infrared sensor consisting of a sample cell or cuvette and an infrared optical bench placed within the gas flow pathway at the airway. This measurement location results in real-time CO₂ values within the airway and a real-time graphical representation of the CO₂ waveform plotted over time or by the exhaled volume. Disadvantages of mainstream CO₂ monitoring include: cost of the sensor; potential for damage to the sensor and connecting cable during handling and patient monitoring; increased circuit mechanical dead space; potential for fouling with coughed up secretions and circuit condensate; and the additional weight of the sensor, airway adapter, and cable at the patient’s airway connection. Also, many mainstream devices are limited to use with intubated patients only.¹⁹

Sidestream CO₂ Monitoring

Sidestream CO₂ monitoring devices aspirate a gas sample from a ventilator breathing circuit or other patient interface device through a length of small-bore tubing. Different interface designs for use on non-intubated patients incorporate nasal and oral sampling points to improve measurement accuracy. Several interface designs include the ability to simultaneously administer oxygen through a split channel device. Sidestream sampling devices utilize an infrared CO₂ sensor in a monitor located away from the patient and can only be displayed in a time-based waveform. Time-based sidestream CO₂ monitoring is the type more commonly used in the operating room setting, during non-intubated patient monitoring, and during CPR.

The sidestream sample method often requires use of a water trap and or specialized tubing that removes water vapor before analysis to prevent blockage and contamination of the sample tubing. Sample analysis located away from the patient results in a time delay often several seconds in duration before measured results are displayed. Since sidestream sampling requires a continuous aspirated sample flow rate from the ventilator circuit, interference with the measurement of ventilation parameters and the triggering mechanism can occur. Also, when sidestream systems are used intra-operatively with inhaled anesthetic agents, a scavenging system is required to prevent ambient contamination and health-care provider exposures.¹⁹

Capnometry Versus Capnography

Capnometry is performed by a capnometer. A capnometer is a monitor that measures CO₂ concentrations in respired gases over time and displays numeric values for P_{ETCO₂}, respiratory frequency, and sometimes the inspired CO₂ concentration or partial pressure. Capnometers can be either mainstream or sidestream in design.¹⁰,²¹

The terms capnometry and capnography are often used synonymously, but in contrast to capnometry, capnography is performed by a capnograph, a monitor that is functionally the same as a capnometer but incorporates the additional feature of displaying the CO₂ waveform known as a capnogram (Fig. 1). Capnographs can also be mainstream or sidestream in design. The additional clinical monitoring value of capnography is the ability to visually interpret the waveform and morphology of the capnogram. The value of viewing the capnogram is synonymous with the revelation of knowing the heart rate and seeing the electrocardiogram. Interpretation of the different phases; the shape, area, and slope of the capnogram segments; and integration of the exhaled capnogram to exhaled tidal volume reveal clinically valuable information regarding ventilation and perfusion and cardiopulmonary physiology.¹⁰,²¹

Indications for Exhaled CO₂ Monitoring

Exhaled CO₂ monitoring is essential and useful in clinical practice for an array of monitoring indications, including ventilation, circulation, metabolism, improving patient safety, and influencing and predicting outcomes of care. Following is a review of the indications for exhaled CO₂ monitoring for in- and out-of-hospital monitoring of intubated and non-intubated adult and pediatric patients.
Monitoring Adequacy of Ventilation

Continuous monitoring of exhaled CO\textsubscript{2} from the onset of intubation to extubation, whether by capnometry or capnography, is an accepted method to ensure adequate ventilation during mechanical ventilation in both adult and pediatric patients.\textsuperscript{14,22} CO\textsubscript{2} monitoring in non-intubated adult,\textsuperscript{13,23,24} neonatal, and pediatric patients\textsuperscript{25-27} can also be effective. As a reflection of this potential benefit, the ASA has identified CO\textsubscript{2} monitoring as a standard of care in anesthesia monitoring since 1986.\textsuperscript{28} In healthy patients during mechanical ventilation, P\textsubscript{ETCO\textsubscript{2}} closely approximates P\textsubscript{aCO\textsubscript{2}} and is usually 2–5 mm Hg lower\textsuperscript{29,31} and therefore can be an effective index of the adequacy of ventilation (see Fig. 1).

However, it should be well understood by all clinicians that in diseased states, such as ARDS, COPD, and asthma, ventilation/perfusion (V/Q) mismatch in the lungs can cause the P\textsubscript{aCO\textsubscript{2}} – P\textsubscript{ETCO\textsubscript{2}} difference to increase. An increased P\textsubscript{aCO\textsubscript{2}} – P\textsubscript{ETCO\textsubscript{2}} difference can occur to varying degrees with increased physiologic dead space, shunt perfusion, low cardiac output, and conditions of low V/Q.

It has been suggested that the lack of agreement with P\textsubscript{aCO\textsubscript{2}} in diseased lungs has negatively impacted the perception of value and the use of CO\textsubscript{2} monitoring.\textsuperscript{8} Contrary to this misinterpretation, when a large P\textsubscript{aCO\textsubscript{2}} – P\textsubscript{ETCO\textsubscript{2}} difference exists, P\textsubscript{ETCO\textsubscript{2}} can be an effective means of trending changes in P\textsubscript{aCO\textsubscript{2}} and the efficiency of ventilation and changes in the physiologic dead space fraction (V\textsubscript{D}/V\textsubscript{T}).\textsuperscript{32} It is therefore important to recognize that the P\textsubscript{aCO\textsubscript{2}} – P\textsubscript{ETCO\textsubscript{2}} difference can be an indication of the degree of lung injury and correlates with increased V\textsubscript{D}/V\textsubscript{T}.\textsuperscript{32,33}

Furthermore, intra-operative monitoring of the P\textsubscript{aCO\textsubscript{2}} – P\textsubscript{ETCO\textsubscript{2}} difference has been shown to predict mortality in trauma patients. Patients with a P\textsubscript{aCO\textsubscript{2}} – P\textsubscript{ETCO\textsubscript{2}} difference \textgreater\textunderscore\textless 8–10 mm Hg had higher mortality rates both intra-operatively\textsuperscript{34-37} and following emergent surgeries.\textsuperscript{34,37}

Other sometimes overlooked benefits of monitoring the P\textsubscript{aCO\textsubscript{2}} – P\textsubscript{ETCO\textsubscript{2}} difference to assess the adequacy of ventilation include: the reduction of arterial blood gas utilization,\textsuperscript{38} which impacts unnecessary blood loss and costs; the identification and prevention of excessive ventilation and hyperventilation in neurotrauma patients\textsuperscript{39-43}; and the affect that visual interpretation of the capnogram has had on enhancing monitoring during mechanical ventilation and airway management.\textsuperscript{54}

Confirmation of Endotracheal Intubation

Perhaps one of the most significant impacts of exhaled CO\textsubscript{2} monitoring is in its use as a definitive method for confirming endotracheal intubation and the reduction in harm associated with identifying the serious consequences of accidental esophageal intubation, death and anoxic brain injury. Use of a CO\textsubscript{2} monitor in addition to direct visualization of the endotracheal tube passing through the vocal cords represent the accepted standards in clinical practice for confirming intubation in adult, pediatric, and neonatal patients.\textsuperscript{45-49}

Capnography and capnometry compared with auscultation have been shown to be the most reliable methods to confirm endotracheal tube placement in the prehospital emergency setting.\textsuperscript{50} Several studies have demonstrated that when continuous P\textsubscript{ETCO\textsubscript{2}} monitoring is used, the sensitivity (true positive rate) and specificity (true negative rate) for confirming endotracheal intubation are both 100\%\textsuperscript{, 50-52} Colorimetric detectors were also found to be highly sensitive (88–98\%) and 100\% specific in confirming proper endotracheal intubation\textsuperscript{17,18} and useful in guiding and predicting successful resuscitation in non-cardiac arrest patients.\textsuperscript{17,18,53} Rates of unrecognized misplaced endotracheal tubes in out-of-hospital arrests as high as 23\% have been reported when continuous P\textsubscript{ETCO\textsubscript{2}} monitoring was not used.\textsuperscript{52}

Recognition of these important facts by the ASA,\textsuperscript{28,54} the American Association for Respiratory Care,\textsuperscript{55} the American Heart Association,\textsuperscript{56,57} Emergency Medical Services systems,\textsuperscript{42,58} the Intensive Care Society in the United Kingdom,\textsuperscript{42} the Royal College of Anesthetists, and the Association of Anaesthetists of Great Britain and Ireland,\textsuperscript{19} has resulted in the inclusion of the use of CO\textsubscript{2} monitoring during intubations in their respective standards of practice, clinical practice guidelines, and practice recommendations. This compelling body of evidence mandates the use of CO\textsubscript{2} monitoring during intubation as a universal standard of care for confirming endotracheal intubation.\textsuperscript{11} Nevertheless, it should be well understood that during cardiac arrest, the accuracy for confirming proper endotracheal intubation using CO\textsubscript{2} monitoring is diminished due the absence of cardiac output, pulmonary blood flow, and therefore exhaled CO\textsubscript{2}.\textsuperscript{17,18,50} In this situation, the absence of exhaled CO\textsubscript{2} using any CO\textsubscript{2} monitoring device may be mistakenly interpreted as an esophageal intubation.

Monitoring Respiratory Status

The use of exhaled CO\textsubscript{2} to monitor respiratory status is another area of growing significance and interest. Exhaled CO\textsubscript{2} offers an accurate and reliable means of measuring respiratory frequency. An elevated respiratory frequency is a sensitive and reasonably specific marker of respiratory dysfunction.\textsuperscript{59} A low respiratory frequency is an indicator of respiratory depression from opioid analgesia and can be detected early by exhaled CO\textsubscript{2} monitoring.\textsuperscript{60}

Opioid-induced respiratory depression in the post-anesthesia care period is a major concern emphasized by ASA-mandated standards,\textsuperscript{28} the Joint Commission Sentinel Event Alerts,\textsuperscript{61} and the Centers for Medicare and Medicaid Ser-
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Table 1. Characteristics of Bradypneic (Type 1) and Hypopneic (Type 2) Hypoventilation

<table>
<thead>
<tr>
<th>Hypoventilation Classification</th>
<th>Respiratory Frequency</th>
<th>Tidal Volume</th>
<th>Anatomic Dead Space</th>
<th>VD/Vt</th>
<th>P_{ETCO2}</th>
<th>PaCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 (bradypneic)</td>
<td>– – –</td>
<td>–</td>
<td>No change</td>
<td>Minimal change</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Type 2 (hypopneic)</td>
<td>– – –</td>
<td>–</td>
<td>No change</td>
<td>+ + +</td>
<td>– or no change</td>
<td>+</td>
</tr>
</tbody>
</table>

\[V_d = \text{dead space volume}\]
\[V_t = \text{tidal volume}\]
\[P_{ETCO2} = \text{end-tidal CO}_2\]
\[- = \text{decrease}\]
\[+ = \text{increase}\]

A significant limitation to consider while using \(P_{ETCO2}\) monitoring to detect respiratory depression is that there are 2 different types of drug-induced hypoventilation (Table 1). Type 1 or bradypneic hypoventilation is characterized by a decreased respiratory frequency, a slightly decreased tidal volume, and an increased \(P_{ETCO2}\) and \(PaCO_2\). Type 2 or hypopneic hypoventilation, on the other hand, is characterized by a significant decrease in tidal volume, slightly decreased respiratory frequency, and a decreased or normal \(P_{ETCO2}\), whereas the \(PaCO_2\) can be elevated.

During hypopneic hypoventilation, the shallow breathing and smaller tidal volumes in proportion to the anatomical dead space cause decreased alveolar ventilation, increased dead space ventilation, increased \(PaCO_2\), and an increased \(PaCO_2 - P_{ETCO2}\) difference. This significant distinction between bradypneic and hypopneic hypoventilation is critical for clinicians to acknowledge and comprehend. Low or normal \(P_{ETCO2}\) during hypopneic hypoventilation can be accompanied by significant respiratory depression and a markedly elevated \(PaCO_2\), which may go unrecognized if patient monitoring focuses on the value of \(P_{ETCO2}\).

Another area of concern is the growing evidence that the use of patient-controlled analgesia (PCA) imposes significant risks to patients and potential liability exposure to health-care providers and hospitals. This is again reflected in position statements and guidelines from the ASA, Joint Commission, the Centers for Medicare and Medicaid Services, the National Patient Safety Foundation, and the Institute for Safe Medication Practices, which recommend continuous \(P_{ETCO2}\) monitoring to guard against opioid-induced respiratory depression during PCA use. Of particular concern driving these recommendations are well-documented cases of “PCA by proxy” in which a family member or health-care provider, and not the patient, administers PCA doses. This has led to a serious and fatal outcomes considered possibly preventable if \(P_{ETCO2}\) monitoring were being used.

Furthermore, the value of \(CO_2\) monitoring during procedural sedation and in the emergency department as an early indicator of respiratory depression, especially when patients are receiving oxygen, to aid in the identification of the severity of illness and to improve patient safety is also increasingly being mandated for adult and pediatric patients.

Monitoring During CPR

It has been well substantiated that exhaled \(CO_2\) monitoring during CPR provides invaluable information regarding the correct placement of an advanced airway, the effectiveness of cardiac compressions, the return of spontaneous circulation, and the prediction of outcome and survival during cardiac arrest.

The value of exhaled \(CO_2\) monitoring as a guide to the effectiveness of cardiac compressions was first demonstrated in 1978 from a series of 3 patients during CPR. Subsequent animal studies and human subjects, both in and out of the emergency department, were performed to confirm this evidence.

These data provide evidence to support a \(P_{ETCO2}\) threshold target value >10 mm Hg during CPR. Additional investigations also demonstrated that changes in \(P_{ETCO2}\) during resuscitation attempts predicted outcomes and return of spontaneous circulation, suggesting that \(P_{ETCO2}\) could be useful in deciding when to terminate resuscitation efforts in adult and pediatric patients.
PETCO2 at 20 min after the initiation of CPR was used as a screening test to predict return of spontaneous circulation, a threshold value of 14 mm Hg or less had a sensitivity, specificity, positive predictive value (accuracy of positive results), and negative predictive value (accuracy of negative results) of 100%.

PETCO2 monitoring during CPR can be an effective tool to detect the effectiveness of external cardiac compression and the development of rescuer fatigue. Additionally, a sudden increase in continuously monitored PETCO2 during high quality CPR was associated with the return of spontaneous circulation (Fig. 3).

This evidence supports the use of PETCO2 monitoring during CPR in both in- and out-of-hospital resuscitations. The use of quantitative waveform capnography interpretation has been incorporated into advanced cardiac life support training to confirm advance airway placement and to monitor resuscitation effectiveness since 2010.

Volumetric Capnography

Volumetric capnography differs from standard capnography in that exhaled CO2 is plotted against the exhaled tidal volume. Analysis of the phases of the volumetric capnogram, the shape and curve morphology, and measurements based on calculations from the volumetric capnogram can reveal important information in regard to the efficiency of ventilation and perfusion, the physiologic dead space fraction, and the metabolic rate of the patient.

Phases of the Volumetric Capnogram

The 3 phases of the volumetric capnogram are synonymous with the phases of the time-based capnogram. Phase 1 characterizes emptying of the anatomic dead space (the conducting airways), where exhaled CO2 is near zero. Phase 2 represents a mixture of gas from the anatomic dead space and alveolar gas containing CO2. Phase 3 signifies emptying of alveolar air spaces (also known as the alveolar plateau), the end point of which is equal to the end-tidal CO2 (Fig. 4). An increase in slope of the rise of phase 3 signifies an increase in the number alveolar gas exchange units with varying degrees of V/Q mismatch, such as during airway obstruction and elevated alveolar dead space.

Fowler Dead Space

Using the principles described by Fowler, the anatomic dead space volume can be identified and measured.
by computer analysis of the volumetric capnogram. The midpoint of phase 2 of the volumetric capnogram signifies the boundary between conducting airways and gas-exchange airways (respiratory bronchioles). When phase 2 is dissected by a vertical line originating from a line superimposed on the incline of phase 3, the intersection at the x axis such that the 2 areas on either side of the vertical line that are equal in area can be created. This point of intersection and equivalent areas is equal to the anatomic dead space volume on the volumetric capnogram (Fig. 5).

Anatomical dead space in male and female volunteers at rest was originally approximated to be 156 and 104 mL, respectively. Since the conducting airways are distensible, the anatomic dead space volume can increase with maximal voluntary inspiratory lung volume and by the application of positive pressure. The application of PEEP up to 18 cm H₂O was shown to increase the anatomic dead space volume by an average of 5%. This increase in the anatomical dead space volume causes an incremental increase in the total physiologic dead space. The ability to measure anatomic dead space by volumetric capnography enables the components of physiologic dead space to be partitioned by single-breath analysis.

Single-Breath CO₂ Analysis

The single-breath CO₂ waveform analysis builds upon identification of the Fowler anatomical dead space and enables extraction of additional information regarding ventilation efficiency and further analysis and study of physiologic dead space.

When the perpendicular line that identifies the anatomic dead space is drawn through the volumetric capnogram to the x axis, the point of intersection to this line from an additional line superimposed on phase 3 of the capnogram allows the component volumes in a exhaled tidal breath to be partitioned into anatomical VD, alveolar VD, and alveolar VT (Fig. 6).

This dissection of the volumetric capnogram area allows further study of the various components and their relationships. For instance, alveolar VD and anatomical VD were both found to be indices of lung recruitment and overdistention, and the alveolar VD/alveolar VT ratio decreased or increased in parallel to a positive or negative response to PEEP with respect to oxygenation and shunt.

Additionally, the classic sloping “shark’s fin” shape and morphology of the time-based or volume-based volumetric capnogram can be a visual indication of V̇/Q̇ mismatch due to bronchospasm and airway obstruction (Fig. 7) and an elevated V̇D/V̇T in patients with ARDS (Fig. 8).

Measuring Physiologic Dead Space

The traditional technique for bedside measurement of V̇D/V̇T used the method of exhaled gas collection and analysis to measure the partial pressure of the mean expired CO₂ (P̅ECO₂). Advancements in technology introduced the use of metabolic analyzers and volumetric capnography to measure the P̅E̅CO₂.

The simplified bedside calculation of V̇D/V̇T uses the Enghoff modification of the Bohr equation. The Enghoff equation differs from the original Bohr equation by the substitution of P̅CO₂ for the partial pressure of mixed alveolar CO₂ (P̅ACO₂). Since P̅ACO₂ was difficult to accurately measure or estimate at the bedside, the Enghoff equation became the standard method for many years in...
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Fig. 6. Single-breath CO₂ analysis further dissects the area of the volumetric capnogram and allows for the calculation of the alveolar dead space volume (V₇₅₉alv), anatomic dead space volume (V₇₅₉anat), alveolar tidal volume (V₇₅₉Talv), and the physiologic dead space volume (V₇₅₉phys) in relation to P₇₅₉CO₂ and partial pressure of end-tidal CO₂ (Pᵢ₇₅₉CO₂). From Reference 106, with permission.

Fig. 7. A “shark’s fin” time-based capnogram waveform showing severe airway obstruction. From Reference 14.

Fig. 8. A shark’s fin volumetric capnogram of a patient diagnosed with ARDS with elevated dead-space fraction.

In the past, Pᵢ₇₅₉CO₂ measurements using the gas collection bag method were cumbersome, time consuming, and error-prone and entailed collecting up to 30–60 L of expired gas for a mean CO₂ sample measurement. Also, the gas collection bag method is no longer feasible due to the common presence of bias flow on current ventilators. The introduction of metabolic analyzers for the Pᵢ₇₅₉CO₂ measurement requires use of a correction for ventilator circuit compression volume and relies on the accurate measurement of the fraction of mean expired CO₂ (F₇₅₉CO₂), whereby

\[ P₇₅₉CO₂ = F₇₅₉CO₂ \times (P₇₅₉ - 47). \]  (3)

(P₇₅₉ represents barometric pressure, 47 is water vapor pressure at 37°C) The introduction of the volumetric CO₂ monitor has simplified the bedside measurement by continuously measuring Pᵢ₇₅₉CO₂ and allowing intermittent input of P₇₅₉CO₂ for the calculation of V₇₅₉/V₇₅₉T.¹¹⁵

Pᵢ₇₅₉CO₂ can also be derived from ventilator volumetric capnography measurements using V₇₅₉CO₂ and expired minute ventilation (Vₑ),¹¹⁶ whereby

\[ V₇₅₉/V₇₅₉T_{Eng} = \frac{(P₇₅₉CO₂ - Pᵢ₇₅₉CO₂)}{P₇₅₉CO₂} \]  \hspace{1cm}  (1)

and the original Bohr equation is

\[ V₇₅₉/V₇₅₉T_{Bohr} = \frac{(P₇₅₉CO₂ - Pᵢ₇₅₉CO₂)}{P₇₅₉CO₂}. \]  \hspace{1cm}  (2)
By using Equation 3 to calculate $P_{CO_2}$, Equation 1 can then be used for the calculation of $V_D/V_T$.\textsuperscript{116}

**Clinical Usefulness of Physiologic Dead Space Measurements**

Measuring $V_D/V_T$ in the critically ill patient during mechanical ventilation is important for several reasons. The prognostic value of $V_D/V_T$ has been linked to the severity of lung injury and the risk of death in patients with ARDS. Furthermore, $V_D/V_T$ can be useful as an indicator of lung recruitment versus overdistention in patients with ARDS, may be helpful as a predictor of extubation success in adult and pediatric patients, and may be useful in assessing the severity and confirming the suspicion of pulmonary embolism.

**Assessing the Severity of Lung Injury**

$V_D/V_T$ is known to be a marker of the type\textsuperscript{119} and severity of lung injury during ARDS in regard to the degree of hypoxemia,\textsuperscript{120} histopathological changes,\textsuperscript{120,121} V/Q defects,\textsuperscript{122,123} intrapulmonary shunt,\textsuperscript{119,123,124} and the need for supportive rescue therapies.\textsuperscript{119,124} Monitoring serial changes in $V_D/V_T$ over the course of critical illness in addition to other markers of disease severity is therefore warranted.

**Predicting Survival in ARDS Patients**

$V_D/V_T$ has been shown to be predictive of the mortality risk in patients with ARDS in both the early and intermediate phases of the disease.\textsuperscript{125-131} During the first 2 d following an ARDS diagnosis, $V_D/V_T$ was significantly higher among non-survivors\textsuperscript{131} (Fig. 9). Patients with $V_D/V_T = 0.57$ were found to have higher mortality, with a 45% increase in the odds of dying for every 0.05 increase in dead-space fraction.\textsuperscript{127} The mean dead-space fraction was also significantly higher in patients who died compared with those who survived (Fig. 10). Consequently, in the face of continually rising $V_D/V_T$ during the course of ARDS as a sign of possible futility, it may be appropriate to use this information to help guide plan of care decisions during critical illness.

**Indication of Lung Recruitment Versus Overdistention**

$V_D/V_T$ measurements in patients with ARDS have been found to be useful for titrating PEEP and optimizing cardiopulmonary function\textsuperscript{105,108,132} and may be useful as a tool to monitor lung recruitment versus overdistention.\textsuperscript{133-135}

In one of the classic papers in critical care medicine published in 1975, Suter et al\textsuperscript{105} demonstrated the value of measuring $V_D/V_T$ as a guide to optimizing gas exchange and pulmonary mechanics in patients with lung injury (Fig. 11). This early work has been repeatedly validated and therefore supports assessing and monitoring $V_D/V_T$ to assist with management decisions in patients with ARDS.\textsuperscript{108,132,134,135}
Predicting Successful Liberation From Mechanical Ventilation

$V_D/V_T$ assessments may also be used to predict extubation success in pediatric$^{136}$ and adult patients.$^{137,138}$ Values for $V_D/V_T \leq 0.50$ and $\geq 0.65$ in infants and children were found to predict extubation success or failure$^{136}$ (Fig. 12), whereas in adult patients, the cutoff value for $V_D/V_T = 0.58$ offered the best sensitivity and specificity for predicting extubation failure.$^{137}$ It has also been suggested that elevated $V_D/V_T$ may be useful for predicting the need for noninvasive ventilation after extubation$^{138}$ and therefore the potential for averting the need for re-intubation.

Diagnosis of Pulmonary Embolism

$V_D/V_T$, in addition to other clinical assessments and diagnostic tests, can be useful in excluding or diagnosing pulmonary embolism. $V_D/V_T > 40\%$ was found to be
Bohr Versus Enghoff Approach to Physiologic Dead Space Measurements

The Bohr dead space equation relies on the calculation or estimation of $P_{ACO_2}$ from mixed alveolar gas and $P_{E_{CO_2}}$, which signifies the combined effect of the volume of anatomical $V_D$, alveolar $V_D$, and alveolar $V_T$. $P_{ACO_2}$ is affected by the dilution of $CO_2$ from the alveolar side of the alveolar-capillary membrane by gas exchange units with low or no perfusion. $P_{E_{CO_2}}$ is determined by the volume of $CO_2$ excreted from the lungs ($V_{CO_2}$) compared with the total $V_E$ (Equations 3 and 4). Bohr dead space is affected by areas of ventilation to perfusion inequality, such as during alveolar overdistention by excessive PEEP and/or $V_T$, occlusion of the pulmonary vasculature, and low pulmonary perfusion secondary to hypovolemia or shock. Bohr dead space is recognized as true dead space, or the balance between effective and ineffective ventilation occurring in the lungs\(^{(14)}\) (Fig. 13).

The Enghoff dead space equation, on the other hand, relies on the $P_{ACO_2}$ of arterial blood and is thus affected by global gas exchange inefficiency and the effects of shunt and venous admixture (Fig. 14). $P_{ACO_2}$ can be elevated from all sources of low ventilation to perfusion matching and shunt, such as atelectasis, pneumonia, COPD, and asthma. $P_{ACO_2}$ can also rise when an increase in metabolism and $CO_2$ production is not accompanied by an increase in $CO_2$ excretion. When $V_{CO_2}$ increases without a proportional rise in alveolar ventilation, production of $CO_2$ exceeds the rate of excretion, and $P_{ACO_2}$ increases. Therefore, it is important to understand that the Enghoff equation overestimates $V_D/V_T$ in the presence of shunt and low $V/Q$.

The determination of $P_{ACO_2}$ using volumetric capnography for the calculation of Bohr dead space has been demonstrated by mathematical modeling\(^{(15)}\) and measured in an animal model of lung injury\(^{(16)}\). $P_{ACO_2}$ calculated from the phase 3 midpoint of the volume capnogram was compared with the $P_{ACO_2}$ derived mathematically using the multiple-inert gas elimination technique. This demonstrated a close linear correlation between the 2 methods for $P_{ACO_2}$ calculation ($r = 0.99$, $P < .001$) and Bohr dead space ($r = 0.96$, $P < .001$). The Bohr dead space and the mean $P_{ACO_2}$ from volumetric capnography were similar to the multiple-inert gas elimination technique calculations, with a mean bias of 10 mL (95% CI −44 to 64 mL) and −0.10 mm Hg (95% CI −2.18 to 1.98 mm Hg), respectively.

The ability to measure $P_{ACO_2}$ from the volumetric capnogram and therefore enabling the calculation of Bohr dead space has several significant implications. Measurement of Bohr dead space returns a more accurate reflection of effective and ineffective ventilation and perfusion in the lungs that is not impacted by the effects of shunt and low $V/Q$ on $P_{ACO_2}$ (Fig. 15).

The effects of shunt on the measurement of $V_D/V_T$ was investigated using a computer model simulation that controlled for variations of $P_{ACO_2}$, alveolar $V_D$, anatomical $V_T$, pulmonary shunt, and $V/Q$ ratio distribution\(^{(17)}\) (Fig. 16) and in a lung lavage animal model using the midpoint of phase 3 to define $P_{ACO_2}$\(^{(18)}\) (Fig. 17). Both experiments confirmed that increasing levels of shunt and low $V/Q$ markedly affects dead space values calculated by Enghoff’s (Equation 1) but not Bohr’s equation (Equation 2).

An estimate of the Bohr dead space can also be calculated by substituting $P_{ET_{CO_2}}$ for $P_{ACO_2}$, whereby the Bohr estimate equation is...
The comparison of $V_D/V_{T\text{Bohr Est}}$, $V_D/V_{T\text{Engh}}$, and $V_D/V_{T\text{Bohr}}$ in regard to the area representing anatomical $V_D$ and alveolar $V_D$ on the volumetric capnogram is depicted in Figure 18. Example calculations based on the different equations in relation to the volumetric capnogram are shown in Figure 19.
Figures 18 and 19 demonstrate that the Enghoff equation overestimates true \( V_D/V_T \). Using the Bohr estimate equation also overestimates \( V_D/V_T \), but this difference will always be closer to the true Bohr dead space than the Enghoff equation, whether \( V_D/V_T \) is normal or elevated. Although identifying \( P_ACO_2 \) from the midpoint of phase 3 of the volumetric capnogram is technically achievable, using the Bohr estimate equation and substituting \( P_{ETCO_2} \) for \( P_ACO_2 \) would simplify the calculation, especially when the midpoint of phase 3 is not clearly identifiable.

Since \( P_ECO_2 \) can be calculated using Equation 4, and \( P_{ETCO_2} \) is available during volumetric CO₂ monitoring, the continuous measurement of \( V_D/V_T \) is technically feasible and would eliminate the requirement of periodic arterial blood gas sampling to measure \( P_ACO_2 \) for \( V_D/V_T \) calculation. The clinical value of constant monitoring and trending of \( V_D/V_T \) during mechanical ventilation of the critically ill patient requires further investigation.

It has also been suggested that simultaneous assessment of Enghoff and Bohr dead space using volumetric capnography may be useful in regard to recognizing the effects of shunt and V/Q inequality versus true dead space or wasted ventilation in critically ill patients with elevated \( V_D/V_T \). Since many studies that identified \( V_D/V_T \) as a predictor of outcome, disease diagnosis, and disease severity used the Enghoff equation, the conclusions of these studies may need to be reexamined using this new approach.

**Estimating Metabolic Rate and Resting Energy Expenditure**

Estimation of metabolic rate can be accomplished by \( V_{CO_2} \) measurements from volumetric capnography. The Weir equation is the accepted standard used during metabolic testing for calculating the nutritional support requirements in critically ill patients. Modifications to the Weir equation can be used to calculate resting energy expenditure (REE) by deriving a value for \( V_O_2 \) adjusted for a normal respiratory quotient (RQ) based on a measurement of \( V_{CO_2} \). The REE by the Weir equation and the REE based on \( V_{CO_2} \) (REE-CO₂) can be calculated, where

\[
REE = (3.9 \times V_O_2) + (1.1 \times V_{CO_2}) \times 1.44 \quad (6)
\]

and

\[
REE-CO_2 = (3.9 \times V_{CO_2}/0.85) + (1.1 \times V_{CO_2}) \times 1.44.
\]  

(7)

When the actual RQ is equal to 0.85, the REE-CO₂ calculation results in an REE value equivalent to the value calculated by the standard Weir equation. The CCM Ex-
press metabolic analyzer (Medical Graphics Corporation, St Paul, Minnesota) uses Equation 7 to calculate REE-CO2 with an accuracy of approximately 10% compared with the REE. The REE measured by the CCM Express using the standard Weir method was compared retrospectively with the REE-CO2 calculation in 67 adult ICU patients. The correlation coefficient \( r = 0.99 \) and the coefficient of determination \( r^2 = 0.98 \), with bias and precision between measurements of \(-15 \pm 126 \) cal/d. When the differences between REE and REE-CO2 were compared with the measured RQ, as the value for RQ moved toward 0.70, the percentage error (mean bias/mean REE for the range of RQ) became more positive, and as RQ moved toward 1.0, the percentage error became more negative. Furthermore, when RQ was normal in the range between 0.80 and 0.90, the average error was approximately \(-5\%\) (Fig. 20).

It should be noted that when using this approach, if the \( V\dot{\text{CO}}_2 \) measuring device has a substantial bias and precision difference from measurements by a metabolic analyzer, additional variance between REE and REE-CO2 will result. This difference in measurement accuracy can be compensated for by use of a measurement bias correction.

The REE-CO2 equation can be further simplified by solving the equation with any combination of \( V\dot{\text{CO}}_2 \) and \( V\dot{\text{O}}_2 \) that equals an RQ of 0.85, and dividing the calculated REE by the measured \( V\dot{\text{CO}}_2 \), a single factor can be derived for calculating REE-CO2, whereby

\[
\text{REE-CO2} = 8.19 \times V\dot{\text{CO}}_2. \tag{8}
\]

For example, when \( V\dot{\text{CO}}_2 = 221 \) mL/min and \( V\dot{\text{O}}_2 = 260 \) mL/min, RQ = 221/260 = 0.85, and the Weir equation returns a calculated REE of 1,810 kcal/d, whereby

\[
\text{REE} = (3.9 \times 260) + (1.1 \times 221) \times 1.44 = 1,810 \text{ kcal/d}. \tag{9}
\]

REE-CO2 can be calculated as follows:

\[
\text{REE-CO2} = [3.9 \times (221/0.85) + (1.1 \times 221) \times 1.44
\]
\[= 1,810 \text{ kcal/d}. \tag{10}
\]
REE-CO2 factor = 1,810/221 = 8.19,  

and

REE-CO2 = 8.19 × 221 = 1,810 kcal/d.  

The caloric equivalence and carbon dioxide and oxygen can also be used to indirectly calculate REE from measurements of V˙CO2 (Table 2).158-160 When the RQ = 0.90, the CO2 caloric equivalent factor equals 5.52 kcal/L, where

REE-CO2 equivalent = 5.52 × V˙CO2 × 1.44  

This technique was compared with the Harris-Benedict calculation and the Weir equation. The Harris-Benedict equation significantly underestimated REE, but there was no significant difference between the Weir and REE-CO2 equivalent calculation158 (Table 3). Because of the technical difficulty of measuring V˙O2, the REE-CO2 equivalent calculation is simpler and should be the preferred method, especially when the FIO2 is >0.60.159

The ability to perform metabolic measurements using V˙CO2 from volumetric capnography has several important implications. V˙CO2 measurement capabilities are increasingly more available on standalone monitors and ventilators. This makes estimates of REE more readily accessible when metabolic analyzers are not available. When V˙CO2 is being monitored either continuously or intermittently during mechanical ventilation, if the REE-CO2 calculation is incorporated into the ventilator, estimates of the metabolic rate and nutritional requirements could be available in real time and trended over the course of critical illness.9

Additionally, since FIO2 does not affect the accuracy of the REE-CO2 calculation, FIO2 > 0.60 may no longer be a limitation of measuring a reasonable estimate of REE. The
implications of using the REE-CO2 calculations are significant in that even the most severe critically ill patients receiving mechanical ventilation receiving 100% oxygen and high levels of PEEP can have REE estimates performed to manage their complex nutritional needs.

Since volumetric capnography and V˙CO2 monitoring are becoming more readily available and are less costly than traditional metabolic testing, their use should be considered for incorporation into a standard nutrition assessment and treatment process. Further validation studies and measurements of outcome are needed to verify the impact of these alternative methods of indirect calorimetry.

Summary

Monitoring exhaled CO2 goes beyond the basic use of evaluating and assessing ventilation. The uses of exhaled CO2 monitoring include improvements in patient safety, utilization in assessing care and evaluating interventions, identifying abnormal physiology, quantifying the severity of illness, and predicting outcomes. In recognition of these significant benefits, the importance of exhaled CO2 monitoring has been increasingly emphasized by practice standards, guidelines, and advisory statements from professional organizations and regulatory agencies.

Future advancements in volumetric capnography will include the capability to continuously estimate Bohr dead space and metabolic rate during mechanical ventilation. These advancements are currently at the verge of technical feasibility, and device manufacturers will soon bring these important enhancements in patient monitoring into clinical practice at the bedside. The critical impact and implications of these valuable monitoring methods utilizing exhaled CO2 will be important for all health-care providers to comprehend and utilize.

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