Review
Carbon dioxide kinetics and capnography during critical care
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Abstract
Greater understanding of the pathophysiology of carbon dioxide kinetics during steady and nonsteady state should improve, we believe, clinical care during intensive care treatment. Capnography and the measurement of end-tidal partial pressure of carbon dioxide (PETCO₂) will gradually be augmented by relatively new measurement methodology, including the volume of carbon dioxide exhaled per breath (VCO₂.br) and average alveolar expired PCO₂ (PAE–CO₂). Future directions include the study of oxygen kinetics.

Keywords: airway, capnography, carbon dioxide, carbon dioxide kinetics, expirogram, nonsteady state, ventilation

Introduction
Carbon dioxide is produced in the tissues by aerobic plus/minus anaerobic metabolism (Fig. 1a), transported in blood to the lung by venous return (essentially equal to cardiac output [Qt]), and eliminated from the lung by minute ventilation (VE) [1]. In this model the lung is a simple mixing chamber and the alveolar fractional carbon dioxide (FACO₂) is given by

\[ FACO₂ = \frac{\dot{V}CO₂,ti}{\dot{V}A} + FICO₂ \] (1)

where \( \dot{V}CO₂,ti \) is the tissue carbon dioxide production, \( \dot{V}A \) is alveolar ventilation, and \( FICO₂ \) is the inspired \( FCO₂ \). If one assumes no diffusion defect for carbon dioxide, then the partial carbon dioxide tension (PCO₂) of arterial blood (PaCO₂) leaving the lung is the perfusion-weighted average alveolar PCO₂ (PACO₂). Note that pulmonary shunt will add mixed venous blood with high PCO₂ (PvCO₂) to arterial blood and slightly increase PaCO₂ [2]. \( \dot{V}A \) is the product of respiratory frequency and expired tidal volume (Vt). Expired Vt is composed of alveolar Vt and total physiologic dead space (Vdphy). The fraction Vdphy/Vt is given by

\[ Vdphy/Vt = (PaCO₂ – PE–CO₂)/PaCO₂ \] (2)

where PE–CO₂ is the mixed expired PCO₂ [2]. In turn, Vdphy is partitioned into anatomic dead space (Vaana; conducting airways that do not participate in gas exchange) and alveolar dead space (Vdalv; ventilated alveolar units that are devoid of perfusion; Fig. 2). Vdalv/Vtalv is given by

\[ Vdalv/Vtalv = (PaCO₂ – PACO₂)/PaCO₂ \] (3)

where PACO₂ is the alveolar PCO₂, estimated either from PETCO₂ or PAE–CO₂ [2] (see below). The PACO₂–PETCO₂...
gradient results from the presence of $V_{D_{alv}}$ or high alveolar ventilation-to-blood flow ($\dot{V}A/Q_{A}$) lung regions (see also Capnography during weaning from mechanical ventilation, below).

The normal capnogram is the measurement of $PCO_2$ at the airway opening during the ventilatory cycle (Fig. 1b) [1]. Phase I (inspiratory baseline) reflects inspired gas, which is normally devoid of carbon dioxide. Phase II (expiratory upstroke) is the transition between $V_{D_{ana}}$, which does not participate in gas exchange, and alveolar gas from the respiratory bronchioles and alveoli. Phase III is the alveolar plateau. Traditionally, $PCO_2$ of the last alveolar gas sampled at the airway opening is called the $PETCO_2$. Finally, phase IV is the inspiratory downstroke, the beginning of the next inspiration.

However, the capnogram contains no volume information. Accordingly, the $\overline{PACO_2}$ [2,3], which is the volume-averaged alveolar $PCO_2$, is a better index of $PACO_2$ than is $PETCO_2$, which is just a single measurement of $PCO_2$ at the end of exhalation [2]. A more informative determination of pulmonary carbon dioxide elimination is $VCO_2_{br}$, which is starting to garner clinical acceptance. $VCO_2_{br}$ is the multiplication and integration of airway flow and $PCO_2$ over an entire respiratory cycle [4–6]. See the section on Future directions of carbon dioxide kinetics monitoring, below, for an interpretation and contrast of the measurements of $VCO_2_{br}$ and $PETCO_2$.

The disposition of carbon dioxide can also be represented in a hydraulic model (Fig. 3) [3,7]. The large peripheral tissue compartment drains through a conduit ($Q_{T}$) into the small central pulmonary compartment. The central compartment can be further divided into pulmonary shunt ($\dot{V}A/Q_{A} = 0$), normal lung ($\dot{V}A/Q_{A}$ near unity), and high $\dot{V}A/Q_{A}$ lung units, including $V_{D_{alv}}$. The tissues produce carbon dioxide ($VCO_2$), which empties into the peripheral tissue compartment. Then, carbon dioxide flows by gravity ($Q_{T}$) from the higher level peripheral tissue compartment to the lower level pulmonary compartment. Normally, $\dot{V}A$, which equals $V_{E}$ minus $V_{D_{ana}}$, and the effects of high $\dot{V}A/Q_{A}$ units, eliminates carbon dioxide from the lung. In this model, $Q_{T}$ affects the distribution and total amount of carbon dioxide in the body. For example, at low $Q_{T}$, retention of carbon dioxide occurs in the peripheral tissue compartment, and higher $PvCO_2$ is required to restore carbon dioxide delivery to the lungs. This hydraulic model can help to understand the meaning of $PETCO_2$ during successful cardiopulmonary resuscitation (CPR), and to compare $PETCO_2$ with $Paco_2$ in the assessment of ventilator parameters. See the section, Effect of positive end-expiratory pressure on carbon dioxide kinetics, below, which highlights the utility of the hydraulic model.

**Capnometry: current technologies**

Capnometry is the measurement of $FCO_2$ in tidal gas at the airway opening [1,8]. Capnography is the graphic display of measured $FCO_2$ versus time. Capnometry most commonly utilizes infrared light absorption or mass spectrometry [9]. Both methods are reliable and relatively accurate. Capnometers that are used in clinical practice use two different sampling techniques: sidestream or mainstream.
the peripheral tissue carbon dioxide compartment (left) drains through cardiac output ($\dot{Q}_T$) into the smaller central pulmonary carbon dioxide compartment (right). $F_Co_2$, fractional carbon dioxide; $FRC$, functional residual capacity; $P_{aco_2}$ arterial $PCO_2$; $P_{vco_2}$, mixed venous $PCO_2$; $V/W/Q$, ventilation : perfusion ratio; $V_{co_2,ti}$, tissue carbon dioxide production; $V_{o,ana}$, anatomical dead space; $\dot{V}_e$, exhaled ventilation (see text). Adapted from Breen and Mazumdar [3].

**Mainstream capnometry**

The main advantage of the mainstream analyzer is its rapid response, because the measurement chamber is part of the breathing circuit. The sample cuvette lumen, through which inspired and expired gases pass, is large in order to minimize the work of breathing, and pulmonary secretions generally do not interfere with carbon dioxide analysis. Compared with sidestream sampling, the airway cuvette is relatively bulky and can add dead space. However, within the past few years lighter and smaller airway cuvettes have been developed to allow its use in neonates [10,11]. The analyzer is warmed to prevent condensation on the sample chamber window, and caution must be taken to prevent burns. The monitoring of $PETCO_2$ in nonintubated patients is more difficult with mainstream sampling.

**Sidestream capnometry**

The sidestream $PCO_2$ analyzer adds only a light T-adapter to the breathing circuit, and can be easily adapted to nonintubation forms of airway control. Because the sampling tubing is small-bore, it can be blocked by secretions. During sidestream capnography, the dynamic response, the steepness of the expiratory upstroke and inspiratory downslope, tends to be blunted because of the dispersive mixing of gases through the sampling line [4,12,13], where gas of high $PCO_2$ mixes with gas of low $PCO_2$. In addition, a washout time is required for the incoming sampled gas to flush out the volume of the measuring chamber. The overall effect is an averaging of the capnogram, resulting in a lowering of the alveolar plateau and an elevation of the inspiratory baseline. Thus, $PETCO_2$ may be underestimated and rebreathing can be simulated [12,14]. These problems are exacerbated by high ventilatory rates and by the use of long sampling catheters. In addition, the capnogram is delayed in time by transport delay, the time required to aspirate gas from the airway opening adapter through the sampling tubing to the sampling chamber [4,12]. In conditions of low fresh gas flow (eg closed circle circuit anesthesia), the amount of gas sampled and removed from the breathing circuit needs to be considered.

**Portable capnometers**

Although portable capnometers exist, their use in the field can be hindered by cost and requirement for calibration [15]. The portable infrared analyzer will not operate in temperatures that are subzero or greater than 40°C. Another device that is used for measurement of $PCO_2$ is the chemical colorimetric airway detector [16], which uses a pH-sensitive indicator to detect breath-by-breath exhaled carbon dioxide [15]. The colorimetric airway detector is interposed between the ETT and the ventilation device. They have an unopened shelf-life of 15 months. Both adult and pediatric adaptors exist, but they cannot be used in infants who weigh less than 1 kg. Because of excessive flow resistance, they are not suited for patients who are able to breath spontaneously, and excessive humidity will render them inoperative in 15–20 min. The devices can be damaged by mucus, edematous or gastric contents, and by administration of intratracheal epinephrine. Despite these drawbacks, colorimetric sensors have been found to be useful in guiding prehospital CPR both in intubated patients and those with a laryngeal mask airway [15,17].

**Traditional use of capnography: airway patency and assessment of ventilation**

Because the lung is the only body compartment in which carbon dioxide normally and continuously accumulates, the presence of cyclic exhaled carbon dioxide can be used to confirm airway patency and pulmonary ventilation. Although initially adopted for anesthesia monitoring in the operating room, the use of capnography to confirm airway patency and lung ventilation has expanded over the past 8 years to include critical care, emergency medicine, field resuscitation, and conscious sedation settings [1,8,15,18–22]. However, there are pitfalls in the use of capnography to confirm endotracheal intubation. Potential problems with
technology are described above. In addition, several scenarios have been described that impact on the ability of capnography to assess the airway and ventilation.

First, during circulatory arrest, pulmonary ventilation will result in low and decreasing values of exhaled carbon dioxide because Qt and carbon dioxide transport from the tissues to the lung are decreased or absent in the presence of continuing Va [23–25]. In the clinical setting, however, Vukmir et al [19] demonstrated that infrared capnography was 100% specific and sensitive in the detection of endotracheal versus esophageal intubation in 100 critical care cases of airway management, 17 of which were cardiac arrests.

Second, positive-pressure ventilation by face mask can force pharyngeal gas, containing exhaled carbon dioxide from the previous breath, into the esophagus and stomach [1]. Likewise, ingestion of carbonated beverages can also generate carbon dioxide in the stomach [26]. Subsequent esophageal intubation and gastric ventilation can result in initial cyclic ‘exhaled’ carbon dioxide. However, esophageal intubation usually causes an initial ‘PETCO2’ that is less than 10 mmHg and that decreases with each ‘exhaled breath’ as inspiration dilutes carbon dioxide in the stomach [27]. In the case of suspected esophageal intubation, consider interpreting the value of exhaled carbon dioxide after the sixth breath [15].

Third, in a case report in a neonate weighing under 700 g [28], although the ETT tube was correctly positioned in the trachea, displacement of the ETT against the lateral wall of the trachea resulted in a flat capnogram and an erroneous diagnosis of esophageal intubation.

Fourth, pathology that causes absence of ventilation, including severe bronchospasm, patient apnea, or plugged ETT will result in absence of expired carbon dioxide and a falsely negative diagnosis that the ETT is not in the trachea.

Finally, it is prudent to remember that a normal capnogram confirms ventilation of the lungs through a patent airway, but not necessarily a secure airway. In a case report [29], a normal capnogram resulted during ventilation through an ETT positioned at the glottic opening, but not securely placed in the trachea.

Despite these potential drawbacks, capnography remains the most reliable monitor of airway patency in a variety of experimental and clinical settings. Mickelson et al [30] demonstrated that exhaled carbon dioxide was the most reliable indicator of esophageal intubation in canine model. Likewise, Knapp et al [31] studied current methods of verifying tracheal tube placement in the critical care setting, and found that capnography was superior to auscultation or other devices such as the lighted stylet. Capnography can also recognize esophageal intubation in neonates [32]. In the field, compared with other devices carbon dioxide monitoring best detects esophageal intubation by limiting the number of false negatives and false positives [15].

In addition to confirmation of ETT placement in the trachea, capnography may aid in cases of difficult intubation. During awake, blind, nasotracheal intubation, the end of a sidestream capnometer sampling probe can be placed through and positioned at the distal end of the ETT [33]. Then, increasing values of cyclic exhaled PCO2 can help guide the ETT to the glottic opening. During a difficult intubation, effective ventilation can be maintained through a tube at the tip of the pharynx (guided by the expiratory carbon dioxide waveform), until other adjuncts to intubation are available [34].

Sidestream capnography adapts well to the nonintubated, sedated patient. Croswell et al [35] compared monitoring by capnography, pulse oximetry and clinical observation in sedated, pediatric, dental patients. Capnography provided a minimum 15 s warning of potential arterial desaturation, and was the most sensitive method for detecting airway compromise, especially during deeper levels of sedation. With oral/nasal capnometry in pediatric patients after active seizures, Abrams et al [36] demonstrated that PETCO2 is a useful predictor of hypercapnia and is more sensitive than pulse oximetry in predicting impending respiratory failure. Other studies [8,37] have supported the assertion that capnography provides the earliest warning of airway obstruction and respiratory compromise.

Finally, capnography is a useful monitor during transport of intubated, critically ill patients [38,39]. Beside the obvious advantage of early warning against ETT dislodgment and/or compromise of ventilation, monitoring of PETCO2 (as an estimate of PaCO2) may aid the management of patients in whom hypercapnia is detrimental, such as patients with head injury with raised intracranial pressure and pediatric patients with pulmonary hypertension [38].

**Capnography during weaning from mechanical ventilation**

Capnography has been considered a potentially useful noninvasive monitor to assess the weaning of patients from mechanical ventilation in critical care settings [40]. However, studies have shown variable results in the ability of PETCO2 to predict PaCO2. Whether the use of PETCO2 can limit the need for invasive arterial blood gas monitoring has yet to be established.

In a 1985–1991 literature review of the efficacy of noninvasive blood gas monitoring in the adult critical care unit [41], the Technology Subcommittee of the Working
Group on Critical Care (Ontario Ministry of Health) concluded that changes in PETCO₂ need to be interpreted with extreme caution. Healey et al. [42] compared the correlation of PETCO₂ with PaCO₂ before and after withdrawal of assist control mechanical ventilation. PETCO₂ paralleled changes in PaCO₂ (r = 0.82). Saura et al. [43], in a prospective study to evaluate the relationship between PaCO₂ and PETCO₂ before and during weaning with continuous positive airway pressure ventilation, also found that PETCO₂ could detect clinically relevant hypercapnic episodes. However, there was a high incidence of false positives that led to arterial blood gas sampling. Withington et al. [44] found that, after a gradient between PaCO₂ and PETCO₂ was established, PETCO₂ was a useful parameter in the weaning of postcardiac surgery patients.

The assessment of PETCO₂ may be misleading if not considered in the context of changing hemodynamics and ventilatory pattern. Although there can be significant correlation of PETCO₂ with PaCO₂, clinically acceptable sensitivity and specificity may only occur in the absence of significant changes in QT or VA/Q relationships. In evaluating the use of capnography as a noninvasive monitor of PaCO₂ in critical care patients, Morley et al. [45] observed that PETCO₂ was useful as a predictor only in patients without significant parenchymal lung disease. Prause [46] found that PETCO₂ was useful for the adjustment of ventilatory parameters in prehospital emergency care patients only if they had no major cardiopulmonary damage. As depicted in Fig. 2, the gradient between PETCO₂ and PaCO₂ depends on VD/VA (ie the amount of lung regions with high or infinite VA/Q ratios) [2,25]. Lung regions with high VA/Q ratios can result from high alveolar pressures (eg large VT, positive end-expiratory pressure [PEEP]), low pulmonary perfusion pressures (eg low QT, upright position), and obstruction of pulmonary blood flow (eg thrombus, gas, or fat embolism). Thus, in the critically ill patient, VD/VA often changes and affects the ability of PETCO₂ to predict PaCO₂ and be a substitute for arterial blood gas sampling.

**Capnography during nonsteady-state conditions**

Capnography during cardiopulmonary resuscitation

An important and relatively successful application of capnography in the nonsteady-state clinical setting has been during CPR [1,3,25]. During cardiac arrest, the abrupt decrease in QT results in reduction in carbon dioxide transport from the tissues to lung and, hence, decreased carbon dioxide elimination from the lung. With subsequent successful CPR, the increase in QT restores pulmonary blood flow and carbon dioxide transport, and increases pulmonary elimination of carbon dioxide. Contrast this nonsteady-state effect of QT upon carbon dioxide kinetics with the steady-state equation (Eqn 1) for carbon dioxide kinetics. QT does not even appear in Equation 1, although it is the conduit for VCO₂,in.

The measurement of exhaled carbon dioxide is the best signal of return of spontaneous circulation during CPR [23,24]. Capnography is also a useful noninvasive index of the adequacy of pulmonary perfusion during closed-chest cardiac compression [47,48]. In fact, capnography may be used to compare the efficacy of different modes of chest compression [49]. Moreover, the quantitative measurement of PETCO₂ may have predictive value during CPR. This was recognized as early as 1939, when Eisenmenger wrote “If during a resuscitation attempt the analysis of the expired air, performed about twice per hour, still shows plenty of carbon dioxide, then continuation of artificial respiration (and circulation) would be indicated” [50]. Asplin and White [20] measured the 1-min value, the 2-min value, and the maximum value of PETCO₂ during CPR in 27 patients. The initial PETCO₂ values were prognostic for return of spontaneous circulation. Finally, the predictive value of PETCO₂ has been studied in hospital settings. Domsky et al. [51], in a retrospective chart review of 100 critically ill surgery patients, found that a persistent PETCO₂ of 28 mmHg or less was associated with a mortality rate of 55%, versus a mortality of 17% in patients with higher PETCO₂. Mortality rate was also increased in patients with a persistent PaCO₂–PETCO₂ difference of 8 mmHg or more. Quantitative capnography during resuscitation will continue to evolve.

**Future directions of carbon dioxide kinetics monitoring**

The following three sections examine how clinically relevant perturbations (application of PEEP, onset of pulmonary embolism, and recovery from pulmonary embolism) affect nonsteady-state carbon dioxide kinetics. The use of relatively new measurements (VCO₂, br, PaECO₂) will help define pathophysiology and will improve, we believe, clinical diagnosis and treatment.

**Effect of positive end-expiratory pressure on carbon dioxide kinetics**

The addition of PEEP to mechanical ventilation should acutely decrease VCO₂, br due to decreased VA (increased VD,phy) and decreased carbon dioxide transfer to the lung (decreased QT and venous return) [1,3]. Then, gradual recovery of VCO₂, br would occur if peripheral tissue carbon dioxide retention caused sufficient increase in PViCO₂ (especially at sustained low QT) to restore carbon dioxide delivery to the lung (Fig. 3).

The initial effects during the first 25 breaths after adding 11 cmH₂O PEEP to mechanical ventilation of anesthetized dogs are shown in Fig. 4 [3]. The summation of the decreases in VT, compared with the baseline value, permitted calculation of increased functional residual capacity (FRC) at 1152 ml. PETCO₂ paralleled the decrease in VT, but recovered to baseline by breath 10. VCO₂,br decreased from baseline (7.6 ml) to zero in the first couple of exhala-
tions. However, VCO₂\text{br} had only increased to 4.9 ml by breath 25. From a baseline value (3.3 l/min), Q˙\text{T} (ascending aorta flow probe) decreased to 1.6 l/min by breath 10, which was sustained through breath 25. During measurements extended to 25 min, depressed Q˙\text{T} was sustained and VCO₂\text{br} was still 17% less than baseline. PEEP caused an immediate and sustained increase in VD\text{phy} from 312 to 366 ml, resulting entirely from the increase in VD\text{ana}. PETCO₂ continued to increase to the 25 min value (43 ± 6 mmHg), which was significantly greater than baseline. There were parallel changes in PaCO₂ and PV–CO₂.

To examine these hypotheses, an animal model similar to the PEEP study (above) was invoked, except that the perturbation was abrupt tightening of a snare around the right pulmonary artery (RPA) [1,55]. Compared with baseline (9.3 ml), average VCO₂\text{br} decreased to 7.0 ml by 1 min after RPA occlusion (Fig. 5). At the same time, PETCO₂ decreased from 29 to 22 mmHg. During the following 70 min of RPA occlusion, VCO₂\text{br} steadily increased to approach the baseline value. In contrast, at 70 min of RPA occlusion, PETCO₂ was still 13% less than baseline. PaCO₂ and PV–CO₂ progressively converged on their maxima (high values) by 70 min. Q˙\text{T}, despite an initial tendency to decrease, did not change significantly.

In summary, large experimental pulmonary embolus immediately decreased VCO₂\text{br} by 25%, almost entirely due to an increase in VD\text{ana} (Fig. 2). VCO₂\text{br} increased and recovered to baseline as carbon dioxide was retained in the body, signaled by the progressive increases in PaCO₂ and PV–CO₂. PETCO₂ remained significantly less than baseline due to persistent increased VD\text{ana}, and detected neither the
increase and recovery of $\text{VCO}_2$, nor the increase in $\text{PaCO}_2$. Because $\dot{Q}$ did not significantly decrease, $\text{PvCO}_2$ could increase sufficiently to restore carbon dioxide delivery to the lung.

**Resolution of pulmonary embolism**

Patients with large pulmonary embolism can suffer progressive hypercapnia and may require emergent embolectomy, either by the transvenous or open thoracic approach. Conceivably, the functional recovery of carbon dioxide exchange could signal reperfusion of the affected pulmonary circulation and help guide the course of surgical therapy.

Accordingly, using the experimental model of pulmonary embolism (above), the RPA was occluded for 70 min to approach steady state. Then, the RPA snare was abruptly released and measurements were repeated during 70 min of RPA reperfusion [1,56]. At onset of RPA reperfusion, $\text{VCO}_2$ abruptly increased from 9 to 12 ml. By 70 min of RPA reperfusion, $\text{VCO}_2$ returned to the baseline value. Immediately after RPA reperfusion, $\text{PETCO}_2$ increased from 25 to 33 mmHg because $\text{VDalv}/\text{VTalv}$ decreased by 41%. At 70 min, $\text{PETCO}_2$ was still greater than baseline. $\text{PaCO}_2$ and $\text{PvCO}_2$ steadily decreased during 70 min of RPA reperfusion, modeling the release of carbon dioxide retention in the central pulmonary and peripheral tissue carbon dioxide compartments. $\dot{Q}$ did not change significantly.

In summary, $\text{VCO}_2$ detects and follows the resolution of carbon dioxide retention in lung and tissues during reperfusion after experimental pulmonary embolus. In contrast, $\text{PETCO}_2$ did not detect the secondary slow decrease in $\text{VCO}_2$ back to baseline because $\text{PETCO}_2$ measures neither exhaled volume nor the shape of the $\text{PCO}_2$ waveform.

Accordingly, during onset and resolution of pulmonary embolism, this analysis of nonsteady-state carbon dioxide kinetics may aid the clinical assessment of pulmonary embolism [57].

Although beyond the scope of the present review, volumetric capnography (ie the carbon dioxide expirogram, the plot of exhaled $\text{PCO}_2$ versus exhaled volume) can also yield information about lung volume [58], dead space [59], and pulmonary blood flow (carbon dioxide rebreathing technique) [60].

**Conclusion**

In our opinion, better understanding of pathophysiology of carbon dioxide kinetics during steady and nonsteady state should improve clinical care during intensive care treatment. Capnography and the measurement of $\text{PETCO}_2$ will gradually be augmented by relatively new measurement methodology (including $\text{VCO}_2$ and $\text{PvCO}_2$). Future directions include the study of oxygen kinetics [1].

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