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Advances in monitoring expired CO_2 in critically ill patients

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Reviews the potential uses and pitfalls of capnography in critically ill patients, especially for haemodynamic and respiratory monitoring.

Expired CO_2 can be easily monitored in the intensive care unit (ICU), especially in patients under invasive mechanical ventilation, using infrared measurement by sampling mainstream expiratory flow using an in-line chamber, or sidestream expiratory flow (by continuous aspiration through a sampling line connected between the intubation tube and the Y-piece of the ventilator).

Expired CO_2 is determined by three parameters:

1. CO_2 production (CO_2) mainly due to tissue metabolic activity
2. CO_2 transport related to cardiac output (CO) and haemoglobin level
3. CO_2 clearance by alveolar ventilation.

Given its high diffusive capacity, CO_2 is easily eliminated by alveolar ventilation, although end-tidal CO_2 partial pressure ($PEtCO_2$) is higher than alveolar CO_2 partial pressure ($PACO_2$) due to ventilation-perfusion mismatch. The gradient between $PEtCO_2$ and arterial CO_2 partial pressure ($PaCO_2$) is usually low (3-5 mmHg) but increases with increasing alveolar dead space, even though $PEtCO_2$ remains highly correlated with $PaCO_2$.

By allowing a combined analysis of respiratory, haemodynamic and metabolic status, capnography is a versatile tool with developing clinical applications in the ICU. While capnography is commonly used in the operating room, this technique may be underused in the ICU (Cook et al. 2011; Georgiou et al. 2010; Ono et al. 2016). The aim of this paper is to highlight the advances and the usefulness of expired CO_2 monitoring in the specific ICU setting.

Capnography and respiratory intensive care

Airway management

Capnography is a reliable tool to confirm the correct placement of endotracheal (Guggenberger et al. 1989) or supraglottic devices, given the lack of significant CO_2 production in the oesophagus. Despite a high diagnostic performance (Silvestri et al. 2005), false negatives are encountered in the cardiac arrest setting (Heradstveit et al. 2012) or as a consequence of technical pitfalls (leaks around endotracheal cuff (Dunn et al. 1990), kinking of the sampling line, ventilator failure…). False positives may happen if the stomach contains CO_2 (e.g. in patients receiving noninvasive ventilation for hypercapnic respiratory failure). Finally, despite recommendations for systematic use during intubation in the ICU, the clinical impact of this strategy remains to date unknown in the ICU setting. Indeed, most of the recommendations are made from the NAP 4 audit (Cook et al. 2011), which showed that 74% of deaths related to airway issues in the ICU (tube displacement, oesophageal intubation) were associated with the lack of capnography.

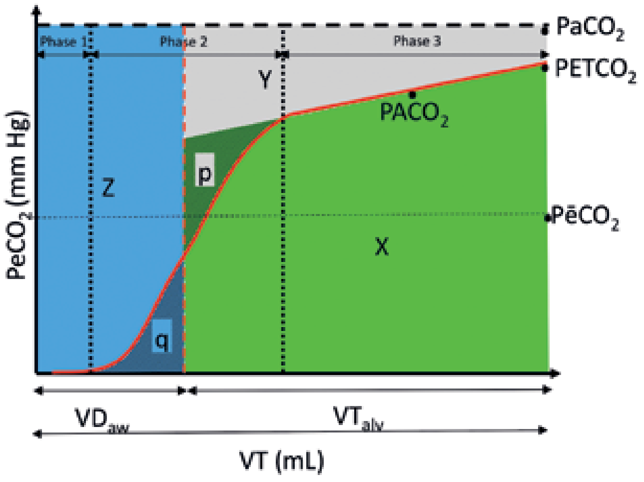
Dead space measurement and volumetric capnography

Partial pressure of expired CO_2 is usually plotted against time on a capnogram, allowing assessment of $PEtCO_2$. Partial pressure of expired CO_2 may also be plotted as a function of expired tidal volume to provide volumetric capnography. An ideal volumetric capnography curve can be described in three expiratory phases (**Figure 1**) (Verscheure et al. 2016):

- **Phase 1** - exhaled CO_2 amounts to zero and reflects the lack of CO_2 content in the conducting airways
- **Phase 2** - CO_2 increases linearly, reflecting mixing of CO_2 content of distal airways and alveoli close to the main airways
- **Phase 3** - CO_2 reaches a slowly rising plateau (reflecting alveolar gas compartment), whose slope is an indication of ventilation-perfusion mismatch. Both anatomical (VD_{aw}) and alveolar dead space (VD_{alv}) can be computed by combining capnography and arterial blood sampling using graphical analysis of the volumetric capnography curve (Fletcher et al. 1981). Assuming $PaCO_2$ approximates $PACO_2$, physiological dead space (VD_{phys}) can also be computed using the Enghoff modification of the Bohr equation, as follows:

VD_{phys} Bohr-Enghoff = ($PaCO_2$-$PACO_2$)/$PaCO_2$ with $PACO_2$ = mean expired CO_2 partial pressure.

However, VD_{phys} assessed with the Bohr-Enghoff equation overestimates the true VD_{phys}, since venous admixture and low ventilation-perfusion areas increase the difference between $PaCO_2$ and $PACO_2$. It



$$\frac{VD_{aw}}{VT} \qquad \frac{Z}{X+Y+Z}$$

$$\frac{VD_{alv}}{VT} \qquad \frac{Z}{X+Y+Z}$$

$$\frac{VD_{phys}}{VT} \qquad \frac{Z}{X+Y+Z}$$

Area q = Area p

Figure 1. Typical volumetric capnography curve

Phase 1: emptying of conducting airways; **phase 2:** emptying of distal airways and alveoli close to the main airways; **phase 3:** emptying of alveolar gas compartment. Right side of rectangle Z is defined such as area q equals area p (Fletcher et al. 1981). Area X (green-filled), Y (grey-filled) and Z (blue-filled) are used to compute anatomical, alveolar, and physiological dead space using Fletcher's approach (Fletcher et al. 1981).

$PaCO_2$ arterial CO_2 partial pressure $PeCO_2$ expired CO_2 partial pressure $P\bar{e}CO_2$ mean expired CO_2 partial pressure $PEtCO_2$ end-tidal CO_2 partial pressure VD_{aw} anatomical dead space VD_{alv} alveolar dead space VT tidal volume VT_{alv} alveolar tidal volume

was recently shown that the midportion of phase 3 is a reliable estimator of $PACO_2$ (Tusman et al. 2011), allowing a continuous assessment of true physiological dead space, without arterial blood sampling, using Bohr's original equation, as follows:

$VD_{phys}\ B_{ohr} = (PACO2\text{-}P\bar{e}CO2)/PACO2$. $VD_{phys\ Bohr}$ as assessed by volumetric capnography has been shown to be closely related to dead space measurement using the multiple inert gas technique (Tusman et al. 2011), and is not impacted by the effect of shunt or low ventilation-perfusion areas.

Finally, plotting the volume of expired CO_2 as a function of expired tidal volume allows computation of VD_{alv} (Fletcher et al. 1981) and alveolar ejection volume (Romero et al. 1997), defined at the predicted point where alveolar emptying begins (**Figure 2**), as an attempt to better quantify phase 3 of the volumetric capnography curve.

The following clinical applications of volumetric capnography have been reported:

- Nuckton et al. (2002) reported that dead space (computed from the Bohr-Enghoff equation) was strongly associated with acute respiratory distress syndrome (ARDS) mortality. In addition, Gattinoni et al. (2003) showed that decrease of dead space during prone position was associated with lower ARDS mortality. Alveolar ejection volume is also associated with ARDS mortality (Lucangelo et al. 2008), with the advantage of being independent of ventilatory settings (Romero et al. 1997). Whether strategies aiming to minimise deadspace decrease ARDS mortality remains however unknown.

> **" capnography is a versatile tool with developing clinical applications in the ICU "**

- As early as 1975, Suter et al. (1975) showed that the "best positive end-expiratory pressure (PEEP)" (i.e. PEEP level associated with the highest oxygen transport) was associated with the lowest dead space (computed from the Bohr-Enghoff equation with a correction for the effect of shunt [Kuwabara et al. 1969]). Increase in dead space below and above the best PEEP level was interpreted as evidence of lung overdistension (and hence compression of alveolar vessels) at low and high lung aerated volume.
- Increased dead space fraction has been reported as an excellent predictor of extubation failure in a single study on ICU adult patients (González-Castro et al. 2011), a finding that should be confirmed before application in clinical practice.

However volumetric capnography presents the following limitations: measurement errors due to air leaks (e.g. during noninvasive ventilation) or obstruction of airway adaptor by secretions or condensation droplets, requirement of sufficient expiratory time in order to allow complete CO_2 exhalation, deviation from the ideal 3 phases curve in some clinical situations, dependency to ventilatory settings etc.

$PaCO_2$ surrogate

$PEtCO_2$ can be used as a surrogate of $PaCO_2$, e.g. after changing ventilatory settings, assuming the $PEtCO_2$-$PaCO_2$ gap remains constant over time (i.e. hypothesising that the dead space remains constant). It was shown as a cost-effective intervention (Rowan et al. 2015) with a reduction of a third of blood gases analyses and a saving of $880,496 over 6 months in an American paediatric ICU. In specific populations where tight control of $PaCO_2$ is important (e.g. patients with brain injury), $PEtCO_2$ monitoring can be useful as it allows a continuous noninvasive estimation of $PaCO_2$. It should, however, be stressed that interventions that can alter dead space (e.g. bronchodilators, major change of PEEP level and so on) should prompt the verification of the $PEtCO_2$-$PaCO_2$ gap. Furthermore, it may be unsafe to use only $PEtCO_2$ for the setting of the ventilator, given that some patients with unknown enlarged $PEtCO_2$-$PaCO_2$ gap might suffer from severe iatrogenic hypercapnia.

Capnography and haemodynamic intensive care

Cardiac arrest

The use of capnography in the cardiac arrest setting has been well documented and is recommended in both American and European resuscitation guidelines (Link et al. 2015; Soar et al. 2015). In this setting, capnography is a versatile tool that can help

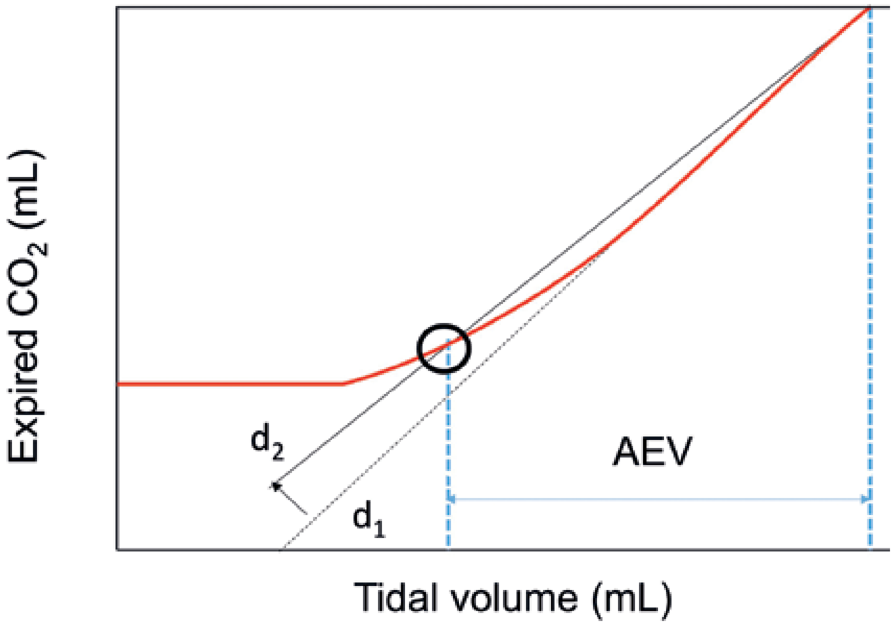


Figure 2. Plot of the expired volume of CO_2 as a function of expired tidal volume to compute alveolar ejection volume.

Alveolar ejection volume is computed as follows (Romero et al. 1997): first, a regression line (dotted black line d_1) is computed from the rightmost linear part of the curve, whose slope b is recorded. Second, a straight line (solid black line d_2) is drawn from the maximum value of expired CO_2 at end-expiration, with a slope amounting to 0.95 times slope b, to account for dead space contamination (dead space allowance). Finally, the intersection of the experimental curve and line d_2 is expected to represent the beginning of alveolar gas ejection.

AEV = alveolar ejection volume

the management of cardiac arrest patients (Heradstveit et al. 2014).

First, as described above, it can confirm the correct placement of an endotracheal tube. Second, capnography may assess the quality of cardiac resuscitation, which is correlated with the PEtCO$_2$ level, since PEtCO$_2$ is related to cardiac output. Hence it is recommended (Paiva et al. 2018) to achieve a PEtCO$_2$>20 mmHg during resuscitation. Third, capnography may help to detect the return to a spontaneous circulation if a sudden rise of PEtCO$_2$ occurs. Fourth, initial low values or failure to maintain “correct” values of PEtCO$_2$ are associated with worse outcome (Levine et al. 1997), and may help the decision to terminate resuscitation or help to triage patients with refractory cardiac arrest eligible for extracorporeal life support (Conseil français de réanimation cardiopulmonaire et al. 2009).

Cardiac output surrogate

As PEtCO$_2$ is highly correlated to CO and monitored on a breath-by-breath basis (Weil et al. 1985), it may be used as a surrogate for continuous cardiac output monitoring over short periods, assuming CO_2 production and elimination remain constant. In this connection, some authors recently investigated whether PEtCO$_2$ variations could be used to track CO changes related to change in cardiac loading conditions (Monnet et al. 2012). In a study on 65 mechanically ventilated patients with acute circulatory failure, PEtCO$_2$ increased by at least 5% during a passive leg raising manoeuvre predicted fluid responsiveness with 100% specificity and a sensitivity of 71%. For patients under veno-arterial extracorporeal membrane oxygenation (ECMO), PEtCO$_2$ might reflect transpulmonary (or native) cardiac output. Naruke et al. (2010) reported that patients that were successfully weaned from veno-arterial ECMO exhibited a rise of PEtCO$_2$ of at least 5 mmHg after reduction of ECMO flow, which was interpreted as a rise of native CO. If confirmed, this method could allow a more precise screening of patients who could be safely weaned from ECMO.

CO can be measured noninvasively with the differential Fick method, using measurements of CO_2 elimination (*V*CO$_2$) and PEtCO$_2$ on a breath-by-breath basis before and during a CO_2 rebreathing manoeuvre (Jaffe 1999). Since cardiac output is computed from expired CO_2, blood flow from non-ventilated lung regions is not accounted for and a correction for shunt fraction has to be performed using arterial oxygen saturation assessed by a pulse oximeter and an iso-shunt diagram (Rocco et al. 2004). The NICO® system is a commercially available device based on this technique, using a rebreathing loop controlled by a pneumatic valve inserted at the Y-piece level. This technique has an acceptable reliability (Gueret et al. 2006) in cardiac surgery patients, but a lack of reliability in conditions of high intrapulmonary shunt (Rocco et al. 2004). In addition, the technique is hampered by several additional limitations: CO monitoring is not continuous (1 measurement every 3 minutes) making the technique unsuitable to assess fluid responsiveness by the passive leg raising test or other postural tests (Yonis et al. 2017); the technique is contraindicated in patients requiring strict control of PaCO$_2$ (e.g. brain-injured patients); haemodynamic and respiratory instability (with rapidly changing *V*CO$_2$ between the basal and rebreathing phase) may decrease the reliability of the CO measurement. The ideal patient for this technique would be mechanically ventilated, with no active breathing and no pulmonary disease, which probably makes the technique suitable for intraoperative monitoring.

Capnography for metabolic intensive care

As highlighted in the introduction, PEtCO$_2$ is highly correlated to *V*CO$_2$. The analysis of *V*CO$_2$ and oxygen consumption (*V*O$_2$) allows estimation of the energy expenditure, through indirect calorimetry (Oshima et al. 2017). This method is the gold standard for the estimation of the daily nutrition needs in the ICU, and is now implemented in some ICU ventilators. However, to be accurate, indirect calorimetry should be done under respiratory and haemodynamic stable conditions, in aerobic condition, and with FiO$_2$ below 60%. Some authors have proposed a new estimation of energy expenditure using only

VCO_2 assessed by a commercial ventilator (Stapel et al. 2015), by computing respiratory quotient of the administered nutrition using the Weir formula to compute VO_2 (Weir 1949). The reliability of this method was acceptable, with a less than 10% overestimation of energy expenditure. Whatever the method to determine energy expenditure, no study has, to date, explored the impact of its use on ICU outcome as compared to traditional predictive equations including anthropometric parameters.

Capnography for intrahospital transport

The use of $PEtCO_2$ for intrahospital transport mechanically ventilated patients is highly recommended in the United Kingdom and in selected patients in France (Intensive Care Society 2016; Quenot et al. 2012). This recommendation is based on the frequency of airway related adverse events (hypoxia, extubation, ventilator failure etc.). As for the intubation procedure, strong evidence is lacking, and recommendations are based on observational studies and expert opinions.

Conclusion

In this review, we have highlighted the possible applications of capnography in the ICU. The versatility of this tool also makes its frailty. However, it often requires that the patient is haemodynamically stable, passively ventilated, with no change in energy expenditure. ICU patients do not fulfil these criteria most of the time. Finally, we are lacking studies showing improvement of critically ill patients' outcome by using any of the CO_2 monitoring tools. Whether this statement will remain true in the future depends on the will of critical care teams to embrace this technology, study it, and ultimately... use it! ■

Conflicts of interest

Mehdi Mezidi declares that he has no conflict of interest. Jean-Christophe Richard declares that he has no conflict of interest.

Abbreviations

ARDS	acute respiratory distress syndrome
CO	cardiac output
CO_2	carbon dioxide
ECMO	extracorporeal membrane oxygenation
ICU	intensive care unit
$PACO_2$	CO_2 alveolar partial pressure
$PaCO_2$	CO_2 arterial partial pressure
$PeCO_2$	mean expired CO_2 partial pressure
PEEP	positive end-expiratory pressure
$PEtCO_2$	end-tidal CO_2 partial pressure
VCO_2	CO_2 production
VD_{alv}	alveolar dead space
VD_{aw}	anatomical dead space
VD_{phys}	physiological dead space
VO_2	O_2 consumption

References

For full references, please email editorial@icu-management.org or visit https://iii.hm/qp9