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Advances in monitoring expired CO$_2$ in critically ill patients

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 understated 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:

  \[
  VD_{phys} = \frac{Paco_2 - Paco_2}{Paco_2} \times VD_{alv} = \frac{PaCO_2}{PACO_2} \times VD_{alv}
  \]

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
was recently shown that the midportion of phase 3 is a reliable estimator of \( \text{PACO}_2 \) (Tusman et al. 2011), allowing a continuous assessment of true physiological dead space, without arterial blood sampling, using Bohr’s original equation, as follows:

\[
\text{VD}_{\text{phys Bohr}} = \frac{(\text{PACO}_2 - \text{P}\text{C}O_2)}{\text{P}\text{C}O_2}.
\]

As early as 1975, Suter et al. (1975) showed that the "best positive expiratory pressure (PEEP)" (i.e. PEEP level associated with the highest oxygen transport) was associated with 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. As early as 1975, Suter et al. (1975) showed that the "best positive expiratory pressure (PEEP)" (i.e. PEEP level associated with the highest oxygen transport) was associated with 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. As early as 1975, Suter et al. (1975) showed that the "best positive expiratory pressure (PEEP)" (i.e. PEEP level associated with the highest oxygen transport) was associated with 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**

\[
\begin{align*}
\text{VD}_{\text{aw}} & = \frac{X + Y + Z}{VT} \\
\text{VD}_{\text{alv}} & = \frac{Y + Z}{VT} \\
\text{VD}_{\text{phys Bohr}} & = \frac{X + Y + Z}{VT}
\end{align*}
\]

\[
\text{Area q} = \text{Area p}
\]

**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 distal airways and alveoli close to the main airways

Final, plotting the volume of expired CO\(_2\) as a function of expired tidal volume allows computation of \( \text{VD}_{\text{aw}} \) (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.
Figure 2. Plot of the expired volume of CO₂ 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 d₁) is computed from the rightmost linear part of the curve, whose slope b is recorded. Second, a straight line (solid black line d₂) is drawn from the maximum value of expired CO₂ at end-expiration, with a slope amounting to 0.95 times slope b, to account for dead space contamination in the rightmost linear part of the curve, whose slope b is recorded. Second, a straight line (solid black line d₂) is drawn from the maximum value of expired CO₂ 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 d₂ is expected to represent the beginning of alveolar gas ejection.

AEV = alveolar ejection volume

Cardiac output surrogate

As PETCO₂ 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 CO₂ production and elimination remain constant. In this connection, some authors recently investigated whether PETCO₂ 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, PETCO₂ 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), PETCO₂ 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 PETCO₂ 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 CO₂ elimination (VCO₂) and PETCO₂ on a breath-by-breath basis before and during a CO rebreathing manoeuvre (Jaffe 1999). Since cardiac output is computed from expired CO₂, 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 measured 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 (Tonis et al. 2017); the technique is contraindicated in patients requiring strict control of PaCO₂ (e.g. brain-injured patients); haemodynamic and respiratory instability (with rapidly changing VCO₂ 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, PETCO₂ is highly correlated to VCO₂. The analysis of VCO₂ and oxygen consumption (VO₂) 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 FiO₂ below 60%. Some authors have proposed a new estimation of energy expenditure using only...
VCO₂ assessed by a commercial ventilator (Stapel et al. 2015), by computing respiratory quotient of the administered nutrition using the Weir formula to compute VO₂ (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 PEtCO₂ 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 fulfill these criteria most of the time. Finally, we are lacking studies showing improvement of critically ill patients’ outcome by using any of the CO₂ 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
CO₂ carbon dioxide
ECMO extracorporeal membrane oxygenation
ICU intensive care unit
PACO₂ CO₂ alveolar partial pressure
PaCO₂ CO₂ arterial partial pressure
PaO₂ CO₂ mean expired CO₂ partial pressure
PACO₂ CO₂ arterial partial pressure
PEEP positive end-expiratory pressure
PECO₂ end-tidal CO₂ partial pressure
VCO₂ CO₂ production
VDalv alveolar dead space
VDaw anatomical dead space
VDphys physiological dead space
VO₂ O₂ consumption

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