One Sepsis Fits All? Are There Different Phenotypes of Sepsis? Diagnostic Approaches and Therapies, A. Edel, S. J. Schaller

Sepsis in Critical Care: Effective Antimicrobial Strategies in ICU, G. B. Nair, M. S. Niederman

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Symmetrical Peripheral Gangrene, C. B. Noel, J. L. Bartock, P. Dellinger


Understanding Carbon Dioxide in Resuscitation F. S. Zimmerman, G. Pachys, E. A. Alpert, S. Einav
Peri-arrest CO₂ measurement may serve to assess resuscitation efficacy and guide clinical decisions. This paper reviews current knowledge and future research directions for CO₂ measurement and clinical application during CPR.

### Carbon Dioxide During Normal Heart-Lung Function
CO₂ is produced by the mitochondria as a major end product of tissue aerobic respiration. Approximately 70% of CO₂ produced by the mitochondria undergoes a chemical reaction with water catalysed by carbonic anhydrase to form H₂CO₃, dissolved in the plasma as its component ions, HCO₃⁻ and H⁺. Another 23% of CO₂ produced by the mitochondria binds to haemoglobin to form carbaminohaemoglobin. The remaining 7% is dissolved directly in the plasma. CO₂ is highly soluble in the blood and therefore has a high diffusion coefficient. The dissolved CO₂ is transported to the lung, thus maintaining the mixed venous partial pressure of CO₂ (PmvCO₂) – as measured in the pulmonary artery – at around 45 mmHg.

In the healthy individual with normal cardiac output and lung physiology, pulmonary ventilation matches pulmonary perfusion. This allows maintenance of the partial pressure of CO₂ in the alveoli (PACO₂) at approximately 40 mmHg, thus maintaining a CO₂ diffusion gradient between the pulmonary capillaries and alveoli of 5 mmHg. The high diffusion coefficient of CO₂ and efficient alveolar perfusion and diffusion across the alveolar membrane in the patient with normal heart and lung function result in an arterial partial pressure of CO₂ (PaCO₂) – as measured in the pulmonary artery – at around 45 mmHg.

### Carbon Dioxide During Decreased Cardiac Output and the No-Flow State
Changes in cardiac output result in substantial changes in arterial and venous CO₂ levels, as well as in the alveolar CO₂.

A decrease in cardiac output decreases blood flow to both peripheral tissues and the lungs. In peripheral tissues, this results in less effective removal of CO₂, leading to its accumulation in tissues and venous blood. In the lungs, decreased cardiac output decreases pulmonary perfusion pressures, resulting in a ventilation/perfusion (V/Q) mismatch. Thus, CO₂ transport to the lungs is reduced, decreasing CO₂ alveolar concentration (West 1974).

Cardiac arrest results in a no-flow state, with no organ perfusion despite ongoing cellular metabolic activity. These circumstances lead first to cellular hypoxia and subsequently to a transition to anaerobic cellular respiration, resulting in release of cellular by-products of this process to the extracellular space. These include carbon dioxide, lactate and hydrogen ions, thus resulting in a combined respiratory and metabolic acidosis (Ahn et al. 2011; Prause et al. 2001; Takasu et al. 2007). In the no-flow state of cardiac arrest, no changes in CO₂ are initially noted, as the cellular by-products from unperfused tissue remain in-situ (Tucker et al. 1994).
Carbon Dioxide During the Low Flow State – Initiation of CPR

During CPR, chest compressions, along with positive pressure ventilation, restore organ perfusion and oxygenation to some extent. In ideal conditions, CPR can achieve as much as 25% of normal cardiac output, converting the no-flow state of cardiac arrest to a low-flow state (Bellamy et al. 1984; Johnson and Weil 1991; Link et al. 2015).

The low-flow state that occurs during CPR results in an increase in PmvCO₂ – reflecting poor systemic perfusion. It also leads to a decoupling of the PetCO₂ and the PaCO₂, with a decrease in the former and an increase in the latter, both due to poor alveolar perfusion (De Backer et al. 2015; Nowak et al. 1987; Steedman and Robertson 1992). These can be expressed in the ventilation – perfusion ratio equation (Idris et al. 1994; West 1974).

Given that CPR effectiveness is directly related to patient survival (Ashoor et al. 2017; Sell et al. 2010) and that the CO₂ changes noted during CPR can be partly reversed with effective CPR (Hartmann et al. 2015; Kim et al. 2016; Niemann et al. 1985; Ornato et al. 1985; Spindelboeck et al. 2016; von Planta et al. 1991; Yakaitis et al. 1975), the measurement of partial pressures of CO₂ at various points in the systemic and pulmonary circulation, as well as measurement of alveolar CO₂, as reflected by PetCO₂, may be useful for optimising CPR performance, as well as for prognosticating CPR outcomes. Thus, a detailed understanding of CO₂ changes in various compartments is important in assessing and optimising the quality of an ongoing resuscitation.

End-tidal CO₂

When cardiac output is 5 litres per minute, as in the healthy, sedentary adult, the PetCO₂ ranges between 36-40 mmHg. For every one litre decrease in cardiac output, this value decreases by 4-6 mmHg, assuming constant ventilatory conditions (Askgro 1966; Leigh et al. 1961; Maslow et al. 2001; Shibutani et al. 1994). Under constant and optimal ventilation conditions, the PetCO₂ may therefore serve as an effective surrogate measure of pulmonary blood flow (Isserles and Breen 1991; Jin et al. 2000; Ornato et al. 1990). Consistent with this, animal and human studies have shown a direct correlation between quantitative waveform capnography pressure during resuscitation, cardiac output and coronary perfusion (Link et al. 2015).

Furthermore, a meta-analysis examining the relationship between PetCO₂ values and resuscitation outcomes demonstrated that patients eventually achieving return of spontaneous circulation (ROSC) had a mean PetCO₂ of 25.8 ± 9.8 mmHg versus a mean PetCO₂ of 13.1 ± 8.2 mmHg in those not achieving ROSC (p=0.001). In contrast, administration of sodium bicarbonate, changes in minute ventilation and varying resuscitation protocols were not associated with PetCO₂ changes (Hartmann et al. 2015).

Resultantly, American Heart Association and European Resuscitation Council guidelines recommend use of quantitative waveform capnography in all cardiopulmonary resuscitations in order to optimise chest compressions and identify ROSC (Kodali and Urman 2014; Link et al. 2015; Soar et al. 2021).

Arterial CO₂

Arterial CO₂ has been studied during CPR, immediately after ROSC and at a later stage, after ICU admission.

Multiple studies in both humans and animals have shown that the level of arterial and venous acidosis during resuscitation is determined mainly by partial pressures of CO₂ (Angelos et al. 1992; Gründler et al. 1986; Martin et al. 1985; Nowak et al. 1987; Ornato et al. 1985; Sanders et al. 1988; Weil et al. 1986), with a more profound acidosis in venous versus arterial blood (Gabrielli et al. 2005; Martin et al. 1985; Nowak et al. 1987; Ralston et al. 1985).

Profound acidosis during CPR has been associated with resuscitation failure (Niemann et al. 1985; von Planta et al. 1991; Yakaitis et al. 1975), though some earlier studies have noted poor correlations between arterial blood gas values and tissue metabolism (Nowak et al. 1987; Steedman and Robertson 1992). Nevertheless, a study of 136 out-of-hospital cardiac arrest (OHCA) patients transported to the hospital during cardiac arrest showed less profound acidosis in blood samples obtained during CPR from patients who eventually achieved ROSC versus those who did not (pH=6.96 versus 6.85; p=0.009). PaCO₂ and lactate levels were also lower in the former versus the latter group (74.0 versus 89.5 mmHg, P=0.009; 11.6 versus 13.6 mmol/L, P=0.044, respectively). Thus, PaCO₂ during resuscitation may be a marker of ischaemia severity (Kim et al. 2016). Similarly, less acidosis and lower PaCO₂ at emergency room arrival were noted in patients achieving ROSC in the pre-hospital setting versus those admitted to the emergency room in ongoing resuscitation (Ornato et al. 1985).

Greater arterio-alveolar CO₂ difference (AaDCO₂) has also been associated with resuscitation failure. A multicentre study examining AaDCO₂ during or immediately post-CPR in OHCA showed an association between increased AaDC and failure to achieve sustained ROSC. No patients with an AaDCO₂ greater than 33.5 mmHg during CPR achieved sustained ROSC (Spindelboeck et al. 2016). Similar findings were noted in those with an elevated AaDCO₂ an hour after ROSC (Moon et al. 2007).

In contrast, in post-OHCA patients hospitalised in an ICU, lower levels of PaCO₂ were associated with poorer prognosis (Helmhorst et al. 2015; Schneider et al. 2013), and, in such patients, a relatively increased CO₂ was associated with improved cerebral function (Roberts et al. 2013; Vaahersalo et al. 2014; Wang et al. 2015), possibly due to the injurious effects of hypocapnia on the brain (Aufderheide and Lurie 2004; Buunk et al. 1996; Coles et al. 2007; Schneider et
al. 2013). However, it should be noted that hypercapnia, as well, has been associated with increased mortality in some studies (Roberts et al. 2013).

In conclusion, a higher PaCO₂ during and immediately post-resuscitation appears to be associated with a poorer prognosis; whereas, in the later post-resuscitation period, a lower PaCO₂ is associated with a poorer prognosis.

**Pulmonary artery/mixed venous CO₂**

Though pulmonary artery sampling can provide information regarding tissue oxygen consumption in the tissues and cardiac output, use of pulmonary artery catheters has not been associated with improved patient outcomes and is therefore not recommended in most critically ill patients (Binanay et al. 2005; Harvey et al. 2005; Mark 2013; Rajaram et al. 2013; Richard et al. 2003) and is generally not possible nor recommended during CPR. Thus, PmvCO₂ is generally not available during resuscitation.

In non-cardiac arrest hypoperfusion states (e.g. septic shock), Pv-aCO₂ can assist in evaluation of cardiac output, tissue perfusion and anaerobic metabolic activity (Mallat et al. 2016), and increased values have been associated with increased mortality (Ospina-Tascon et al. 2013; Ospina-Tascon et al. 2015; van Beest et al. 2013).

Small retrospective studies showed substantial differences in PaCO₂ and PmvCO₂ during CPR due to OHCA (Nowak et al. 1987; Steedman and Robertson 1992). Indeed, PmvCO₂ may differ substantially from PaCO₂, as the latter reflects pulmonary gas exchange and former tissue perfusion, with differences being especially prominent in states of low cardiac output and especially during CPR (Bloom et al. 2014; Byrne et al. 2014; Kelly 2010; Spindelboeck et al. 2016). As PmvCO₂ may more accurately reflect tissue perfusion it may be a better clinical decision tool than PaCO₂ during resuscitation (Adrogué et al. 1989; Nowak et al. 1987; Steedman and Robertson 1992; Weil et al. 1986).

Indeed, multiple studies have noted an association between PmvCO₂ levels and resuscitation outcomes (Niemann et al. 1975). Differences between PaCO₂ and PmvCO₂ (Pv-aCO₂) may also be associated with prognosis, and thus may also serve as a useful tool during and after resuscitation (Ospina-Tascon et al. 2015).

**Peripheral venous CO₂**

Peripheral blood sampling is a simple procedure and is the common practice in most departments of emergency medicine (Kelly 2016). As such, PmvCO₂ may be more useful clinically as an index of resuscitation efficacy than PaCO₂. Several studies have also noted substantial correlation between PmvCO₂ and PaCO₂ (Adrogué et al. 1989; Bloom et al. 2014; Byrne et al. 2014; Kelly 2010; Spindelboeck et al. 2016). However, PmvCO₂ may be confounded by the location of sampling as there may be relative ischaemia of the tissue being drained by the sampled vein. Therefore PmvCO₂ may not accurately reflect global tissue perfusion (Adrogué et al. 1989; Bloom et al. 2014; Byrne et al. 2014; Kelly 2010; Toftgaard et al. 2008). Unfortunately few data are available on the association between PmvCO₂ and other measures of CO₂ during resuscitation, nor between PmvCO₂ and resuscitation outcomes.

**Conclusion**

In conclusion, measurements of CO₂ during and after resuscitation, including PetCO₂, PaCO₂ and PmvCO₂, may serve to assess resuscitation efficacy. Such measurements may therefore be useful adjuncts in clinical decision-making during resuscitation as they have been shown to correlate overall with patient prognosis. Given that PmvCO₂ is rarely available during resuscitation, research is needed regarding the usefulness of substituting PvCO₂ for PmvCO₂. More research is needed into effective interventions towards modifying PCO₂ indices during resuscitation and their possible effects on outcomes.

**Conflict of Interest**

None.

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**References**


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