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Frederic S Zimmerman
Department of Intensive Care
Barzilai Medical Center
Ashkelon, Israel

shmuelz@bmc.gov.il

Gal Pachys
Department of Emergency Medicine
Shamir Medical Center (Assaf Harofeh)
Zerifin, Israel

gal.pachys@gmail.com

Evan Avraham Alpert
Emergency Department
Shaare Zedek Medical Center
Jerusalem, Israel

alperta@szmc.org.il

Sharon Einav
Intensive Care Unit
Shaare Zedek Medical Center and Hebrew University Faculty of Medicine
Jerusalem, Israel

einav_s@szmc.org.il

Understanding Carbon Dioxide in Resuscitation

Peri-arrest CO_2 measurement may serve to assess resuscitation efficacy and guide clinical decisions. This paper reviews current knowledge and future research directions for CO_2 measurement and clinical application during CPR.

Sudden cardiac death (SCD) necessitating cardiopulmonary resuscitation (CPR) is a substantial driver of morbidity and mortality. In the United States, approximately 450,000 deaths annually are associated with SCD and CPR, with 400,000 such deaths annually in the European Union (Atwood et al. 2005; Callans 2004). Current guidelines call for the use of carbon dioxide (CO_2) measurement to guide resuscitative efforts (Link et al. 2015; Soar et al. 2021). This paper reviews current knowledge and directions of future research for measurement and clinical application of CO_2 during CPR.

Carbon Dioxide During Normal Heart-Lung Function

CO_2 is produced by the mitochondria as a major end product of tissue aerobic respiration. Approximately 70% of CO_2 produced by the mitochondria undergoes a chemical reaction with water catalysed by carbonic anhydrase to form H_2CO_3, dissolved in the plasma as its component ions, HCO_3- and H^+. Another 23% of CO_2 produced by the mitochondria binds to haemoglobin to form carbaminohaemoglobin. The remaining 7% is dissolved directly in the plasma. CO_2 is highly soluble in the blood and therefore has a high diffusion coefficient. The dissolved CO_2 is transported to the lung, thus maintaining the mixed venous partial pressure of CO_2 ($PmvCO_2$) – 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 CO_2 in the alveoli ($PACO_2$) at approximately 40 mmHg, thus maintaining a CO_2 diffusion gradient between the pulmonary capillaries and alveoli of 5 mmHg. The high diffusion coefficient of CO_2 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 CO_2 ($PaCO_2$) which approximates the $PACO_2$ – about 40 mmHg.

As direct measurement of $PACO_2$ is complex, $PACO_2$ is usually evaluated indirectly via the end-tidal CO_2 ($PetCO_2$). In patients with normal heart and lung function, the $PetCO_2$ is usually less than 5 mmHg below the $PACO_2$. Thus, in the healthy patient, the $PetCO_2$ is also less than 5 mmHg below the $PaCO_2$ (Hall 2016).

Carbon Dioxide During Decreased Cardiac Output and the No-Flow State

Changes in cardiac output result in substantial changes in arterial and venous CO_2 levels, as well as in the alveolar CO_2.

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 CO_2, 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, CO_2 transport to the lungs is reduced, decreasing CO_2 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 CO_2 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 $PmvCO_2$ – reflecting poor systemic perfusion. It also leads to a decoupling of the $PetCO_2$ and the $PaCO_2$, 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 CO_2 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 CO_2 at various points in the systemic and pulmonary circulation, as well as measurement of alveolar CO_2 as reflected by $PetCO_2$, may be useful for optimising CPR performance, as well as for prognosticating CPR outcomes. Thus, a detailed understanding of CO_2 changes in various compartments is important in assessing and optimising the quality of an ongoing resuscitation.

End-tidal CO_2

When cardiac output is 5 litres per minute, as in the healthy, sedentary adult, the $PetCO_2$ ranges between 36-40 mmHg. For every one litre decrease in cardiac output, this value decreases by 4-6 mmHg, assuming constant ventilatory conditions (Askrog 1966; Leigh et al. 1961; Maslow et al. 2001; Shibutani et al. 1994). Under constant and optimal ventilation conditions, the $PetCO_2$ 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 $PetCO_2$ values and resuscitation outcomes demonstrated that patients eventually achieving return of spontaneous circulation (ROSC) had a mean $PetCO_2$ of 25.8 ± 9.8 mmHg versus a mean $PetCO_2$ 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 $PetCO_2$ changes (Hartmann et al. 2015).

> **a detailed understanding of CO_2 changes in various compartments is important in assessing and optimising the quality of an ongoing resuscitation**

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 CO_2

Arterial CO_2 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 CO_2 (Angelos et al. 1992; Grundler 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). $PaCO_2$ 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, $PaCO_2$ during resuscitation may be a marker of ischaemia severity (Kim et al. 2016). Similarly, less acidosis and lower $PaCO_2$ 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 CO_2 difference ($AaDCO_2$) has also been associated with resuscitation failure. A multicentre study examining $AaDCO_2$ *during or immediately post-CPR* in OHCA showed an association between increased AaDC and failure to achieve sustained ROSC. No patients with an $AaDCO_2$ greater than 33.5 mmHg *during* CPR achieved sustained ROSC (Spindelboeck et al. 2016). Similar findings were noted in those with an elevated $AaDCO_2$ *an hour after ROSC* (Moon et al. 2007).

In contrast, in *post-OHCA patients* hospitalised in an ICU, lower levels of $PaCO_2$ were associated with poorer prognosis (Helmerhorst et al. 2015; Schneider et al. 2013), and, in such patients, a relatively increased CO_2 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 $PaCO_2$ during and immediately post-resuscitation appears to be associated with a poorer prognosis; whereas, in the later post-resuscitation period, a lower $PaCO_2$ is associated with a poorer prognosis.

Pulmonary artery/mixed venous CO_2

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; Marik 2013; Rajaram et al. 2013; Richard et al. 2003) and is generally not possible nor recommended during CPR. Thus, $PmvCO_2$ is generally not available during resuscitation.

In non-cardiac arrest hypoperfusion states (e.g. septic shock), $Pv\text{-}aCO_2$ 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 $PaCO_2$ and $PmvCO_2$ during CPR due to OHCA (Nowak et al. 1987; Steedman and Robertson 1992). Indeed, $PmvCO_2$ may differ substantially from $PaCO_2$, 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 $PmvCO_2$ may more accurately reflect tissue perfusion it may be a better clinical decision tool than $PaCO_2$ *during resuscitation* (Adrogue et al. 1989; Nowak et al. 1987; Steedman and Robertson 1992; Weil et al. 1986).

> **measurements of CO_2 during and after resuscitation may serve to assess resuscitation efficacy**

Indeed, multiple studies have noted an association between $PmvCO_2$ levels and resuscitation outcomes (Niemann et al. 1985; von Planta et al. 1991; Yakaitis et al. 1975). Differences between $PaCO_2$ and $PmvCO_2$ ($Pv\text{-}aCO_2$) 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 CO_2

Peripheral blood sampling is a simple procedure and is the common practice in most departments of emergency medicine (Kelly 2016). As such, $PvCO_2$ may be more useful clinically as an index of resuscitation efficacy than $PmvCO_2$. Several studies have also noted substantial correlation between $PmvCO_2$ and $PvCO_2$ (Abdelmoneim et al. 1999; Byrne et al. 2014). However, $PvCO_2$ may be confounded by the location of sampling as there may be relative ischaemia of the tissue being drained by the sampled vein. Therefore $PvCO_2$ may not accurately reflect global tissue perfusion (Abdelmoneim et al. 1999; Bloom et al. 2014; Byrne et al. 2014; Kelly 2010; Toftegaard et al. 2008). Unfortunately few data are available on the association between $PvCO_2$ and other measures of CO_2 during resuscitation, nor between $PvCO_2$ and resuscitation outcomes.

Conclusion

In conclusion, measurements of CO_2 during and after resuscitation, including $PetCO_2$, $PaCO_2$ and $PmvCO_2$, 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 $PmvCO_2$ is rarely available during resuscitation, research is needed regarding the usefulness of substituting $PvCO_2$ for $PmvCO_2$. More research is needed into effective interventions towards modifying PCO_2 indices during resuscitation and their possible effects on outcomes.

Conflict of Interest

None. ■

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