Regional capnometry to evaluate the adequacy of tissue perfusion

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Tissue hypoperfusion is a major cause of morbidity and mortality in critically ill patients but cannot always be detected by measuring standard whole-body hemodynamic and oxygen-related parameters (e.g., blood pressure, cardiac output, and central venous oxygen saturation). Preclinical and clinical studies have demonstrated that low-flow states are consistently associated with large increases in venous and tissue PCO₂. Monitoring regional PCO₂ with gastric tonometry (PgCO₂) is known to have independent prognostic value for predicting postoperative complications and mortality. The PgCO₂ gap might also be of value as a treatment target (endpoint) in critically ill patients. However, this tool has several limitations and has not yet been developed commercially, thus restricting its use. Regional capnography with sublingual and transcutaneous sensors might be an alternative noninvasive option for evaluating the adequacy of tissue perfusion in critically ill patients. However, further studies are needed to determine whether or not this monitoring technique is of value—particularly as an endpoint for guiding resuscitation. Bladder PCO₂ has only been evaluated in animal studies, and so remains to be validated in patients.

Keywords: Regional capnography; anaerobic metabolism; hypoperfusion

Introduction

In clinical practice, it is difficult to find relevant hemodynamic and oxygenation parameters that can serve as titration endpoints for hemodynamic interventions. In patients with shock or having undergone major surgery associated with high incidence of postoperative complications, the accepted goal for hemodynamic optimization is to increase O₂ delivery (DO₂) and thus O₂ consumption (VO₂) (1). However, recent studies have failed to confirm that hemodynamic optimization reduces morbidity and mortality (2-4). Even when macrocirculatory targets are met, microcirculatory disturbances can persist and lead to organ dysfunction (5). Hence, improved hemodynamic management might only be achieved by detecting VO₂’s responsiveness to an increase in DO₂ (i.e., in patients with anaerobic metabolism) (6). To date, several variables have been described as markers of tissue perfusion: oxygen venous saturation (SvO₂) (7), the veno-arterial PCO₂ gradient (PCO₂ gap) (8), the arterial lactate level, and the ratio of the veno-arterial PCO₂ gradient to the arteriovenous content difference in O₂ (i.e., the PCO₂ gap/DavO₂ ratio) (9-12). Although these variables have been studied in intensive care units (ICUs) and operating theaters, they do have some limitations (described in other chapter of this publication). Moreover, these conventional variables are markers of systemic hypoperfusion, and so are not able to detect regional hypoperfusion (5).

In the 1990s, Nakagawa et al. and Tang et al. suggested that an increase in tissue PCO₂ (“stagnant hypercapnia”) was a marker of inadequate tissue perfusion (13,14). Indeed, the difference between regional tissue PCO₂ and PaCO₂...
The tissue-arterial PCO₂ gap is an earlier, more accurate marker of regional tissue hypoperfusion than whole-body parameters are (15,16). This concept has been validated in many animal models and clinical studies (13,17-20). From a physiological point of view, an increase in tissue PCO₂ results from two mechanisms that must both be present to produce “stagnant hypercapnia”. Firstly, an increase in tissue CO₂ which can result from rises in aerobic metabolism with greater CO₂ generation by the cells or results from tissue hypoxia with an increase in anaerobic glycolysis and excessive production of lactic acid (17). Secondly, the maintenance of blood flow easily removes CO₂ into the venous circulation via the “washout phenomenon” (21). Thus, stagnant hypercapnia can occur only when blood flow is abnormally low. These findings have been confirmed by some clinical studies (18,24,25)—most notably by Vallet et al.’s study of limb-PCO₂ gap (26). These researchers demonstrated that the PCO₂ gap increased when the DO₂ fell after a reduction in blood flow (ischemic hypoxia) but not when DO₂ fell with maintenance of blood flow (hypoxic hypoxia). These results have been confirmed in animal studies of the tissue-arterial PCO₂ gap (19,20); the latter increased during ischemic hypoxia but not during non-ischemic hypoxia.

Hence, these findings suggest that the tissue-arterial PCO₂ gap is a marker of tissue hypoperfusion in general, and not just in cases of hypoxia. The normal reference range for the tissue PCO₂ gap is 8 to 10 mmHg (20,27).

The objectives of the present review were to describe the sites at which regional PCO₂ and tissue-arterial PCO₂ gap have been measured (gastric, sublingual, transcutaneous and bladder sites), assess this parameter’s prognostic value, and evaluate its utility in goal-directed therapy.

**Gastric intramucosal PCO₂ (PgCO₂)**

The tonometric measurement of regional CO₂ pressures is based on equilibration of a gas’s partial pressure between two compartments separated by a semi-permeable membrane. Using air or saline as an equilibration medium enables the gas analyzer to automatically measure the PCO₂ at a balloon located at the end of a gastric tube (Figure 2). The PCO₂ in the collected air is measured using infrared spectrometry. The stomach is easy to access, and is known to be highly sensitive to tissue hypoperfusion (28). Furthermore, PgCO₂ measurements have been used to detect early splanchnic ischemia (29).

In the event of tissue hypoxia and low VO₂, CO₂ production by the gastric mucosa increases. Thus, it has been suggested that PgCO₂ is a marker of tissue hypoxia (30) and can predict morbidity and mortality in critically ill patients (31). However, as mentioned in the introduction, the PgCO₂ − PaCO₂ gradient (PgCO₂ gap) might be more valuable because it reflects the adequacy
of gastric mucosal blood flow. In critically ill patients, the \( \text{PgCO}_2 \) gap values measured on admission to the ICU and 24 h later constituted an independent prognostic factor for 28-day mortality, with a cut-off of >20 mmHg (16). In a perioperative setting, this index was predictive of postoperative complications (27,32).

When used as a prognostic tool in critically ill patients, the \( \text{PgCO}_2 \) gap decreases upon fluid challenge. The change is related to the baseline \( \text{PgCO}_2 \): \( \text{PCO}_2 \) gap responders were defined by a decrease of more than 3 mmHg. Even more interestingly, whole-body indexes of oxygenation (\( \text{SvO}_2 \), \( \text{VO}_2 \) and \( \text{PCO}_2 \) gap) remained unchanged after fluid challenge, when the \( \text{PgCO}_2 \) gap decreased (33).

The main limitations of this method are the need for concomitant \( \text{H}_2 \)-blocker use and the discontinuation of enteral feeding (34). Moreover, this type of device has not been developed commercially, thus limiting its availability.

Esophageal tonometry has been proposed as a convenient alternative to gastric tonometry in animal models of shock (35,36). Good inter-variable correlations were found at this measurement site. However, this site is more difficult to access, which explains its scarce use in clinical practice.

**Sublingual PCO\(_2\) (PsICO\(_2\))**

The most intensively developed and well-studied sublingual \( \text{CO}_2 \) sensor is the CapnoProbe\(^\circledR\) \( \text{CO}_2 \)-sensing optode (Nellcor, Pleasanton, CA, USA) (31,37-40). The optode contains a \( \text{CO}_2 \)-sensing fluorescent dye that is excited by light conducted through an optical fiber. The emitted fluorescence is then transmitted back to the instrument (Figure 3) (31).

Interest in the sublingual region has been stimulated by orthogonal polarization spectral imaging studies that have evidenced a decrease in sublingual capillary density in the event of septic shock (41,42). A study performed in the 1980s found that PsICO\(_2\) was elevated in a model of hemorrhagic shock (43). In animal studies of hemorrhagic and septic shock, sublingual \( \text{CO}_2 \) measurements are well correlated with \( \text{PgCO}_2 \) and whole-body markers of tissue hypoperfusion (13,43,44). The main advantages of this technique relate to its noninvasive nature, the absence of a requirement for withdrawing enteral feeding, and the correlation with the splanchnic region.

The basal value of PsICO\(_2\) was found to be predictive of mortality in acute circulatory failure and was associated with arterial lactate levels. When PsICO\(_2\) exceeded a threshold of 70 mmHg, its positive predictive value was excellent. Conversely, PsICO\(_2\) fell more quickly than arterial lactate during resuscitation (45).

However, the most interesting marker appears to be the PsICO\(_2\) – \( \text{PaCO}_2 \) gradient (the PsICO\(_2\) gap). It is reportedly a better prognostic factor than whole-body markers (\( \text{SvO}_2 \), cardiac index, \( \text{DO}_2 \), and arterial lactate), and the best cut-off value was 25 mmHg (15). The PsICO\(_2\) gap may serve as an index of tissue dysoxia and the severity of tissue
hypoperfusion in critically ill patients (38,39).

With regard to the PsICO\textsubscript{2} gap’s potential as a treatment target (endpoint), it has been showed that the reperfusion of the damaged sublingual microcirculation (assessing using orthogonal polarization spectral imaging) was associated with the normalization of the PsICO\textsubscript{2} gap during the resuscitation of patients with septic shock (37). However, the PsICO\textsubscript{2} gap’s potential value as an endpoint during resuscitation has not yet been evaluated in critically ill patients. Although, this technique has been tested at the bedside, the CapnoProbe\textsuperscript{®} is no longer commercially available.

**Transcutaneous PCO\textsubscript{2} (PcICO\textsubscript{2})**

Transcutaneous measurement of tissue CO\textsubscript{2} is a simple, noninvasive technique. Interest in this method has been stimulated by studies of capnometry at the earlobe (46). The system includes a Severinghaus heated PCO\textsubscript{2} electrode and a pulse oximetry sensor clipped to the earlobe (TOSCA\textsuperscript{®} 500 monitor, Linde Medical Sensors, Basel, Switzerland). In a study of patients in the ICU, the transcutaneous PCO\textsubscript{2} (PcICO\textsubscript{2}) was well correlated with PaCO\textsubscript{2} (47-49). Other devices based on the same technology (SenTec AG, Basel, Switzerland) have yielded the same accuracy (50). However, a recent study found that measurement repeatability was poor (51).

Another study focused on the gradient between PcICO\textsubscript{2} and PaCO\textsubscript{2} (the PcICO\textsubscript{2} gap) (52). The baseline PcICO\textsubscript{2} gap levels were significantly higher in patients with septic shock, and the decrease after resuscitation was significantly greater in survivors than in non-survivors. Interestingly, survivors and non-survivors did not differ with regard to the change over time in whole-body parameters (cardiac output and ScVO\textsubscript{2}). A PcICO\textsubscript{2} gap above 16 mmHg on day one was associated with a poor outcome. Interestingly, the variations in the PcICO\textsubscript{2} gap during fluid challenge were inversely correlated with changes in microcirculatory skin blood flow.

Even though a large number of studies have investigated transcutaneous PCO\textsubscript{2} in the field of neonatology, a Cochrane Collaboration review concluded that there was no evidence to recommend the use of transcutaneous CO\textsubscript{2} monitoring in neonates (53).

In critically ill patients, the PcICO\textsubscript{2} gap might be of value as an additional resuscitation endpoint when other parameters (e.g., arterial lactate and ScVO\textsubscript{2}) are in the normal range despite persistent tissue hypoperfusion (54). However, well-designed, adequately powered, randomized, controlled studies of the efficacy and safety of transcutaneous CO\textsubscript{2} monitoring are now required.

**Bladder PCO\textsubscript{2} (PbICO\textsubscript{2})**

The results of several animal studies have suggested that monitoring the intramucosal CO\textsubscript{2} in the bladder (PbICO\textsubscript{2}) may be a minimally invasive technique for monitoring perfusion (55-57). This technique measures PbICO\textsubscript{2} via the gas analysis of saline samples collected from the balloon of a Foley catheter inserted into the bladder. The PbICO\textsubscript{2} value is well correlated with DO\textsubscript{2} and PgICO\textsubscript{2} (55,56). However, these results were not confirmed by another group of researchers (57). Clinical studies of the accuracy of this device are required.

**Conclusions**

Conventional whole-body hemodynamic markers cannot always predict tissue hypoperfusion. By analogy with measurement of the whole-body PCO\textsubscript{2} gap, the tissue PCO\textsubscript{2} gap has been described as a marker of blood flow adequacy and can be used to detect tissue hypoperfusion. Monitoring PgICO\textsubscript{2} gap has given good results, although several technical limitations and failure to develop this tool commercially has prevented the wider use of this technique. Further studies are needed to assess the efficacy and safety of PsICO\textsubscript{2} gap and PcICO\textsubscript{2} measurements. Although measurement in the bladder are promising, PbICO\textsubscript{2} must be now studied in patients. Lastly, the blood flow distribution across the various organs cannot yet be assessed.

**Acknowledgments**

None.

**Footnote**

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Bar S, Fischer MO. Regional capnometry to evaluate the adequacy of tissue perfusion. J Thorac Dis 2019;11(Suppl 11):S1568-S1573. doi: 10.21037/jtd.2019.01.80