Regional carbon dioxide monitoring to assess the adequacy of tissue perfusion

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Purpose of review

Tissue dysoxia is now widely regarded as the major factor leading to organ dysfunction in critically ill patients. Recent data suggests that early aggressive resuscitation of critically ill patients, which limits and/or reverses tissue dysoxia may prevent progression to organ dysfunction and improve outcome. The traditional clinical and laboratory markers used to assess tissue dysoxia are, however, insensitive and have numerous limitations. Regional carbon dioxide monitoring appears to be ideally suited to monitoring the adequacy of resuscitation. This review provides an update on this evolving technology.

Recent findings

Gastric intramucosal carbon dioxide as measured by gastric tonometry has proven to be useful as a prognostic marker, in evaluating the response to specific therapeutic interventions and as an end point of resuscitation. Gastric tonometry is, however, cumbersome and has a number of limitations that may have prevented its widespread adoption. The measurement of carbon dioxide in the sublingual mucosa by sublingual capnometry is technically simple, noninvasive, and provides near instantaneous information. Clinical studies have demonstrated a good correlation between gastric intramucosal carbon dioxide and sublingual mucosa carbon dioxide. Sublingual mucosa carbon dioxide responds more rapidly to therapeutic interventions than does gastric intramucosal carbon dioxide and may be a better prognostic marker.

Summary

Sublingual capnometry may be the ideal technology for guiding early goal directed therapy. This technology may be useful for monitoring tissue oxygenation, titrating therapeutic interventions, and as an end point for resuscitation in critically ill and injured patients.

Keywords

critical care, gastric tonometry, sepsis, shock, sublingual capnometry, tissue carbon dioxide, tissue oxygenation

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Introduction

Despite improvements in resuscitation and supportive care, progressive organ dysfunction occurs in a large proportion of patients with acute, life-threatening illnesses. It has been proposed that the multi-organ dysfunction syndrome (MODS) of the critically ill is a consequence of tissue dysoxia due to inadequate oxygen delivery, often exacerbated by microcirculatory changes and increased tissue metabolic demands [1,2]. This may be further complicated by cytopathic hypoxia due to mitochondrial dysfunction [3,4]. A number of different but mutually compatible mechanisms might foster the development of cytopathic hypoxia. These mechanisms include the diminished delivery of pyruvate into the mitochondrial tricarboxylic acid (TCA) cycle, the inhibition of key mitochondrial enzymes that are involved in either the TCA cycle or the electron transport chain, and the activation of the enzyme poly(ADP-ribose) polymerase (PARP-1) [3–5].

In patients with sepsis tissue dysoxia may be an early finding. Experimental data suggests that tissue dysoxia occurring in the early phase of sepsis is predominantly due to decreased oxygen delivery, however, with time cytopathic hypoxia may play an increasing role [6]. Emerging data suggests that early aggressive resuscitation of critically ill patients may limit and/or reverse tissue dysoxia, progression to organ, and improve outcome. In a landmark study, Rivers *et al.* [7] demonstrated that a protocol of early goal directed therapy, reduces organ failure and improves survival. Similarly, Levy *et al.* [8] have demonstrated that the early (within 24 hours) reversal of shock, renal and respiratory failure was associated with improved survival in patients with sepsis. Nguyen *et al.* [9] have shown that the rate of clearance of lactate within 6 hours of presentation to the emergency room was predictive of outcome. Likewise, data from the ENHANCE study demonstrated that if activated protein C (Drotrecogin alpha-activated) is administered within 24 hours in patients with severe sepsis the mortality was 33% compared with 52% if the drug was administered after the second hospital day ($P = 0.015$) [10]. These clinical studies suggest that early aggressive resuscitation that restores oxygen delivery and microcirculatory flow may limit tissue dysoxia, organ dysfunction, and ultimately patient outcome. This suggests that the end points of resuscitation should be indices of tissue oxygenation. However, the traditional clinical and laboratory markers used to assess tissue dysoxia are insensitive and have numerous limitations. Regional carbon dioxide (CO_2) monitoring appears to be an evolving technology

ideally suited to monitoring the adequacy of tissue oxygenation in the critically ill patient.

Assessing the adequacy of resuscitation

The assessment of intravascular volume and the adequacy of volume resuscitation are amongst the most difficult clinical challenges. Systolic blood pressure, heart rate, and urine output change minimally in early shock. Furthermore, these variables provide little information as to the adequacy of tissue perfusion. Hypotension, tachycardia, cold extremities, decreased urine output, and poor capillary refill are only present in patients who have lost in excess of 30% of their blood volume (class III hemorrhage) [11]. The central venous pressure (CVP) and the changes in the CVP in response to volume loading are poor indicators of intravascular volume and recruitable cardiac index [12,13••]. In the study by Rivers *et al.* [7], the central venous oxygen saturation ($ScvO_2$) was used as the end point of resuscitation in the intervention group, while in the control group treatment was guided by standard clinical end points including the CVP. While this study clearly demonstrates the value of early aggressive volume resuscitation, and while $ScvO_2$ does correlate quite well with $SmvO_2$, the use of $ScvO_2$ to guide early resuscitation is not practical and has important limitations (see below) [14,15].

While flow to the brain and myocardium are preserved in patients with compensated shock, splanchnic and renal perfusion may be seriously compromised [16]. The gut is highly susceptible to diminished tissue perfusion and oxygenation as it has a higher critical oxygen requirement than the whole body and other vital organs, and the mucosal counter-current microcirculation renders the villi particularly vulnerable to ischemia [17,18]. Splanchnic hypoperfusion leads to both functional and structural changes in the gut mucosa with increased permeability and translocation of bacteria and bacterial products [17]. Increased mucosal permeability has been strongly associated with the development of the multi-organ dysfunction syndrome [17,19].

Global indices of tissue dysoxia

While commonly measured in critically ill patients, blood lactate is an insensitive marker of tissue dysoxia [20–22]. If glycolysis occurs at a more rapid rate than is necessary for oxidative metabolism, some pyruvate may not be oxidatively metabolized in the Krebs cycle and will be converted to lactate. The result will be a concomitant increase in both pyruvate and lactate with an unchanged lactate/pyruvate ratio (L/P) [23]. Gore and co-workers measured lactate and pyruvate concentrations and the rates of pyruvate production and oxidation prior to and after dichloroacetate (DCA) administration in septic patients with severe lactic acidosis [5]. The patients in this report had significantly elevated levels of glucose, lactate, and pyruvate (normal L/P ratio), with an increase in oxygen consumption and a significant decrease in glucose, lactate, and pyruvate (unchanged L/P ratio) after the administration of DCA.

It was concluded from this study that accumulation of lactate during sepsis was due to a markedly increased rate of pyruvate production. Furthermore, the arterial blood lactate level depends upon the rate of production as well as the rate of metabolism by the liver (Cori cycle). Due to decreased splanchnic blood flow and hepatocellular dysfunction, lactate removal may be impaired in critically ill patients.

Mixed venous oxygen suturation ($SmvO_2$) measured in either the pulmonary artery (with a pulmonary artery catheter) or the right atrium (with a central venous catheter) has been used to monitor critically ill patients and their response to therapeutic interventions [7,15,24–26]. However, the $SmvO_2$ has been demonstrated to correlate poorly with cardiac index and indices of tissue dysoxia, particularly in patients with sepsis [21,27]. Patients with sepsis and liver disease may have a high $S_{MV}O_2$ despite evidence of poor tissue perfusion [28,29]. This may be a consequence of the microcapillary shunting and/or the inability of the tissues to use oxygen (cytopathic hypoxia) [1,3,4,30].

Tissue CO_2 monitoring as an index of regional tissue oxygenation

The development of tissue dysoxia in the gastrointestinal tract appears to be a common and early finding in patients with deranged hemodynamics. Dantzker [31] has suggested that the gastrointestinal tract may be the 'canary of the body', with gastrointestinal dysoxia an 'early warning of impending trouble.' Because direct gastrointestinal oxygen uptake and delivery are difficult to assess in patients, indirect techniques have been developed. Gastric tonometry and sublingual capnometry are based on the principle that tissue CO_2 levels rise sharply in conditions associated with poor tissue perfusion [27,28,32–36]. The increased tissue CO_2 (in part) is due to intracellular buffering of excesses of hydrogen ions by bicarbonate. The excesses of hydrogen ions are, in turn, traced to the degeneration of high-energy phosphate compounds during tissue dysoxia. Krebs *et al.* [37] noted that the acidosis that occurs during increased glycolysis caused by inadequate cellular oxygen delivery is produced by ATP that is continually being hydrolyzed.

The interpretation of tissue pCO_2, is however, relatively complex and determined by three variables, namely; the arterial CO_2 content ($CaCO_2$), regional blood flow, and tissue CO_2 production (aerobic or anaerobic). In stable respiratory conditions when $CaCO_2$ is constant, tissue CO_2 essentially reflects the balance between tissue blood flow

and local CO_2 production. CO_2 production occurs in both aerobic and anaerobic conditions. Increases in aerobic metabolism are associated with higher CO_2 production by the cells, which is generally associated with parallel increase in blood flow, so that tissue PCO_2 does not increase (washout phenomenon). When oxygen delivery decreases and reaches a critical value, aerobiosis can no longer be sustained and aerobic production of CO_2 by cells increases.

It has been demonstrated that changes in gastrointestinal mucosal pCO_2 ($PimCO_2$) mirrors changes in gastrointestinal oxygen uptake during progressive flow stagnation and that increases in $PimCO_2$ commence at the approximate onset of oxygen supply dependence [38,39]. Thus during low flow states, anaerobic CO_2 generation represents dysoxia, which can be detected by gut $PimCO_2$ measurement. It has been assumed that the increased tissue CO_2 seen in low flow states was a consequence of the intracellular buffering of excess hydrogen ions by bicarbonate. However, increased $PimCO_2$ may also result from flow stagnation and impaired washout of CO_2 produced aerobically or anaerobically [38,40–42]. Neviere *et al.* [43] reduced systemic oxygen delivery in a stepwise manner beyond critical oxygen delivery by lowering either the FiO_2 (hypoxic hypoxia) or reducing blood volume (ischemic hypoxia) in a pig model. While the ileal-arterial PCO_2 gap increased in both groups, the increase was much more dramatic in the ischemic group, with the pCO_2 only increasing at very low FiO_2 levels (0.08) in the hypoxic group. Furthermore, in the hypoxic group the arterial lactate increased much earlier and to a greater degree than the ileal-arterial pCO_2 gap. This study indicates that the increased tissue CO_2 noted in low flow states is predominantly due to flow stagnation. This suggests that tissue CO_2 monitoring may be useful in low flow states (compensated or uncompensated shock) while lactate levels may be more useful in hypoxic or anemic hypoxia. From a practical point, almost all clinical states of decreased oxygen delivery (tissue hysoxia) result from decreased tissue perfusion and flow stagnation rather than reduced oxygen carrying capacity (which is in itself very easy to diagnose). As such the increased tissue CO_2 which occurs in critically ill patients is likely to be mainly due to flow stagnation with smaller components due anaerobic CO_2 production (due to decreased oxygen delivery and cytopathic hypoxia).

Gastric tonometry

Tonometry is simply a method used to equilibrate gas tension between two compartments. Either gas (e.g., air) or fluid (e.g., normal saline) can be used as the solvent for equilibration of the gas in question (i.e., carbon dioxide). A gastric tonometer is a standard nasogastric tube with a silicone balloon at its distal end. With conventional saline tonometry, the balloon of the tonometer is filled with normal saline and allowed to equilibrate (ideally for 90 minutes). Once equilibrated, the balloon is aspirated and the pCO_2 of the fluid determined using a standard blood gas analyzer. Air tonometry, particularly in conjunction with an automated system has a number of advantages when compared with conventional saline tonometry. Unlike saline tonometry, in-vitro studies have demonstrated that air tonometry has a very low bias with excellent precision [44–46]. Furthermore, automated air tonometry has an equilibration time of less than 20 minutes and being fully automated may eliminate potential sources of error associated with saline tonometry.

Monitoring of gastric intramucosal ph (pHi) was initially used to assess splanchnic dysoxia. However the calculation of the pHi involves a number of assumptions (serum HCO_3^- equal to splanchnic HCO_3^-) that may be incorrect. Consequently, the PCO_2 gap, defined as the difference between the gastric mucosal PCO_2 ($PgCO_2$) and the arterial PCO_2 may more specifically reflect the adequacy of gastric mucosal blood flow, and is not influenced by systemic acid-base status [47].

Gastric intramucosal acidosis (pHi) and intramucosal hypercarbia (PCO_2 gap) have been demonstrated to be a marker of gastric mucosal dysoxia and a predictor of morbidity and mortality in critically ill patients [22,33,39,47–55]. Levy *et al.* [56] measured gastric mucosal PCO_2 (by automated air-tonometry) in 95 consecutive critically ill patients on admission to the ICU and at 24 hours. By univariate analysis the pHi was significantly higher on admission and at 24 hours in the survivors as compared with the non-survivors. By multivariate analysis the organ failure score and the PCO_2 gap at 24 hours were independent predictors of outcome. The 28-day survival was 75% in patients with a PCO_2 gap of less than 20 mm Hg at 24 hours compared with a 28-day survival of 40% in those patients with a PCO_2 gap of greater than 20 mm Hg at 24 hours. This study supports the observation that the failure to improve organ function and tissue perfusion within 24 hours of admission to the ICU is associated with a poor outcome.

Gutierrez *et al.* [54] randomized critically ill ICU patients to a standard treatment group or a protocol group in which treatment was titrated to maintain the gastric intramucosal pH (pHi) greater than 7.35. Survival was significantly improved in the protocol sub-group whose initial pHi was greater than 7.35. This study provides further support to the argument that the early detection and treatment of tissue dysoxia may improve the outcome of critically ill patients. Once the 'golden hours' of resuscitation have lapsed and progressive tissue dysoxia has developed measures that improve tissue dysoxia are unlikely to improve outcome.

Silva *et al.* [57] reported the changes in systemic hemodynamics variables and PCO_2 gap in septic patients following

a fluid challenge. While the fluid challenge was associated with an increase in cardiac index, global measures of tissue oxygenation ($SmvO_2$ and oxygen consumption) were unchanged; there was, however, a significant fall in the PCO_2 gap. Furthermore, neither the baseline hemodynamic variables nor the change in cardiac index were related to the change in the change in the PCO_2 gap. The change in the PCO_2 gap was, however, highly associated with the baseline PCO_2 gap. These results provide further support that regional indices of tissue oxygenation (PCO_2 gap in this case) rather than global parameters should be used when initiating and titrating resuscitative measures in the critically ill.

The base excess (BE) has become the standard end point of resuscitation in trauma patients. Remarkably, while the BE has been demonstrated to be of prognostic value, it has never been assessed prospectively in trauma patients [58–64]. The use of the BE is based on the principle that tissue hypoxia associated with poor perfusion will result in the generation of hydrogen ions and a metabolic acidosis. However, it is likely that tissue hypoperfusion may occur in the absence of a significant change in the BE. Furthermore, as it requires time for the liver and kidney to regenerate bicarbonate [65], it can be expected that there will be a long lag phase between the correction of intravascular volume and normalization of the BE. In a rat hemorrhage model, Totapally *et al.* [66] demonstrated that the BE responded slowly to changes in intravascular volume and that there was a significant increase in the BE only when the mean arterial blood pressure fell by greater than 50%, however, changes in the esophageal CO_2-gap closely mirrored changes in intravascular volume.

Kirton *et al.* have demonstrated that gastric intramucosal pH (pHi) correlates well with the degree of injury and that optimizing the pHi in the first 24 hours following trauma is associated with a reduction in the incidence of organ failure and death [67,68].

Ivatury *et al.* [53] randomized trauma patients to a protocol in which global (oxygen delivery index) or regional (gastric tonometry) indexes were used as the end points of resuscitation. Of the 44 patients with a pHi greater than 7.3 at 24 hours only 3 died (6.8%) as compared with 7 of 13 (53.9%) in whom the pHi was not optimized. This study is in keeping with the sepsis studies cited above, which suggest that the early correction of tissue hypoperfusion may improve outcome.

Gastric tonometry has been shown to be useful in titrating vasopressor support and determining which vasopressor agent or vasoactive drug combination improves gastric perfusion in critically ill patients. Several studies have demonstrated that dobutamine, dobutamine/norepinephrine combination, norepinephrine alone, or dopexamine will increase gastric pHi or decrease PCO_2 gap compared with other agents or placebo in patients with sepsis or septic shock or high-risk surgical patients [69–74]. Paradoxically dopamine may cause gastric mucosal ischemia [69,70,75]. In a porcine shock model, treatment with low-dose dopamine hastened the development of gut ischemia [76]. It is postulated that dopamine causes precapillary vasoconstriction with diversion of blood flow away from the gut mucosa. 'Low dose' vasopressin has recently become popular in the management of septic shock. It has been suggested that sepsis is a vasopressin deficient state and that low doses of vasopressin may restore vascular tone without causing splanchnic ischemia [77–79]. However, van Haren *et al.* [80] have demonstrated that in norepinephrine dependent patients in septic shock, continuous infusions of low-dose vasopressin result in a significant increase in the PCO_2 gap compatible with splanchnic hypoperfusion.

In addition to the indications cited above, gastric tonometry has been demonstrated to be useful in predicting weaning outcome from mechanical ventilation [81–84]. These studies have demonstrated that patients who could not be weaned from mechanical ventilation or failed extubation had a significant fall in pHi during the weaning trial and/or a lower baseline pHi. It was postulated that the increased work of breathing during the weaning trial caused blood flow to be diverted away from the gut leading to splanchnic ischemia. Bocquillon *et al.* [81] demonstrated an increase in cardiac index and a decrease in gastric mucosal blood flow in patients who failed weaning. In this study the fall in the pHi was associated with an increase in arterial CO_2 rather than an increase in the gastric intramucosal-arterial PCO_2 gap.

Sublingual capnometry

While air tonometry has simplified the measurement process (over saline tonometry) and eliminated the possible errors associated with the use of non-buffered saline this technology has a number of limitations [44–46,85,86]. Gastric tonometry is logistically and practically difficult and this may be the main factor that has prevented the widespread use of this technology. Gastric tonometry requires placement of a specialized naso-gastric tube. This precludes its use in pediatric patients and limits its use as a screening tool in patients who may not require nasogastric intubation. Equilibration of carbon dioxide between the gastric mucosa and the balloon is time dependent (about 15 minutes with air tonometry) and likely to be slowly responsive to therapeutic interventions. This slow equilibration time limits the use of gastric tonometry in the acute phase of resuscitation. Histamine type-2 blockers (H2-blockers) are routinely required to limit the intraluminal generation of carbon dioxide from gastric acid. Furthermore, enteral nutrition must be stopped at least 2 hours prior to each measurement; this is likely to interfere with the provision of nutritional support.

To overcome the potential limitations of gastric tonometry, Jin *et al.* [87] postulated that the very proximal gastrointestinal tract, namely, the tongue and/or sublingual mucosa, may serve as appropriate site for measurement of tissue PCO_2. Although the tongue receives its blood supply from the internal carotic artery, the tongue may act functionally as part of the 'splanchnic circulation'. Indeed, Weil *et al.* [87] have demonstrated that with decreased perfusion pressure blood flow to the tongue and splanchnic bed fall to a similar degree. These authors have demonstrated an increase in sublingual PCO_2 ($PslCO_2$) that was closely related to decreases in arterial pressure and cardiac index during circulatory shock produced by hemorrhage and sepsis. [35,88–90]. Furthermore, the increase in $PslCO_2$ closely tracked the increase in $PimCO_2$. Similarly, Marik [27] has demonstrated an excellent correlation between the $PimCO_2$ and $PslCO_2$ ($r = 0.78$; $P < 0.001$) in a heterogeneous group of ICU patients. De Backer *et al.* [91] used orthogonal polarization spectral imaging to investigate the sublingual microcirculation in healthy controls and patients with severe sepsis. The proportion of perfused small vessels (< 20 μm) was significantly reduced in patients with sepsis as compared with controls (48% *vs* 90%, $P < 0.001$). In a follow-up study these authors have demonstrated an improvement in the sublingual microcirculation with an increase in perfused vessels density and an increase in the percentage of small perfused vessels with volume and pressor resuscitation [29].

The currently available system for measuring sublingual pCO_2 consists of a disposable pCO_2 sensor (which is placed under the tongue) and a battery-powered handheld instrument (CapnoProbe N80, Nellcor, CA). This technology is based on a carbon dioxide sensing optode containing a fluorescent indicator, which is excited by light conducted through an optical fiber, which then transmits the fluorescent emission back to the instrument.

Marik and Bankov [28] have shown that in critically ill ICU patients, the $PslCO_2$ better differentiates between survivors and non-survivors than lactate or $S_{MV}O_2$ and is more responsive to therapy than either of these markers. These results were confirmed by Creteur *et al.* [29], who, in addition, demonstrated that the $PslCO_2$ correlated well with microvascular perfusion and that it was more responsive to therapy than the $PimCO_2$. In patients with penetrating trauma, Baron *et al.* [92] demonstrated that the $PslCO_2$ correlated well with the degree of blood loss and was a good predictor of outcome.

Conclusion

Sublingual capnometry is a technically simple, noninvasive, inexpensive technology that provides near instantaneous information as to the adequacy of tissue perfusion in critically ill and injured patients. This technology is ideally suited to the emergency room, operating room, and ICU and $PslCO_2$ monitoring may prove to be a useful end point for goal directed resuscitation. The fact that sublingual capnometry does not require premedication with acid suppressive therapy nor discontinuation of enteral feeding is a major advantage over gastric tonometry. The clinical experience with sublingual capnometry is however limited, and additional studies are needed, which demonstrate the clinical utility of $P_{SL}CO_2$ monitoring and further refinements in the technology are required to allow continuous as well as intermittent measurements.

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