Sublingual Capnometry: A Non-invasive Measure of Microcirculatory Dysfunction in Sepsis.

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Abstract

Sepsis is among the most common reason for admission to intensive care units throughout the world. Sepsis is characterized by a generalized microcirculatory injury, which results in tissue dysoxia. Tissue dysoxia is believed to be the causation of multi-organ dysfunction syndrome (MODS) which commonly complicates the course of sepsis. The expedient detection and correction of tissue dysoxia may limit the development of MODS. The standard oxygenation and hemodynamic variables (blood pressure, arterial oxygenation, cardiac output) which are monitored in critically ill patients are "upstream" markers and provide little information as to the adequacy of tissue oxygenation. Global "downstream" markers of tissue dysoxia such as mixed venous oxygen saturation and blood lactate are insensitive indicators of the extent of the microcirculatory injury in patients with sepsis. Sublingual/buccal mucosal PCO_2 is a regional marker of microvascular perfusion and tissue dysoxia that holds great promise for the risk stratification and end-point of goal-directed resuscitation in patients with sepsis.

Key words: tissue oxygenation, sepsis, shock, critical care, tissue carbon dioxide, gastric tonometry, sublingual capnometry, CO_2

Sepsis is among the most common reason for admission to intensive care units (ICUs) throughout the world. Over the last two decades the incidence of sepsis in the United States has trebled and is now the 10th leading case of death [1,2]. Advances in medical technologies, the increasing use of immunosuppressive agents and the aging of the population have contributed to the exponential increase in the incidence of sepsis. In the United States alone, approximately 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal [1,2]. Septic patients are generally hospitalized for extended periods, rarely leaving the ICU before 2 to 3 weeks. Those that die, rarely die directly from the initial infection but rather its ensuing patho-physiological consequences, namely, the sequential dysfunction and failure of several organ-systems [3]. It has been suggested that this syndrome known as "multi-organ dysfunction syndrome" (MODS) is a consequence of tissue dysoxia [4-6].

The pathogenesis of sepsis is exceedingly complex and involves an interaction between multiple microbial and host factors [7]. However, emerging data suggests that microcirculatory dysfunction may be the final common pathway whereby sepsis progresses to organ failure and death. It is postulated that the generalized microcirculatory injury which has now been recognized to occur with severe sepsis, leads to tissue dysoxia, organ dysfunction and ultimately death [8,9]. The microcirculatory injury in sepsis may be further complicated by cytopathic hypoxia due to mitochondrial dysfunction [10-13].

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The microcirculation in sepsis

The recruitment of neutrophils to an area of localized infection is an essential component of the host inflammatory response. In patients with severe sepsis, this process becomes uncontrolled with widespread neutrophil-endothelial activation resulting in a generalized micro-circulatory injury. This is characterized by endothelial damage with edema and separation of cell junctions, increased capillary permeability, capillary narrowing, and interstitial edema [14-17]. In addition, sepsis is characterized by a disturbance of hemostasis with activation of the procoagulant pathways and down-regulation of anticoagulant mechanisms [18]. This imbalance plays a major role in perpetuating the microcirculatory injury. The coagulation system and platelets are activated in the early stages of sepsis, with the development of a coagulopathy and thrombocytopenia [18-20]. This process may progress to disseminated intravascular coagulation, characterized by bleeding and widespread microvascular thromboses. While the bleeding manifestations usually receive the most attention, the microvascular thromboses are pathologically more important and strongly implicated in the development of organ failure in sepsis [21]. Rheologic changes, including impaired red blood cell deformability and increased leukocyte aggregation may further compromise the microcirculation [22].

In a cecal ligation and perforation model in rats, Lam et al and Piper et al demonstrated that sepsis results in a reduction of perfused capillary density, an increase in the intercapillary distance, an increase in stopped-flow capillaries and an increase in the heterogeneity of perfused capillaries [23,24]. Additional studies have demonstrated arteriolar constriction with increased RBC transit time relative to plasma transit time [25,26]. Using orthogonal polarization spectral imaging, De Backer and colleagues have demonstrated that as compared to control, patients with sepsis have a marked reduction in the number of small capillaries that are perfused, and that the microvascular flow improves with time in survivors but not in non-survivors [8,27].

The decreased microcirculatory flow, decreased capillary density, increased diffusion distance due to tissue edema and capillary fallout as well microcirculatory shunting ultimately leads to distributive hypoxia and organ dysfunction. The decreased tissue oxygen availability may be compounded by the development of cytopathic hypoxia. Cytopathic hypoxia is an acquired defect in cellular respiration with decreased ability of the mitochondrion to utilize oxygen and produce energy in the form of ATP [11].

Assessing the adequacy of resuscitation

The clinical assessment of the adequacy of resuscitation and tissue perfusion is amongst the most difficult clinical challenges [28]. Blood pressure, heart rate and urine output change minimally in early shock and are poor indicators of the adequacy of resuscitation [29]. The central venous pressure (CVP) and the change in the CVP in response to volume loading are poor indicators of intravascular volume and recruitable cardiac index [30,31]. While cardiac output and oxygen delivery can be determined by pulmonary artery catheterization or estimated by non-invasive methods, this information is unhelpful as it does not indicate the adequacy of oxygen delivery for any individual patient [28]. In addition, these variables provide little information as to the adequacy of microvascular perfusion. It is evident that a patient's blood pressure, arterial oxygenation, and cardiac output can be "normalized" yet the patient may continue to have a severe compromise of microcirculatory perfusion. The so-called "upstream" markers of resuscitation therefore provide little information as to the adequacy of microcirculatory resuscitation (**Figure 1**) [32]. While the adequacy of resuscitation in the sublingual microcirculatory bed can be measured by orthogonal polarization imaging and sidestream dark field imaging, this technology is not suitable for routine clinical use [8,27].

Tissue hypercarbia: A universal finding of microcirculatory failure

When oxygen delivery is reduced due to acute perfusion failure, oxygen extraction increases, hydrogen ion concentration increases (due to hydrolysis of ATP) and tissue carbon dioxide tension increases [33]. Consequently the venous blood draining poorly perfused tissue has a low oxygen saturation, low pH and high CO_2. These finding were first described by Dr. Weil and colleagues from the coincidental observations of the pH and PCO_2 of mixed venous and arterial blood samples obtained during cardiac arrest which were reversed after resuscitation [34]. A close relationship has subsequently been documented between

the quantitative increase in the tissue CO_2 (or regional veno-arterial PCO_2 difference) and the severity of the perfusion defect of the heart, splanchnic bed, kidney and liver [35-40]. Tissue hypercarbia has therefore emerged as universal phenomena during low flow states such as the circulatory shock associated with cardiac failure, hemorrhage and sepsis.

Global indices of the adequacy of microvascular resuscitation.

Mixed venous PCO_2 ($PmvCO_2$) represents the equilibration of systemic venous CO_2, which has returned to the right side of the heart and as such is a "global" indicator of tissue dysoxia. The major disadvantage of this global measurement is that it lacks sensitivity; high tissue PCO_2 draining a vital organs will be diluted by blood draining from organs with lower metabolic requirements and a lower PCO_2. Silva and colleagues measured global and regional indicators of tissue dysoxia in septic patients undergoing fluid challenge [41]. While the gastric intramucosal PCO_2 gradient decreased significantly with volume resuscitation the mixed venous PCO_2 gradient and mixed venous oxygen saturation ($SmvO_2$) remained unchanged. Maynard and colleagues and Marik reported the gastric intramucosal pH (see below) to be the best oxy-hemodynamic derived parameter in predicting outcome in patients with sepsis [42,43]. In both of these studies, the global oxy-hemodynamic parameters were poor predictors of outcome. Recently, Poeze and colleagues compared global and regional variables after resuscitation in critically ill septic patients [44]. These authors reported that the global indices were adequate for the initial resuscitation of shocked patients. However, after stabilization gastric intramucosal CO_2 was the best predictor of outcome.

While the $PmvCO_2$ would be expected to be a better marker of tissue dysoxia than the $SmvO_2$, mixed venous pH and base excess, these latter variables are commonly used in resuscitation algorithms [45]. 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 in this patient population, it has never been assessed prospectively in trauma patients [46]. 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, it can be expected that there will be a long lag phase between the correction of intravascular volume deficit and normalization of the BE [46].

$SmvO_2$ 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 [45,47-50]. A low $SmvO_2$ (in the absence of arterial hypoxemia) is usually an indicator of inadequate cardiac output. Despite the presence of decreased myocardial contractility, most volume-resuscitated patients with sepsis have a hyperdynamic circulation with a high cardiac output. Furthermore, due to functional microcirculatory shunting and "arterialization" of mixed venous blood, patients with sepsis may have a high $SmvO_2$ despite evidence of tissue dysoxia [51,52]. Consequently the $SmvO_2$ may be an unreliable end-point of resuscitation in patients with sepsis [45,53,54]. Indeed, Marik and Bankov reported a poor correlation between the $SmvO_2$ and sublingual PCO_2 gradient in patients with sepsis [51].

Blood lactate concentration is commonly used as a global "downstream" marker of the tissue perfusion and the adequacy of resuscitation [45]. Blood lactate, however, is an insensitive marker of tissue dysoxia [43,53,55,56]. 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) [57]. 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 [58]. 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. In addition, the 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. James and colleagues provide a compelling argument that a high blood lactate is a metabolic manifestation of high blood epinephrine levels and is a poor indicator of tissue dysoxia [56]. Similarly, Levy and colleagues have elegantly demonstrated that skeletal muscles may be a major source of lactate production during sepsis as a consequence of increased aerobic glycolysis through Na^+K^+ ATPase stimulation [59]. Lactate levels may therefore be a marker of illness severity rather than a measure of anaerobic metabolism.

Regional indices of tissue oxygenation: Gastric tonometry and sublingual capnometry

Due to the flow distribution away for the gastrointestinal tract the development of tissue dysoxia in the gastrointestinal tract appears to be a common and early finding in patients with deranged hemodynamics. Dantzker has suggested that the gastrointestinal tract may be the "canary of the body", with gastrointestinal dysoxia an "early warning of impending trouble" [60]. The PCO_2 of the stomach wall ($PgCO_2$) and sublingual tissue ($PslCO_2$) has been demonstrated to increase predictably during both hemorrhagic and septic shock [51,54,61-68]. It has been demonstrated that changes in gastrointestinal mucosal pCO_2 ($PimCO_2$) mirrors changes in gastrointestinal oxygen uptake during progressive flow stagnation [69,70].

Gastric tonometry

Gastric intramucosal acidosis (pHi) and intramucosal hypercarbia (PCO_2 gap) have been demonstrated to be a predictor of morbidity and mortality in critically ill patients [42,43,65,70-78]. Levy and colleagues measured gastric mucosal PCO_2 (by automated air-tonometry) in 95 consecutive critically ill patients on admission to the ICU and at 24 hours [79]. By univariate analysis the pHi was significantly higher on admission and at 24 hours in the survivors as compared to the non-survivors. By multivariate analysis the organ failure score and the PCO_2 gap at 24 hours were independent predicts of outcome. The 28-day survival was 75% in patients with a PCO_2 gap of less than 20 mmHg at 24 hours compared to a 28-day survival of 40% in those patients with a PCO_2 gap of greater than 20 mmHg at 24 hours.

Gutierrez et al 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 [77]. 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.

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, gastric tonometry has a number of limitations. Most notably, gastric tonometry is logistically and practically difficult and this may be the main factor, which has prevented the widespread use of this technology. Furthermore, equilibration of carbon dioxide between the gastric mucosa and the balloon is time dependent (about 15 minutes with air tonometry) and is 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 (H_2- blockers) or proton pump inhibitors 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.

In order to overcome the potential limitations of gastric tonometry, Weil and colleagues 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 and colleagues have demonstrated that with decreased perfusion pressure blood flow to the tongue and splanchnic bed fall to a

similar degree [80]. 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 [67,81-83]. Furthermore, the increase in $PslCO_2$ closely tracked the increase in $PimCO_2$. Other authors have demonstrated a good correlation between the $PimCO_2$ and $PslCO_2$ in ICU patients [52,54]. $PslCO_2$ better differentiates survivors from non-survivors than lactate or $SmvO_2$ and is more responsive to therapy than either of these markers [51]. Creteur and colleagues using orthogonal polarization spectral imaging have demonstrated that the improvement in sublingual microcirculatory flow with resuscitation was paralleled by a fall in the sublingual CO_2 [52]. Recently, Pellis and coworkers compared changes in organ blood flow with that of buccal and sublingual PCO_2 in a porcine hemorrhagic shock model [84]. In this study buccal and sublingual PCO_2 levels were nearly identical and closely tracked the changes in hepatic and renal blood flow. The reduction in blood flow to the buccal and sublingual mucosa was comparable to that of the liver and kidney confirming the utility of monitoring the oral mucosal PCO_2.

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. 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. While the Capnoprobe $SLCO_2$ system (Tyco, Pleasanton, CA) was temporarily withdrawn from the US market in 2005 due to contamination of the calibrant solution, this product has now been re-released (Microstat, Sublingual Monitor, Vasamed, Minneapolis, MN).

Conclusion

Sublingual capnometry is a technically simple, non-invasive, inexpensive technology, which provides near instantaneous information as to the adequacy of tissue perfusion in critically ill and injured patients. Sublingual capnometry provides a quantitative measure of the degree of microcirculatory abnormality in patients with sepsis and as such may prove to be useful tool for both the risk stratification and as an end-point for goal-directed resuscitation. The clinical experience with sublingual capnometry is however limited, and additional studies are needed which demonstrate the clinical utility of $PslCO_2$ monitoring and further refinements in the technology are required to allow continuous as well as intermittent measurements.

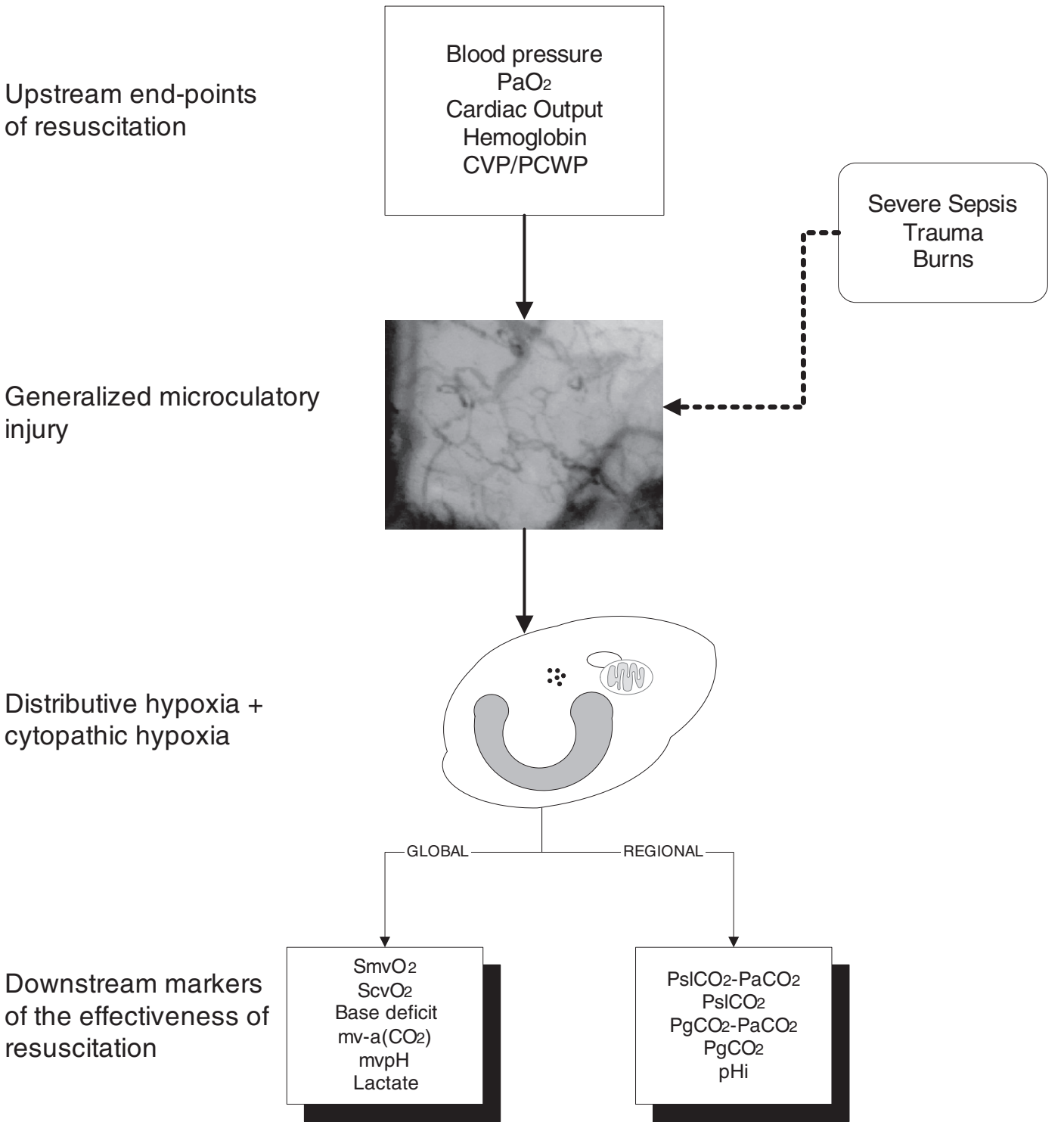
Acknowledgment.

The author acknowledges the assistance of Susan Baik, RN, for her helpful critique and editorial assistance with this manuscript.

Legend for Figure 1.

The upstream end-points of resuscitation do not reflect the severity of the microcirculatory injury nor the degree of tissue dysoxia. The downstream variables are markers of tissue perfusion and the adequacy of the resuscitation. The downstream “global” markers are less sensitive markers of tissue dysoxia and less responsive to change.

FIGURE 1


Upstream end-points of resuscitation
Blood pressure
PaO2
Cardiac Output
Hemoglobin
CVP/PCWP
Severe Sepsis
Trauma
Burns
Generalized microculatory injury
Distributive hypoxia + cytopathic hypoxia
GLOBAL
REGIONAL
Downstream markers of the effectiveness of resuscitation
SmvO2
ScvO2
Base deficit
mv-a(CO2)
mvpH
Lactate
PslCO2-PaCO2
PslCO2
PgCO2-PaCO2
PgCO2
pHi

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