GAS TONOMETRY FOR EVALUATION OF GASTROINTESTINAL MUCOSAL PERFUSION. EXPERIMENTAL MODELS OF TRAUMA, SHOCK AND COMPLEX SURGICAL MANEUVERS – PART 1

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INTRODUCTION

Shock, trauma, sepsis and major surgeries are associated with multiple organ dysfunction syndrome, in part as a consequence of blood flow redistribution, resulting in hypoperfusion of regional vascular beds. However, there is a great deal of controversy on whether tissue distress observed under these conditions is caused exclusively by microcirculatory hypoxia or by disturbances in cellular metabolic pathways. Several authors have shown that despite an apparently sufficient global oxygen delivery, signs of hypoxia and/or...
metabolic dysfunction may persist. The availability of techniques to assess regional hemodynamic and oxygen-related variables has highlighted the inadequacy of the information obtained by global measurements.2

There are several convincing reasons to concentrate on the gut as the organ to detect occult tissue hypoxia during an apparent hemodynamic stability.3 Intestinal mucosal cells are normally under a low oxygen tension, because effective hematocrit within the villi is decreased due to a phenomenon called “plasma skimming” and the villi have a peculiar microvascular architecture, characterized by a countercurrent exchange of oxygen from arteriole to adjacent venule along its length (Figure 1). Under normal conditions, this shunting of oxygen is not harmful to the villi. However, in conditions in which blood flow to the gut becomes greatly curtailed, such as in circulatory shock, the oxygen deficit in the tips of the villi can become so severe that they can suffer ischemic death and disintegrate.4,5

Although several techniques have been proposed to measure the adequacy of gut perfusion,8 only gas tonometry is available for bedside clinical use. It is a minimally invasive technique that measures gut mucosal PCO2 through a modified nasogastric tube with a CO2-permeable balloon at its tip.9 Because of the inverse relationship between tissue PCO2 and local blood flow, gas tonometry has emerged as a tool for tissue perfusion assessment.

In this review, we highlight the current knowledge regarding gas tonometry as a tool to better understand the pathophysiology of tissue oxygen distribution during shock states and principally, sepsis. Moreover, we will focus on the use of gas tonometry to determine the role of gut mucosal acidosis during surgical maneuvers and potential therapeutic interventions, such as fluid resuscitation and vasoactive drugs.

THE TONOMETRIC METHOD

Since the early part of this century, it has been shown that in a hollow viscus, tissue CO2 diffuses from regional blood vessels into its lumen.10 In 1959, Boda and Muranyi11 published the concept of gastric tonometry. They demonstrated a close relationship between gastric PCO2 and end-tidal CO2 and, therefore, to arterial PCO2, using a catheter with a balloon filled with room air into the stomach of healthy volunteers to measure PCO2 of the gas sampled from the balloon. By introducing a saline sample into the gallbladder or urinary bladder lumen, Bergoński12 demonstrated that PCO2 equilibrate with organs’ wall PCO2. A more rapidly equilibration between fluid PCO2 and venous PCO2, drained from an ileal loop mucosa, was observed by Dawson et al.13 More recently, the ability to measure PCO2 by the tonometric method was clearly validated in vitro using solutions with known PCO2 concentrations.14

Additionally, the gut is the organ with the highest critical oxygen delivery (DO2) in the body.6 Since the gut is richly innervated by the sympathetic nerve system, the response to a decrease in global DO2, such as during hemorrhage (Figure 2), aortic occlusion (Figure 3) or hepatic vascular exclusion (Figure 4), intestinal vasoconstriction is greater than most vascular beds, when blood is redistributed to the vital organs, and may persist when systemic hemodynamic variables have been reestablished (Figures 2 and 4). These conditions jeopardize the integrity of gut mucosal cells, predisposing to increases in gut permeability and translocation of bacteria and their toxins. Consequently, a systemic inflammatory response, incriminated in the development of multiple organ failure,4,7 is induced by regional cytokine synthesis and several other inflammatory mediators, released by hepatic and systemic mononuclear cells.4
Fiddian-Green et al.\textsuperscript{15} adopted the saline tonometric technique for the assessment of gut luminal PCO\textsubscript{2} and extended its use to the calculation of gastrointestinal intramucosal pH (pHi). They assumed that the arterial bicarbonate level, measured by arterial blood gas analyzer, was the same as the intramucosal bicarbonate, and calculated pHi by the Henderson-Hasselbach equation as follows:

\[
\text{pHi} = 6.1 + \log \frac{[\text{HCO}_3^-]}{[\text{PCO}_2]} \times 0.031
\]

where $[\text{HCO}_3^-]$ is the bicarbonate concentration, calculated from arterial PCO\textsubscript{2} and pH, $[\text{PCO}_2]$ is the CO\textsubscript{2} tension, measured on saline aspirated directly from the stomach, and 0.031 is the solubility coefficient for CO\textsubscript{2} in plasma. Subsequently, this technique was modified to use a CO\textsubscript{2}-permeable, silicone balloon catheter, from which aliquots of saline could be withdrawn and evaluated by routine blood gas analyzers.

Validity and reproducibility of pHi, measured by gastric tonometry, were examined in experimental models of sepsis, graded hemorrhage and mesenteric artery occlusion; compared to the pH measured by implanted microelectrodes, pHi matched closely.\textsuperscript{16-20} It has been also shown, by several different techniques, that decreases in blood flow to the gut are paralleled by concordant decreases in pHi and increases in tissue PCO\textsubscript{2} determined by tonometry.\textsuperscript{19,21-28} Also, in critically ill patients, mucosal gastric perfusion, measured by laser Doppler\textsuperscript{29} or reflectance spectroscopy,\textsuperscript{30} was lower when an increased $\text{P}_{\text{gCO}_2}-\text{P}_{\text{aCO}_2}$ gradient or a subnormal pHi was present.

Hence, PCO\textsubscript{2} estimated by tonometry should correspond to that of tissue PCO\textsubscript{2}. When fluid is instilled into the lumen of a hollow organ, gaseous CO\textsubscript{2} equilibrates with CO\textsubscript{2} in interstitial fluid and cells in the superficial layers of the organs wall.\textsuperscript{31} However, the stomach may be an exception, because PCO\textsubscript{2} of gastric...
juice may, in some instances, exceed PCO₂ of gastric wall and gastric venous blood PCO₂. PCO₂ is also generated into the gastric lumen, from the H⁺ neutralization by the bicarbonate contained in the gastric juice or in the backflow of duodenal fluid. Back diffusion of CO₂ into the gastric mucosa itself increases gastric wall PCO₂, independently of gastric mucosal blood flow. After H₂ blockade by cimetidine, H⁺ production by the stomach is reduced, and PCO₂ of gastric luminal fluid and that of gastric venous blood approximate each other. Accordingly, H⁺ of gastric juice interferes with tonometric measurement of PCO₂, and routine H₂ blockade is therefore recommended to minimize this effect. Although many critically ill patients are treated with H₂ receptor-blocking agents for the prevention of stress ulceration, their benefits are disputed. There are adverse effects of H₂ blockade in such settings, especially an increased risk of nosocomial pneumonia. To avoid the short-comes (food, H₂ blockers, duodenal reflux) of the gastric tract for mucosal PCO₂ measurements, PCO₂ tonometry have been evaluated in several other tissues such as sublingual, esophageal, and bladder mucosa. The feasibility and accuracy of these techniques remains to be validated.

There are limitations inherent to the use of saline samples, such as the time interval required for CO₂ equilibration between the saline into the tonometer’s balloon and the gastric wall. Experimentally, it has been shown that the level of tissue PCO₂ has little effect on the equilibration period. The manufacturer recommends mathematical corrections to adjust for incomplete equilibration, which is usually inversely related to the period of equilibration. These corrections represent average values rather than values indicating the time required for partial equilibration for an individual patient. Another source of error is that, when saline PCO₂ is measured with several blood gas analyzers, there is a wide variation observed, particularly at higher PCO₂ levels, underestimating balloon PCO₂. By using other solutions instead of saline, errors in PCO₂...
estimation were attenuated. Phosphate buffer solutions have been suggested as options to improve the accuracy and reliability of PCO₂ measurement. However, the use of systemic bicarbonate, assuming that it is equal to intramucosal bicarbonate concentration, is the major limitation for the use of calculated pHᵢ in the clinical setting. Isolated regional ischemia may result in lower local bicarbonate levels when compared to systemic values. Conversely, during shock states with systemic acidosis, gastric intramucosal bicarbonate is consistently greater than that of arterial blood. Moreover, other causes of systemic hypercarbia and metabolic acidosis, without hypoperfusion, may also influence pHᵢ calculation, despite a preserved mucosal perfusion. For all those drawbacks, calculated pHᵢ should be replaced by the tonometer-arterial blood PCO₂ gradient, named PCO₂-gap, avoiding the confounding effects of systemic metabolic and respiratory alterations. However, Guzman et al. showed that this gradient remains stable during hypoventilation, but it may increase after hyperventilation. These findings warrant cautious interpretation of PCO₂ gap as an indicator of gastric

Figure 4 - Mean arterial pressure (MAP), cardiac output (CO), superior mesenteric artery blood flow (SMA) and gastric-arterial CO₂ (PCO₂-gap) in dogs randomized to a hepatic vascular exclusion (HVE, n=13) or HVE with supraceliac aortic occlusion (HVE+AO) for 30 min (E10-E30), followed for reperfusion (R10-R60). Portal triad, supra and infraportal inferior vena cava crossclamping promoted significant decreases in MAP, CO and SMA blood flow, while PCO₂-gap increased. Concomitant aortic occlusion prevented severe hypotension. Reperfusion promoted partial restoration of MAP, CO and SMA blood flows, while PCO₂-gap remained similarly increased in both groups. [adapted from Cruz Jr RJ, Poli de Figueiredo LF, Braz JL et al. Systemic and regional effects of supraceliac aortic occlusion during experimental hepatic vascular exclusion. Am J Surg, submitted.]

Figure 5 – Representative tracing of the effects of descending aortic cross-clamping followed by a 60-min reperfusion period on the bladder mucosal pH, PO₂ and PCO₂, measured continuously with a Paratrend 7 chemical probes in pigs. Lower torso ischemia promoted a sharp decrease in bladder mucosal pH and PO₂, while mucosal PCO₂ showed a marked increase. Reperfusion was associated with a progressive pH restoration, a sustained increased PO₂ from reactive hyperemia, and a sudden decrease in bladder mucosal PCO₂ followed by a clear increase, suggesting reperfusion injury [adapted from de Lang JD, Evans DJ, Poli de Figueiredo LF et al. A novel approach to monitor tissue perfusion: bladder mucosal PCO₂, PO₂, and pH during ischemia and reperfusion in pigs. J Intensive Care 1999;14:93-98]
mucosal perfusion during systemic hypocapnia. Despite this concern, PCO₂-gap remains the most reliable marker of tissue perfusion nowadays and should definitively replace pHi.45,46

Further advances in the tonometric method were achieved by Salzman et al.,21 who reinvestigated the concept that PCO₂ measurements could be performed on gas aspirated from the stomach. The PCO₂ of this gas correlated with that measured on saline sampled from a conventional balloon tonometer, when perfusion was decreased by pericardial tamponade. During respiratory acidosis and in the absence of shock, there was a very high correlation between the PCO₂ of stomach gas and that of the saline sampled from the balloon. This concept of air tonometry was recently expanded by Guzman and Kruse,47 who circulated gas through a gastric balloon and measured PCO₂ continuously, by an infrared capnometer. More recently, capnometry and conventional balloon tonometry have been combined and called capnometric recirculating gas tonometry (CRGT), overcoming limitations such as the long equilibration time, saline sampling and a relatively labor-intensive manipulation. Air is used in lieu of saline, and then gas is aspirated and analyzed automatically by infrared capnometry after a 10-minute equilibration, with a commercially available Tonocap (Datex-Engstrom; Tonometrics; Tewksbury, Mass). In experimental models, CRGT has been shown to be capable of detecting changes in gastric mucosal PCO₂ shortly after inducing hypoxemia and hemorrhage.47 CRGT has been also validated in critically ill patients.13,48 Hence, CRGT is actually the best method that, in addition to provide semi-continuous online measurements of gastric PCO₂, can detect significant changes within minutes, and may be used during short-term interventional studies.

PCO₂ AS A MARKER OF BLOOD FLOW AND TISSUE HYPOXIA

In animal models of progressive hemorrhage or cardiac tamponade, in which DO₂ was reduced by a decreased cardiac output, an elevation in veno-arterial DPCO₂ was observed, while VO₂ and CO₂ production remained constant.50-52 In this condition of oxygen supply-independency, an elevation of veno-arterial DPCO₂, following flow reduction, can be explained simply by CO₂ stagnation. When DO₂ was further reduced, below its critical value (DO₂crit), a decrease in VO₂ was observed, suggesting oxygen supply-dependency and consequent anaerobic metabolism. An increase in lactate concentration confirmed this assumption.51,52 The progressive widening of veno-arterial DPCO₂ was magnified by a sharp increase in

PvCO₂ when DO₂ decreased below its critical point (a veno-arterial DPCO₂ around 30 mmHg). It was assumed that this steep increase in DPCO₂ can be used as a reliable marker of tissue dysoxia, since DO₂crit, calculated by either using the relationship between VO₂ to DO₂, lactate to DO₂, or DPCO₂ to DO₂, provided similar results.51,52

However, in a recent review, Tuboul et al.,53 noticed that the aerobic production of CO₂ is theoretically reduced when tissue dysoxia is present (as VCO₂ = R x VO₂), and proposed that an explanation of venous and tissue hypercarbia, in low-flow states, emerges from the curvilinearity of the Fick equation. As mentioned above, if anaerobic CO₂ production occurred under conditions of tissue dysoxia, it would result from the H⁺ excess buffering by HCO₃⁻. However, as highlighted by Tuboul et al.,53 studies addressing the issue of detecting tissue dysoxia by analysis of DPCO₂, used experimental protocols of blood flow reduction; the associated decrease in cardiac output acts as a confounding variable, not allowing a definitive conclusion. In order to clarify this question, V allet et al.,54 using an in situ isolated, innervated canine hind limb model, showed that when DO₂ was decreased, either by blood flow reduction (ischemic hypoxia) or decreasing arterial PO₂ (hypoxic hypoxia), regional veno-arterial DPCO₂ increased only when blood flow was reduced, even though the same oxygen deficit was observed in both protocols. The authors conclude that the absence of an increased veno-arterial DPCO₂ does not preclude the presence of tissue dysoxia. Hence, decreased blood flow appeared to be the major determinant of increased DPCO₂.

If intestinal tonometry is to be used to detect early dysoxia in low flow states, it is essential to know at which level increased tissue PCO₂ represents aerobic (stagnant flow with preserved VO₂) or anaerobic metabolism. Some evidences have emerged from Schlichtig’s group studies.23 These authors observed that mucosal PCO₂, estimated by tonometry, increased to values nearly threefold higher than predicted by Dill’s blood nomogram, which shows the aerobic relationship between PvCO₂ and SvO₂. In this nomogram, a known PvCO₂ can be used to predict SvO₂ (SvO₂Dill). A SvO₂Dill that agrees with a measured SvO₂ in a blood sample indicates that dissolved CO₂ appeared purely on the basis of aerobic metabolism. On the other hand, when SvO₂Dill is less than the measured SvO₂, it represents the conversion of HCO₃⁻ to dissolved CO₂, due to an anaerobic metabolism. Moreover, these authors also observed that gastric mucosal PCO₂ markedly exceeded PCO₂ values in portal venous blood, when flow was decreased below the critical DO₂. Consistency with
aerobic CO₂ was only observed with a maximal mucosal-arterial DPCO₂ gradient, around 25-35 mmHg, while a further increase in mucosal-arterial DPCO₂ was consistent with mucosal dysoxia. However, in this particular study, low blood flow remained as a confounding variable, according to Teboul’s experiments.53

To establish the exact role of a decreased blood flow on tissue PCO₂, Vallet et al.55 evaluated veno-arterial condition in which there is an increase in blood flow, both [P(v-a)CO₂], gut mucosal-arterial CO₂ gap [P(m-a)CO₂], and gastric mucosal blood flow (laser Doppler flow probe). They showed, by using two different mechanisms of tissue hypoxia, that mucosal blood flow is not the only factor that could contribute to gastric mucosal hypercarbia. In one group, systemic hypoxia was induced by progressive reduction in the inspired oxygen fraction (hypoxic hypoxia, HH) or by progressive bleeding (ischemic hypoxia, IH). While IH decreased gastric mucosal blood flow and increased both [P(v-a)CO₂] and [P(m-a)CO₂], HH increased only [P(m-a)CO₂], although gastric mucosal blood flow remained constant. As expected, IH induced a larger increase in DPCO₂ than HH. The peculiar microcirculatory system and its counter-current exchange of oxygen and CO₂ within mucosal villus could explain these findings (Figure 1). Therefore, conditions of low tissue DO₂ may induce both tissue hypoxia and hypercarbia, by incrementing the counter-current oxygen exchange between arteriole and venule, threatening cells at the tips of the villi.

Following fluid resuscitation in sepsis or hemorrhage, tissue DO₂ may be restored but gastric mucosal hypercarbia may be not prevented, due to disturbances in cellular metabolic pathways impairing oxygen utilization, which has been named cytopathic hypoxia.54,55 This may explain the concomitance of high tissue PCO₂ and adequate tissue PO₂ and gastric mucosal blood flow, observed by several authors.25,56,57 In fact, a high gastric to arterial PCO₂ gradient could be a marker of dyoxia, independent of the causes of impaired oxygen utilization.

However, a simplistic conclusion that tissue hypercarbia means necessarily hypoperfusion or anaerobic metabolism may be misleading. The rational behind tonometry is the assumption that an increased mucosal-arterial PCO₂ gradient indicates imbalance between perfusion and metabolism. This assumes that the mucosal-arterial PCO₂ gradient is a surrogate marker of mucosal-arterial CO₂ content difference. However, when oxygen saturation, hemoglobin and/or arterial-venous pH difference change, the relationship between PCO₂ and CO₂ content is not linear. In particular, the condition in which there is an increase in blood flow, but a larger increase in CO₂ production, matching a respective change in oxygen consumption, may lead to the dissociation of PCO₂ gradients between vascular beds with different baseline oxygen extraction. Jakob et al.59 have speculated that, particular changes in tissue oxygen extraction (Haldane effect), may explain the increasing mucosal-arterial PCO₂ gradients, despite preserved or increased mucosal tissue perfusion.

In summary, the major determinant of tissue PCO₂ is blood flow. However, because of the villi’s peculiar vascular arrangement, a high gastric mucosal PCO₂ can be a marker of dyoxia and not simply a marker of disproportional low blood flow to tissue metabolic status.

CONCLUSION

There are clinical and experimental evidences that support the relationship between splanchnic hypoperfusion and multiple organ dysfunction in patients and animals submitted to trauma or major surgical procedures, largely related to mucosal injury leading to increased permeability and systemic inflammatory response. As gut mucosal pCO₂ reflects the balance between flow and metabolism, gas tonometry is a valuable tool to monitor regional effects of hemodynamic interventions and gives insights regarding blood flow heterogeneity in distinct shock states. Next issue we will be presenting our experience with gas tonometry in experimental and clinical sepsis.59 The definitive role of gas tonometry to predict outcome and guide therapy for patients with trauma, sepsis or submitted to complex operations, will be established by large, prospective multicenter trials.

REFERENCES

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RESUMO - Evidências clínicas e experimentais substanciais indicam que o território circulatório mesentérico, principalmente na mucosa intestinal, é altamente vulnerável a redução na oferta de oxigênio e predisposto a lesão precoce na presença de alterações hemodinâmicas induzidas por trauma, choque, sepsis e diversas manobras cirúrgicas complexas. A hipoxia ou isquemia intestinal é um dos possíveis mecanismos contribuintes para a disfunção da barreira gastrointestinal que pode estar associada com o desenvolvimento da resposta inflamatória sistêmica e com a síndrome da disfunção de múltiplos órgãos, causa comum de morte após trauma, sepsis ou cirurgias de grande porte. Monitorar a perfusão intestinal em experimentos pode fornecer dados valiosos quanto a novas intervenções e tratamentos altamente necessários para reduzir a morbidade e mortalidade extremamente elevadas no trauma e na sepsis. Apresentamos nossa experiência com a tonometria a gás como monitor da adequação da perfusão da mucosa gastrointestinal clínica e experimental, em modelos de trauma, sepsis, e manobras cirúrgicas complexas tais como a oclusão da aorta e a exclusão vascular hepática.


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