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

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ABSTRACT - Substantial clinical and animal evidences indicate that the mesenteric circulatory bed, particularly the gut mucosa, is highly vulnerable to reductions in oxygen supply and prone to early injury in the course of hemodynamic changes induced by trauma, shock, sepsis and several complex surgical maneuvers. Gut hypoxia or ischemia is one possible contributing factor to gastrointestinal tract barrier dysfunction that may be associated with the development of systemic inflammatory response and multiple organ dysfunction syndrome, a common cause of death after trauma, sepsis or major surgeries. Monitoring gut perfusion during experiments may provide valuable insights over new interventions and therapies highly needed to reduce trauma and sepsis-related morbidity and mortality. We present our experience with gas tonometry as a monitor of the adequacy of gastrointestinal mucosal perfusion in clinical and experimental models of trauma, shock and surgical maneuvers associated with abrupt hemodynamic changes, such as aortic occlusion and hepatic vascular exclusion. Next issue we will be presenting our experience with gas tonometry in experimental and clinical sepsis.

KEY WORDS – Ischemia. Reperfusion. Catecholamines. Tonometry. Gut mucosa. Hemorrhage. Multiple organ failure. Tonometry. Shock. Multiple trauma.

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.[1] 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

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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"[4] 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]

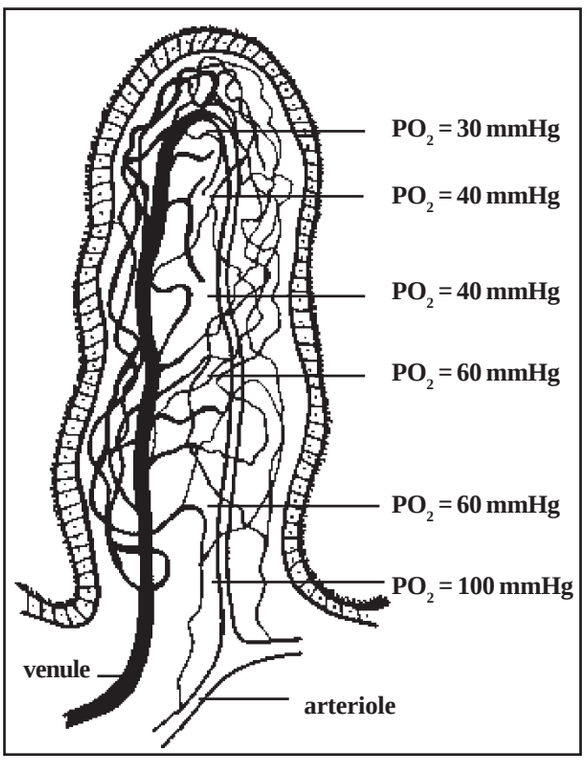

Figure 1 - Countercurrent exchange of O_2 between arteriole and venule within the intestinal villi, showing the progressive decrease in arteriolar PaO_2.

Additionally, the gut is the organ with the highest critical oxygen delivery (DO_2) in the body.[6] Since the gut is richly innervated by the sympathetic nerve system, the response to a decrease in global DO_2, 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]

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 PCO_2 through a modified nasogastric tube with a CO_2-permeable balloon at its tip.[9] Because of the inverse relationship between tissue PCO_2 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 CO_2 diffuses from regional blood vessels into its lumen.[10] In 1959, Boda and Muranyi[11] published the concept of gastric tonometry. They demonstrated a close relationship between gastric PCO_2 and end-tidal CO_2 and, therefore, to arterial PCO_2, using a catheter with a balloon filled with room air into the stomach of healthy volunteers to measure PCO_2 of the gas sampled from the balloon. By introducing a saline sample into the gallbladder or urinary bladder lumen, Bergofsky[12] demonstrated that PCO_2 equilibrate with organs' wall PCO_2. A more rapidly equilibration between fluid PCO_2 and venous PCO_2, drained from an ileal loop mucosa, was observed by Dawson et al.[13] More recently, the ability to measure PCO_2 by the tonometric method was clearly validated *in vitro* using solutions with known PCO_2 concentrations.[14]

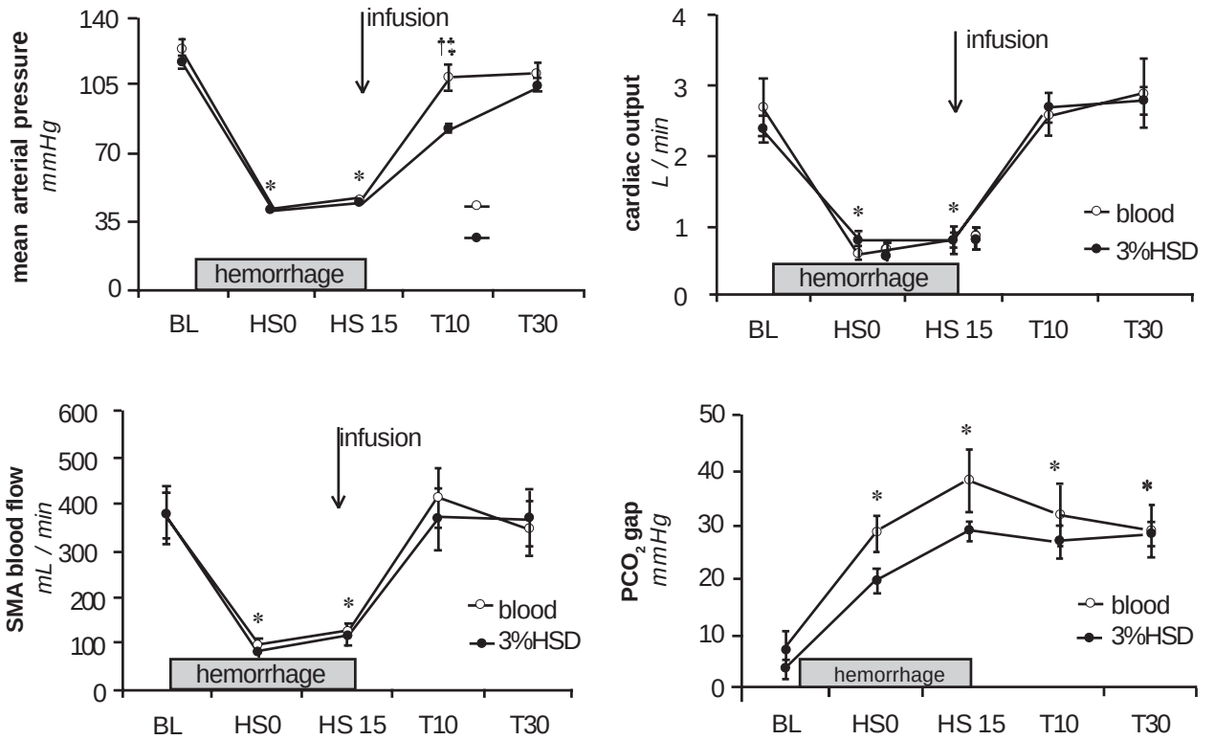

Figure 2 – Mean arterial pressure (MAP), cardiac output (CO), superior mesenteric artery blood flow (SMA) and gastric-arterial CO_2 (PCO_2-gap) in a controlled hemorrhage model in dogs. Blood was removed at a 20 mL/min rate to a mean arterial pressure of 40 mmHg (HS0), and maintained at these levels for 15 min (HS15). Dogs were randomized according to fluid solution infused. *BLOOD* (n=9) received total shed blood retransfusion during 30 min (T10 and T30). 3%HSD (n=8) received 3%NaCl / 10%dextran 40, in a volume equivalent to ¼ of total shed blood in a 4-min bolus injection and followed for 30 min (T10 and T30). Hemorrhage and shock promoted significant reductions on MAP, CO, SMA and marked increases in PCO_2 gap. Treatment with total shed blood or smaller volumes of 3%HSD restored hemodynamic parametes, except for PCO_2 – gap, which remained elevated, in spite of an apparent successful fluid resuscitation. [adapted from *Poli de Figueiredo LF, Silva E, Cruz Jr RJ et al. Sustained gastric mucosal acidosis despite rapid global and regional hemodynamic restoration after hemorrhage and resuscitation with blood or hypertonic/ hyperoncotic solution. J Trauma, submitted*]

Fiddian-Green et al.[15] adopted the saline tonometric technique for the assessment of gut luminal PCO_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:

$$pHi = 6.1 + \log [HCO_3^-] / [PCO_2] \times 0.031$$

where $[HCO_3^-]$ is the bicarbonate concentration, calculated from arterial PCO_2 and pH, $[PCO_2]$ is the CO_2 tension, measured on saline aspirated directly from the stomach, and 0.031 is the solubility coefficient for CO_2 in plasma. Subsequently, this technique was modified to use a CO_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.[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_2 determined by tonometry.[19,21-28] Also, in critically ill patients, mucosal gastric perfusion, measured by laser Doppler[29] or reflectance spectroscopy,[30] was lower when an increased $PgCO_2$-$PaCO_2$ gradient or a subnormal pHi was present.

Hence, PCO_2 estimated by tonometry should correspond to that of tissue PCO_2. When fluid is instilled into the lumen of a hollow organ, gaseous CO_2 equilibrates with CO_2 in interstitial fluid and cells in the superficial layers of the organs wall.[31] However, the stomach may be an exception, because PCO_2 of gastric

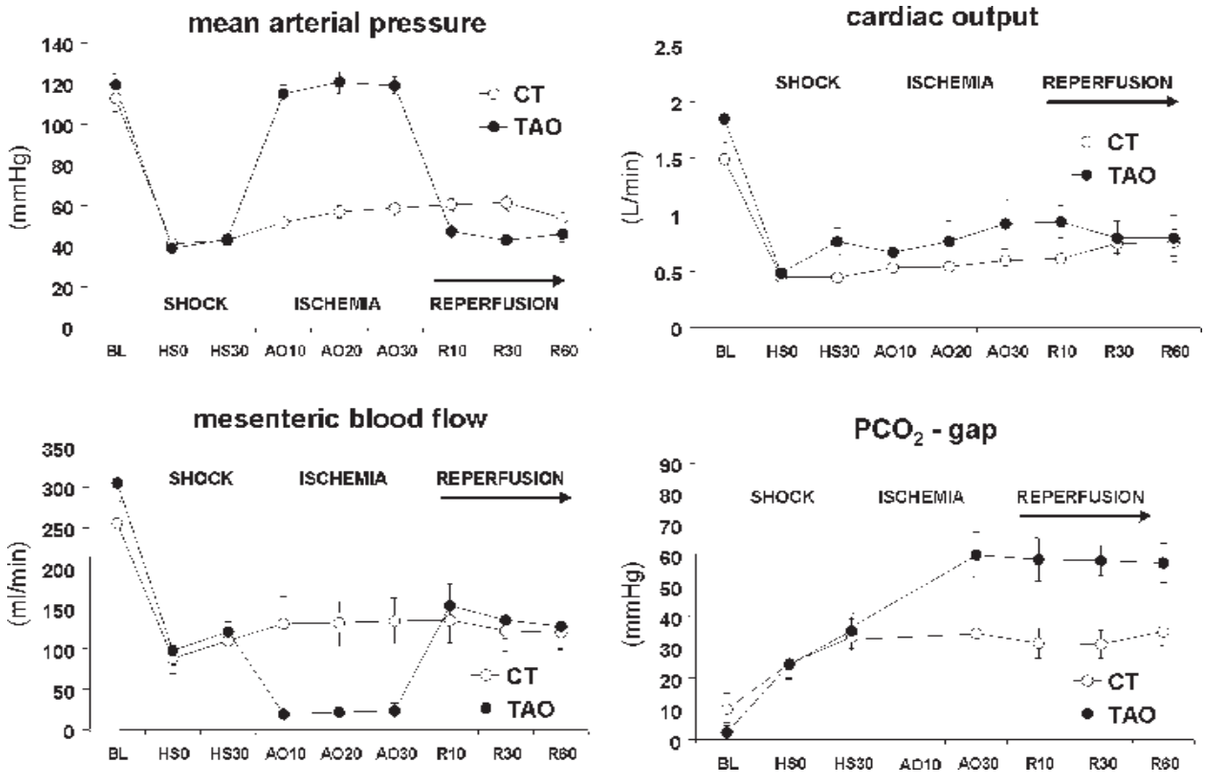

Figure 3 – Mean arterial pressure (MAP), cardiac output (CO), superior mesenteric artery blood flow (SMA) and gastric-arterial CO_2 (PCO_2-gap) in a controlled hemorrhage model, followed by ischemia and reperfusion induced by a transfemoral supraceliac aortic balloon occlusion. Blood was removed at a 20 mL/min rate to a mean arterial pressure of 40 mmHg (HS0), and maintained at these levels for 30 min (HS0 and HS30). Dogs were randomized to CT (controls, n=7), which were followed for 90 min, or TAO (n=7), supraceliac aortic occlusion for 30 min, followed for 60 min after reperfusion. Hemorrhage and shock promoted significant reductions on MAP, CO, SMA and marked increases in PCO_2 gap. Aortic occlusion restored mean arterial but induced further decreases in SMA blood flow and increases in PCO_2 gap. During reperfusion, hemodynamic parametes were similar between groups, while greater increase in PCO_2 – gap was observed in animals submitted to aortic occlusion. [*adapted from Cruz Jr RJ, Poli de Figueiredo LF, Rocha e Silva M. Splanchnic blood flow, oxygen metabolism and PCO_2-gap after aortic occlusion during hemorrhagic shock. Eur J Surg, submitted*]

juice may, in some instances, exceed PCO_2 of gastric wall and gastric venous blood PCO_2. PCO_2 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 CO_2 into the gastric mucosa itself increases gastric wall PCO_2, independently of gastric mucosal blood flow.[32-34] After H_2 blockade by cimetidine, H^+ production by the stomach is reduced, and PCO_2 of gastric luminal fluid and that of gastric venous blood approximate each other. Accordingly, H^+ of gastric juice interferes with tonometric measurement of PCO_2, and routine H_2 blockade is therefore recommended to minimize this effect.[33] Although many critically ill patients are treated with H_2 receptor-blocking agents for the prevention of stress ulceration, their benefits are disputed. There are adverse effects of H_2 blockade in such settings, especially an increased risk of nosocomial pneumonia.[35] To avoid the short-comes (food, H_2 blockers, duodenal reflux) of the gastric tract for mucosal PCO_2 measurements, PCO_2 tonometry have been evaluated in several other tissues such as sublingual,[36-38] esophageal,[22] and bladder mucosa (Figure 5).[39] 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 CO_2 equilibration between the saline into the tonometer's balloon and the gastric wall. Experimentally, it has been shown that the level of tissue PCO_2 has little effect on the equilibration period.[24,40] The manufacturer recommends mathematical corrections to adjust for incomplete equilibration, which is usually inversely related to the period of equilibration. However, 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 PCO_2 is measured with several blood gas analyzers, a wide variation is observed, particularly at higher PCO_2 levels, underestimating balloon PCO_2.[41] By using other solutions instead of saline, errors in PCO_2

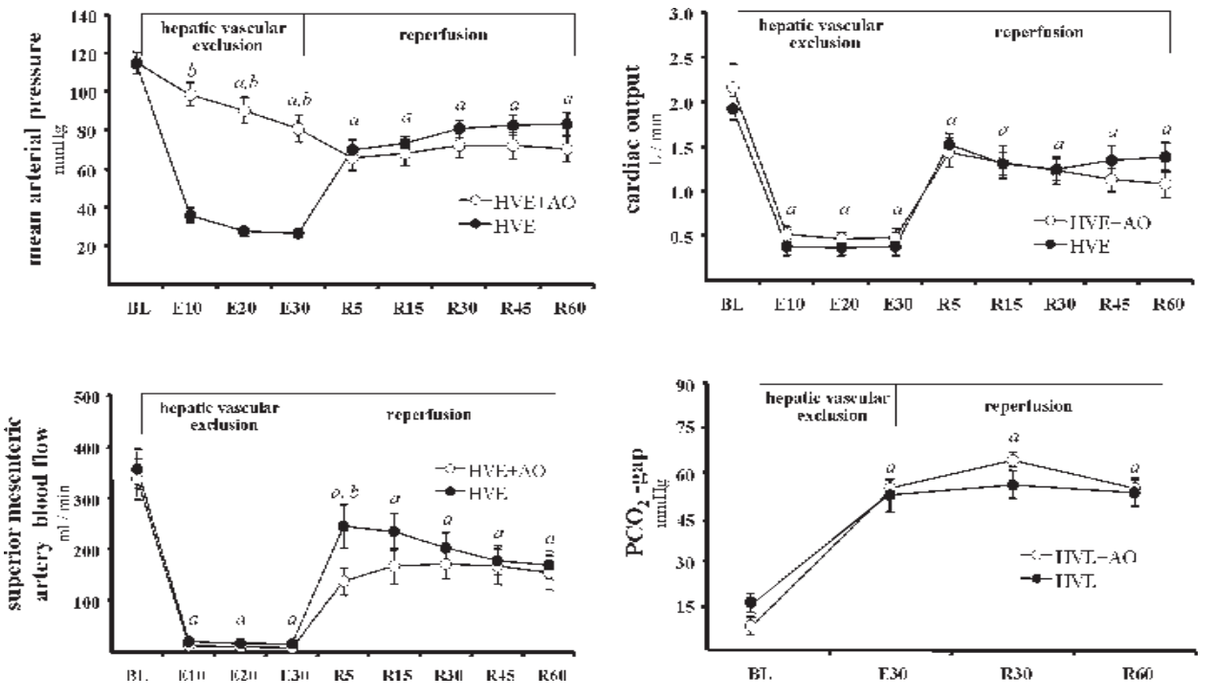

Figure 4 - Mean arterial pressure (MAP), cardiac output (CO), superior mesenteric artery blood flow (SMA) and gastric-arterial CO_2 (PCO_2-gap) in dogs randomized to a hepatic vascular exclusion (HVE, n=13) or HVE with supraceliac aortic occlusion (HVE+AO) for 30 min (E10-E30), followed for reperfusion (R10-R60). Portal triad, supra and infrahepatic inferior vena cava crossclamping promoted significant decreases in MAP, CO and SMA blood flow, while PCO_2-gap increased. Concomitant aortic occlusion prevented severe hypotension. Reperfusion promoted partial restoration of MAP, CO and SMA blood flows, while PCO_2-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*.]

estimation were attenuated.[41,42] Phosphate buffer solutions have been suggested as options to improve the accuracy and reliability of PCO_2 measurement.[43]

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 PCO_2 gradient, named PCO_2-gap, avoiding the confounding effects of systemic metabolic and respiratory alterations. However, Guzman et al.[44] showed that this gradient remains stable during hypoventilation, but it may increase after hyperventilation. These findings warrant cautious interpretation of PCO_2 gap as an indicator of gastric

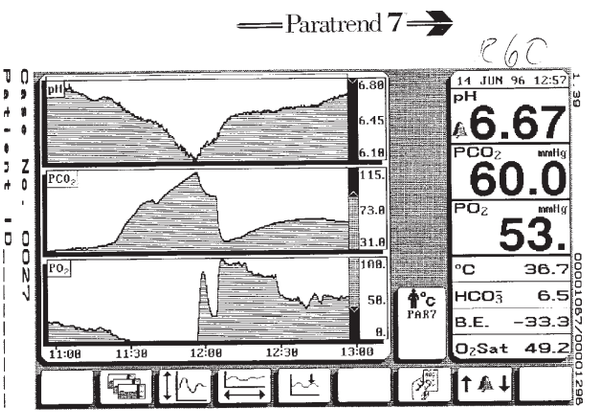

Figure 5 – Representative tracing of the effects of descending aortic cross-clamping followed by a 60-min reperfusion period on the bladder mucosal pH, PO_2 and PCO_2, measured continuously with a Paratrend 7 chemical probes in pigs. Lower torso ischemia promoted a sharp decrease in bladder mucosal pH and PO_2, while mucosal PCO_2 showed a marked increase. Reperfusion was associated with a progressive pH restoration, a sustained increased PO_2 from reactive hyperemia, and a sudden decrease in bladder mucosal PCO_2, 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 PCO_2, PO_2, and pHi during ischemia and reperfusion in pigs. J Intensive Care 1999;14:93-98*]

mucosal perfusion during systemic hypocapnia. Despite this concern, PCO_2-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 PCO_2 measurements could be performed on gas aspirated from the stomach. The PCO_2 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 PCO_2 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 PCO_2 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 PCO_2 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 PCO_2, can detect significant changes within minutes, and may be used during short-term interventional studies.

PCO_2 AS A MARKER OF BLOOD FLOW AND TISSUE HYPOXIA

In animal models of progressive hemorrhage or cardiac tamponade, in which DO_2 was reduced by a decreased cardiac output, an elevation in veno-arterial $DPCO_2$ was observed, while VO_2 and CO_2 production remained constant.[50-52] In this condition of oxygen supply-independency, an elevation of veno-arterial $DPCO_2$, following flow reduction, can be explained simply by CO_2 stagnation. When DO_2 was further reduced, below its critical value (DO_2crit), a decrease in VO_2 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 $DPCO_2$ was magnified by a sharp increase in $PvCO_2$, when DO_2 decreased below its critical point (a veno-arterial $DPCO_2$ around 30 mmHg). It was assumed that this steep increase in $DPCO_2$ can be used as a reliable marker of tissue dysoxia, since DO_2crit, calculated by either using the relationship between VO_2 to DO_2, lactate to DO_2, or $DPCO_2$ to DO_2, provided similar results.[51,52]

However, in a recent review, Teboul et al.[53] noticed that the aerobic production of CO_2 is theoretically reduced when tissue dysoxia is present (as $VCO_2 = R \times VO_2$), 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 CO_2 production occurred under conditions of tissue dysoxia, it would result from the H^+ excess buffering by HCO_3^-. However, as highlighted by Teboul et al.,[53] studies addressing the issue of detecting tissue dysoxia by analysis of $DPCO_2$, 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, Vallet et al.,[54] using an *in situ* isolated, innervated canine hind limb model, showed that when DO_2 was decreased, either by blood flow reduction (ischemic hypoxia) or decreasing arterial PO_2 (hypoxic hypoxia), regional veno-arterial $DPCO_2$ 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 $DPCO_2$ does not preclude the presence of tissue dysoxia. Hence, decreased blood flow appeared to be the major determinant of increased $DPCO_2$.

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 PCO_2 represents aerobic (stagnant flow with preserved VO_2) or anaerobic metabolism. Some evidences have emerged from Schlichtig's group studies.[23] These authors observed that mucosal PCO_2, estimated by tonometry, increased to values nearly threefold higher than predicted by Dill's blood nomogram, which shows the aerobic relationship between $PvCO_2$ and SvO_2. In this nomogram, a known $PvCO_2$ can be used to predict SvO_2 (SvO_2^{Dill}). A SvO_2^{Dill} that agrees with a measured SvO_2 in a blood sample indicates that dissolved CO_2 appeared purely on the basis of aerobic metabolism. On the other hand, when SvO_2^{Dill} is less than the measured SvO_2, it represents the conversion of HCO_3^- to dissolved CO_2, due to an anaerobic metabolism. Moreover, these authors also observed that gastric mucosal PCO_2 markedly exceeded PCO_2 values in portal venous blood, when flow was decreased below the critical DO_2. Consistency with

aerobic CO_2 was only observed with a maximal mucosal-arterial $DPCO_2$ gradient, around 25-35 mmHg, while a further increase in mucosal-arterial $DPCO_2$ 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 PCO_2, Vallet et al.[55] evaluated veno-arterial CO_2 gap [$P(v\text{-}a)CO_2$], gut mucosal-arterial CO_2 gap [$P(m\text{-}a)CO_2$], 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 [$P(v\text{-}a)CO_2$] and [$P(m\text{-}a)CO_2$], HH increased only [$P(m\text{-}a)CO_2$], although gastric mucosal blood flow remained constant. As expected, IH induced a larger increase in $DPCO_2$ than HH. The peculiar microcirculatory system and its counter-current exchange of oxygen and CO_2 within mucosal villus could explain these findings (Figure 1). Therefore, conditions of low tissue DO_2 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 DO_2 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 PCO_2 and adequate tissue PO_2 and gastric mucosal blood flow, observed by several authors.[25,56,57] In fact, a high gastric to arterial PCO_2 gradient could be a marker of dysoxia, 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 PCO_2 gradient indicates imbalance between perfusion and metabolism. This assumes that the mucosal-arterial PCO_2 gradient is a surrogate marker of mucosal-arterial CO_2 content difference. However, when oxygen saturation, hemoglobin and/or arterial-venous pH difference change, the relationship between PCO_2 and CO_2 content is not linear. In particular, the condition in which there is an increase in blood flow, but a larger increase in CO_2 production, matching a respective change in oxygen consumption, may lead to the dissociation of PCO_2 gradients between vascular beds with different baseline oxygen extraction. Jakob et al.[58] have speculated that, particular changes in tissue oxygen extraction (Haldane effect), may explain the increasing mucosal-arterial PCO_2 gradients, despite preserved or increased mucosal tissue perfusion.

In summary, the major determinant of tissue PCO_2 is blood flow. However, because of the villi's peculiar vascular arrangement, a high gastric mucosal PCO_2 can be a marker of dysoxia 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 pCO_2 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.

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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, sepse e diversas manobras cirúrgicas complexas. A hipóxia 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, sepse 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 sepse. Apresentamos nossa experiência com a tonometria a gás como monitor da adequação da perfusão da mucosa gastrointestinal clínica e experimental, em modelos de trauma, sepse, e manobras cirúrgicas complexas tais como a oclusão da aorta e a exclusão vascular hepática.

DESCRITORES – Isquemia. Reperfusão. Tonometria. Choque séptico. Falência de múltiplos órgãos. Catecolaminas. Mucosa intestinal. Sepse. Traumatismo múltiplo.

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