

# GAS TONOMETRY FOR EVALUATION OF GASTROINTESTINAL MUCOSAL PERFUSION. EXPERIMENTAL AND CLINICAL SEPSIS<sup>1</sup>

## PART 2

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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 sepsis and septic shock. 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, the principal cause of death after sepsis. Monitoring gut perfusion during experimental and clinical sepsis may provide valuable insights over new interventions and therapies highly needed to reduce multiple organ dysfunction and sepsis-related morbidity and mortality. We present our experience with gas tonometry as a monitor of the adequacy of gastrointestinal mucosal perfusion in experimental models sepsis and with the use of vasoactive agents for hemodynamic management in patients with septic shock.

**KEY WORDS** – Septic shock. Multiple organ failure. Tonometry. Sepsis. Catecholamines. Gut mucosa.

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Severe sepsis and septic shock are associated with high morbidity and mortality, due to multiple organ dysfunction syndrome. 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. We have presented our experience with gas tonometry in experimental models of trauma, shock and complex

surgical maneuvers<sup>1</sup>. We also analyzed the concepts of the tonometric method and how PCO<sub>2</sub> is a marker of blood flow and tissue hypoxia.<sup>1</sup> In the present issue, we further analyze the role of gas tonometry in experimental and clinical sepsis and septic shock.

### Pathophysiology of tissue hypercarbia in sepsis

There are many reasons for the development of gastric mucosal hypercarbia in septic patients. Metabo-

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lic needs are typically increased by the inflammatory response to infection, increasing CO<sub>2</sub> load. This may further enlarge veno-arterial PCO<sub>2</sub> and tissue-arterial PCO<sub>2</sub> gradients, especially when there is no compensatory increase in cardiac output or tissue blood flow. Particularly during early resuscitation, tissue blood flow can be low (stagnant flow), due to either hypovolemia and/or arterial hypotension. Gastric mucosal hypercarbia may be also due to systemic metabolic acidosis, mainly secondary to lactic acidosis, condition in which tissue hypercarbia is universally observed, produced by bicarbonate buffering of hydrogen ions. Even in the absence of systemic acidosis, tissue CO<sub>2</sub> can be increased by anaerobic metabolism, due to regional blood flow maldistribution, shifting blood flow away from mucosa. Moreover, mucosal acidosis may not be mediated by hemodynamic alterations, but may be due to direct metabolic changes induced by endotoxin.<sup>2</sup> Increasing mucosal blood flow by hemodynamic interventions, in this condition, may fail to reestablish normal mucosal PCO<sub>2</sub>. Finally, a paradoxical increase in PCO<sub>2</sub>-gap may be observed, despite of an increase in mucosal blood flow and oxygen saturation. This phenomenon could be explained by the Haldane effect, which states that at any PCO<sub>2</sub>, arterial oxygenated blood has a lower CO<sub>2</sub> content than reduced venous blood. Hence, for a given CO<sub>2</sub> content, PCO<sub>2</sub> will be higher at a higher hemoglobin saturation. Table 1 summarizes the main causes of elevated tissue CO<sub>2</sub>.

### Splanchnic blood flow distribution

Although pHi and PCO<sub>2</sub> gap are often considered as indexes of splanchnic perfusion,<sup>3,4</sup> this has never been shown conclusively. Some experimental and clinical studies have failed to demonstrate a linear correlation between gut mucosa PCO<sub>2</sub> and hepatosplanchnic blood flow. PCO<sub>2</sub> gap reflects merely perfusion

and/or oxygenation conditions of the gut mucosa. Therefore, we cannot generalize gut mucosa CO<sub>2</sub> measurements to the splanchnic area, because blood flow distribution may vary widely between and within organs, especially in sepsis.

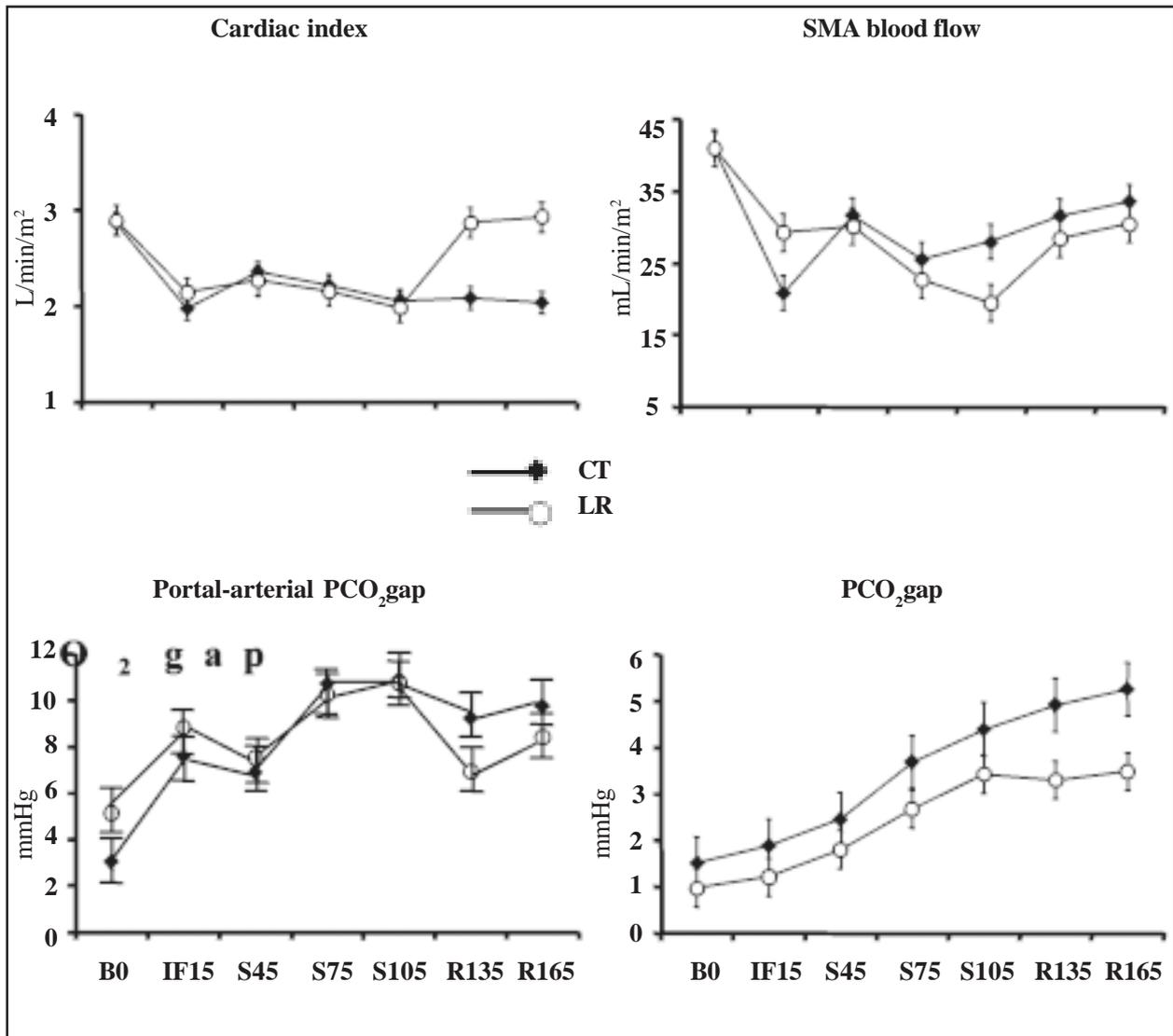
Vallet et al.<sup>5</sup> demonstrated, in a canine model of resuscitated endotoxic shock, a marked redistribution of blood flow within the gut wall, from the mucosa toward the muscularis, with a simultaneous decrease in intestinal mucosal PO<sub>2</sub>. These data contrast with Revelly et al.,<sup>6</sup> who used microspheres to evaluate blood flow distribution within the intestinal wall during endotoxic shock in pigs. Surprisingly, they found that, whereas total mesenteric blood flow was unchanged, blood flow to gut mucosa increased and blood flow to the muscularis decreased. Although marked blood flow redistribution was observed in both studies, their opposite findings could be explained by differences in the methods used to assess mucosal blood flow.

We have recently evaluated the effects of large volume infusion on splanchnic blood flow distribution, using live *E. coli* infusion in dogs (Figure 1). After bacteria infusion, cardiac index (CI) and mesenteric blood flow (MBF, ultrasonic flowprobe) decreased. In contrast, portal-arterial PCO<sub>2</sub> and gastric-arterial PCO<sub>2</sub> (PCO<sub>2</sub> gap) gradients increased. After fluid resuscitation, whereas CI and MBF increased and portal-arterial PCO<sub>2</sub> gradient decreased, PCO<sub>2</sub> gap remained high (Figure 1). If we use CO<sub>2</sub> gradient as a marker of blood flow, we should analyze the behavior of CO<sub>2</sub> gradient in different compartments. There was no correlation between systemic venous-arterial PCO<sub>2</sub>, portal-arterial PCO<sub>2</sub>, and PCO<sub>2</sub> gap, probably reflecting a large blood flow redistribution within these compartments.

**TABLE 1** - Causes of increased gastric intramucosal PCO<sub>2</sub> in septic patients.

Physiologic influence
- Systemic arterial PCO <sub>2</sub>
- Low gastric mucosal blood flow (stagnant flow)
- Increased CO <sub>2</sub> production by aerobic metabolism *
- Increased CO <sub>2</sub> production by anaerobic metabolism *
- Inhibition of pyruvate dehydrogenase *
- Haldane effect

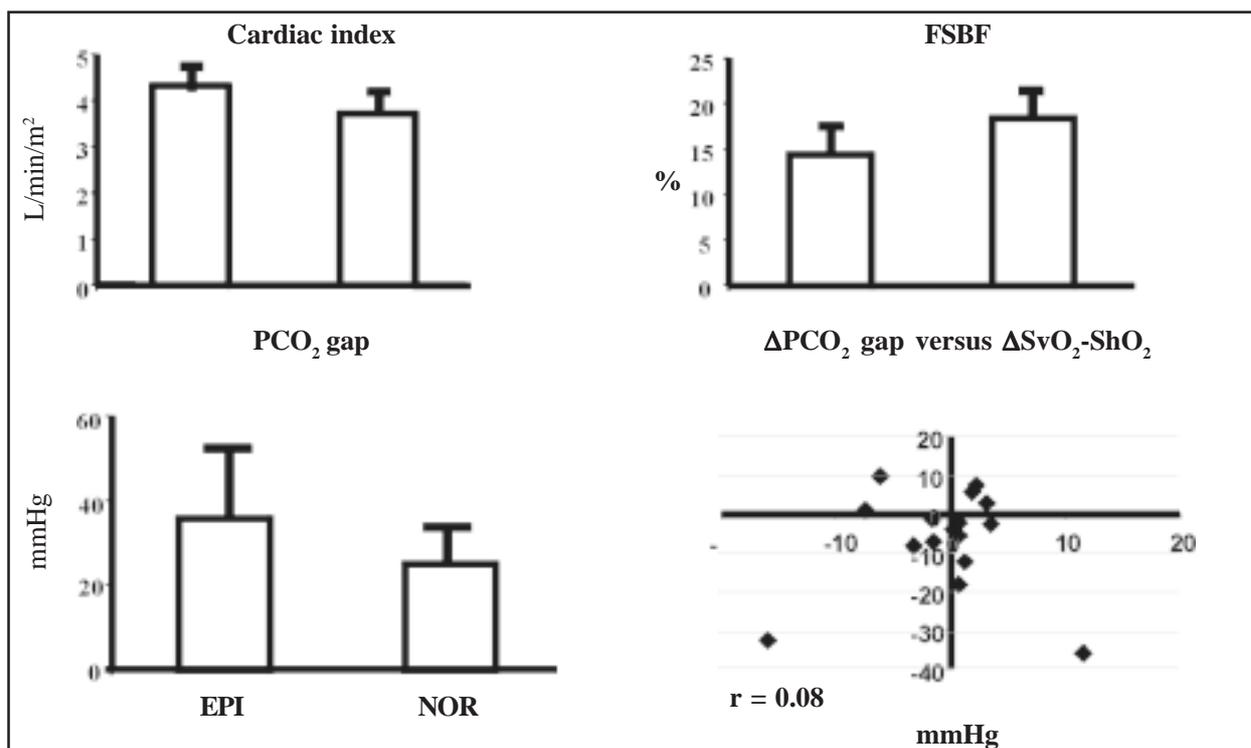
\* without a proportional increase in gastric mucosal blood flow



**FIGURE 1** - Effects of live *E. coli* infusion during 15 min (IF15). After a 90-min period (S45, S75, S105), dogs were randomized to 2 groups: control (CT), no fluids and lactated Ringer (LR), 32 mL/kg, over 60 min (R135, R165). Live bacteria infusion induced sustained decreases in cardiac index (CI) and SMA blood flow, while portal-arterial PCO<sub>2</sub> and mucosal-arterial PCO<sub>2</sub> gradients increased steadily. Only mucosal-arterial PCO<sub>2</sub> gradient was not restored after fluid infusion [adapted from Lagoa CE, Poli de Figueiredo LF, Silva E et al Systemic and splanchnic CO<sub>2</sub> gradients as markers of blood flow distribution after live *E. coli* infusion and volume resuscitation in experimental severe sepsis. *Intensive Care Medicine*, submitted]

Similar findings have emerged from clinical studies. In stable septic patients, Creteur et al.<sup>7</sup> found no significant correlation between PCO<sub>2</sub> gap and hepatosplanchnic blood flow, or between PCO<sub>2</sub> gap and other regional oxygen-derived variables, such as suprahepatic venous blood oxygen saturation and mesenteric veno-arterial PCO<sub>2</sub> gradient. We have studied the effects of norepinephrine and epinephrine infusion on systemic hemodynamic variables, hepatosplanchnic blood flow and gastric mucosal PCO<sub>2</sub> in septic shock patients, and no correlation between them could be

demonstrated.<sup>8</sup> For instance, epinephrine infusion increased CI more than norepinephrine, but fractional splanchnic blood flow was higher with norepinephrine. If the increase in splanchnic blood flow occurred similarly in all gut layers, DPCO<sub>2</sub> gap and DSvO<sub>2</sub>-ShO<sub>2</sub> would decrease proportionally, because SvO<sub>2</sub>-ShO<sub>2</sub> gradient reflects the oxygenation balance in the splanchnic area. However, no correlation between DPCO<sub>2</sub> gap and DSvO<sub>2</sub>-ShO<sub>2</sub> gradient was observed (Figure 2). Our findings support the concept that there is a large blood flow redistribution inter and intra-organs in septic states.<sup>8</sup>



**FIGURE 2** - The effects of epinephrine (EPI)-norepinephrine (NOR) shift on cardiac index (CI), fractional splanchnic blood flow (FSBF) and  $\text{PCO}_2$  gap in 20 septic shock patients. Correlation between the  $\text{PCO}_2$  gap variation ( $\Delta\text{PCO}_2$  gap) and the variation of mixed venous and hepatic venous  $\text{O}_2$  difference ( $\Delta\text{SvO}_2\text{-ShO}_2$ ). \*  $p < 0.05$  [adapted from *Silva E, Creteur J, De Backer D, Vincent JL. Effects of norepinephrine and epinephrine on splanchnic oxygen utilization in septic shock patients. Crit Care Med 1998;26:A63*]

In summary, gut mucosal  $\text{PCO}_2$  is just a surrogate marker of local blood flow, reflecting merely the balance between  $\text{CO}_2$  production and clearance within that layer of the gastrointestinal tract. Actually, we should interpret gut mucosal  $\text{PCO}_2$  as a tool to better understand blood flow distribution in sepsis and its possible clinical implications.

### Clinical uses of gastric tonometry in sepsis

Since gut mucosal hypoperfusion may have a pivotal role in the development of multiple organ dysfunction in sepsis, several authors are attempting to correlate gastric tonometry with outcome. Consequently, many studies have also addressed if gastric acidosis reversal could affect outcome and its response to potential hemodynamic interventions.

### Outcome prediction

Gastric intramucosal acidosis, detected during intensive care admission, has been related to outcome in several trials.<sup>9-13</sup> Its predictive value, after an initial period of treatment in the intensive care unit, has been conflicting. However, those trials have several limitations. The number of patients that has been enrolled is not enough to exclude neither a beta nor an alpha error. Moreover, there is a large heterogeneity regarding inclusion criteria. Mortality has been the main endpoint, which is subject to many influences

other than the ones directly related to the restoration of organ perfusion. Finally, most studies have been using calculated  $\text{pHi}$ , which incorporates systemic bicarbonate, therefore impairing comparison between the effects of systemic and regional perfusion disturbances on outcome, as previously discussed.

Preliminary results from our prospective, ongoing study in patients with severe sepsis and/or septic shock (ACCP/SCCM consensus conference definition), have been suggesting a relationship between  $\text{PCO}_2$  gap and the development of multiple organ dysfunction, assessed by SOFA score.<sup>14</sup> We have already evaluated 44 patients with ages varying between 15-85 years old. Mortality rate has been 40% and APACHE II score, 19. Patients who had a  $\text{PCO}_2$ -gap larger than 15 mm Hg, at the 3<sup>rd</sup> day following resuscitation, either had a high SOFA score ( $>11$ ) or died by the 10<sup>th</sup> day. An interesting finding has been that patients with a sustained high  $\text{PCO}_2$  gap are showing a progressive increase in relative risk for death, on days zero, 1 and 2 (Table 2). Similarly, high SOFA score was associated with mortality.<sup>14</sup> However, caution must be exercised in interpreting these data, because gastric mucosa acidosis could be just a marker of sepsis-induced dysfunction in cellular metabolism, instead of the cause of multiple organ failure, as has been widely claimed. Additional clinical trials are needed to confirm and better clarify this relationship.

**TABLE 2 -** Relative risk for death for septic shock patients on days zero, 1, 2, and 3.  
Adapted from *Silva E et al.*<sup>14</sup>

	Day 0	Day 1	Day 2	Day 3	
PCO <sub>2</sub> gap	1.8	1.7	3.2	2,7	RR
(> 15mmHg)	(0.9-3.4)	(0.9-3.1)	(1.3-7.7)	(1,2-6,3)	CI
	0.15	0.17	0.003	0.002	<i>p</i>
SOFA	1.6	1.9	4.4	3.6	RR
(> 11)	(0.8-3.4)	(0.8-4.2)	(1.5-12.9)	(1,2-10.6)	CI
	0.20	0.11	0.0008	0.006	<i>p</i>

RR – relative risk; CI – confidence interval.

### Hemodynamic management of gastric mucosal acidosis in septic patients

From the preceding discussion, it seems attractive to attempt to reduce intestinal microcirculation abnormalities in sepsis. A reasonable hypothesis to be tested is that the use of vasoactive agents, which optimize intestinal perfusion, can reduce the incidence of MODS in septic patients.<sup>5,15</sup>

Total hepatosplanchnic blood flow, measured by indocyanine green technique, and mucosal blood flow, measured directly by laser Doppler or indirectly by gas tonometry, have been used to assess regional oxygenation during the most commonly used hemodynamic interventions in sepsis, fluid replacement and vasoactive drug infusion.

Absolute or relative hypovolemia is commonly present in septic patients and it is responsible, in part, for tissue hypoperfusion, justifying why fluid replacement is considered an essential, early intervention in sepsis. However, the relationship between fluid resuscitation and gastric mucosal blood flow remains incompletely characterized. Actual knowledge is largely based on experimental studies. In an endotoxic shock model in dogs, De Backer et al.<sup>15</sup> showed that fluid resuscitation increased mesenteric blood flow but did not prevent the decrease in gastric mucosal pH. Also in endotoxemic dogs, Vallet et al.<sup>17</sup> showed that fluid resuscitation increased cardiac output and gut serosal PO<sub>2</sub>, and restored systemic VO<sub>2</sub>; however, gut VO<sub>2</sub>, mucosal PO<sub>2</sub> and pHi remained low and gut lactate output high. We evaluated systemic and regional effects of fluid resuscitation in dogs with sepsis induced by live *E. coli* infusion. Crystalloid infusion restored both systemic and global regional variables, such as superior mesenteric artery blood flow and portal vein-arterial PCO<sub>2</sub> gradient. However, fluid infusion only avoided further increases in PCO<sub>2</sub> gap, with no improvement after 60 minutes (Figure 1).

Data from clinical studies are very limited. In a small group of hypovolemic septic patients, Forrest et al.<sup>18</sup> reported that fluid loading neither increased pHi nor decreased PCO<sub>2</sub> gap. Addressing the repercussion of a fluid challenge (500 mL of hetastarch over 30 minutes), on systemic hemodynamic parameters and PCO<sub>2</sub> gap in patients with severe sepsis or septic shock, we did show a decrease in mean PCO<sub>2</sub> gap.<sup>19</sup> However, significant individual variations in PCO<sub>2</sub> gap response were observed and there was no correlation between changes in cardiac index and PCO<sub>2</sub> gap. These data suggest that PCO<sub>2</sub> gap should not be used isolated to guide fluid replacement.

When tissue oxygenation is not restored despite fluid replacement, vasoactive drugs are commonly used to increase oxygen supply and avoid hypotension. However, they induce different changes on systemic and regional blood flow. We reviewed the effects of vasoactive drugs on gastric pHi.<sup>20</sup> Within the inherent limitations with the use of pHi, in most studies, as the gut mucosal perfusion index, we highlighted that a) although dopaminergic effects can increase splanchnic blood flow, low-dose dopamine usually decreases pHi, suggesting a blood flow redistribution away from gastric mucosa; b) dobutamine most commonly increases splanchnic blood flow and tends to increase pHi in septic patients. In addition, dobutamine can disclose the presence of severe splanchnic hipoperfusion in septic patients. Creteur et al.<sup>21</sup> showed that, in patients with low fractional splanchnic blood flow (SBF/cardiac index), the PCO<sub>2</sub> gap fell significantly with increasing doses of dobutamine; c) dopexamine has been shown to increase splanchnic oxygenation, principally in sepsis, but it can also induce undesirable hypotension; d) data on norepinephrine are more limited, but suggest that it can increase pHi in patients with septic shock; and e) epinephrine could impair splanchnic perfusion in patients with septic shock. More recent data support the benefits of beta-adrenergic agents on gastric

mucosal perfusion.<sup>22,23</sup> These data can be summarized by a commonly employed statement “beta-adrenergic effects have a pivotal role in increasing gut mucosal blood flow in sepsis”.

Targeting the intestinal microcirculation with vasoactive drugs is one approach to counteract the microvascular abnormalities in the pathophysiology of sepsis. However, major individual variations are present in several studies including ours.<sup>19-21,24</sup> Clinicians must exercise prudence to incorporate these evidences in clinical practice and should test different doses of distinct catecholamines to achieve their physiological therapeutic aims.

### Gas tonometry guided-therapy

In critically ill patients, a persistently high PCO<sub>2</sub> gap may be associated with worsening in outcome but it has not been definitively established if this finding is just an epiphenomenon or a pathophysiological event of the development of multiple organ dysfunction. However, in evidence-based medicine (EBM) époque, clinicians have claimed for a large multicenter randomized clinical trial, proving or disproving the effectiveness of PCO<sub>2</sub> gap-guided therapy, before actively incorporating its use in the daily practice.

To date, only five controlled studies have examined whether treatment aimed to increase pHi improve outcome. None of them addressed exclusively septic patients and only two enrolled an expressive number of patients to allow drawing some conclusion. Gutierrez et al.<sup>25</sup> performed a randomized, controlled clinical trial comparing standard therapy (not specified) to additional therapy, described as further fluid and red blood cell replacements plus dobutamine infusion, to correct low pHi in critically ill patients. They showed that mortality rate was significantly reduced in those patients with an admission pHi of > 7.35. More recently, Gomersall et al.,<sup>26</sup> using a more controlled resuscitation protocol, sought if additional therapy, aimed at correcting low pHi, would improve outcome in conventionally treated critically ill patients. In this study, pHi guided-therapy failed to improve outcome. However, both studies, enrolled heterogeneous groups of patients. As one would expect, it is not probable that an isolated, miraculous intervention for different patients could produce outcome improvement. In the Gutierrez's study, mortality in the control group was unexpectedly high, and no attempt was made to standardize treatment.<sup>25</sup> In Gomersall's study, there was no difference in pHi between control and intervention groups at zero, 12, and 24 hours, when the intervention was withhold.<sup>26</sup> We have demonstrated that persistent gastric mucosal acidosis, beyond 24 hours, is very important to predict outcome.<sup>14</sup> So, treatment protocol

could be maintained until 48 or 72 hours after the beginning of resuscitation. Finally, as mentioned, the use of calculated pHi incorporates systemic metabolic and respiratory variables, compromising the interpretation of pHi as a regional parameter to be targeted.

Recently, Chapman et al.<sup>27</sup> published the state of the art on gastrointestinal tonometry. The authors emphasized that, while it may be possible to apply the principles of evidence-based medicine to the evaluation of a single intervention affecting outcome, applying them to the introduction of a new piece of monitoring is even more complex. It is the management driven by and the therapeutic interventions taken in response to the monitor's information which may affect outcome. Both are dependent on many other factors, not simply the numbers displayed on the monitor's screen. For an example, pulse oximetry would not be used in clinical setting based on these principles, because there was no difference in outcome or complication rate with its use. However, it was shown that it allows a rapid, early and safe diagnosis, and correction of arterial hypoxemia with significantly less supplemental oxygen than with the group of patients without pulse oximetry. The same may be true for gas tonometry, which may provide information guiding interventions leading to the reversal of disturbances that may be linked to multiple organ dysfunction.

### CONCLUSIONS

There are clinical and experimental evidences that support the relationship between splanchnic hypoperfusion and multiple organ dysfunction in patients and animals submitted to sepsis, shock, trauma or complex surgical procedures, largely related to mucosal injury leading to increased permeability and systemic inflammatory response. As gut mucosal pCO<sub>2</sub> 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. 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 pela sepse e choque séptico. 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, a principal causa comum de morte na sepse. Monitorar a perfusão intestinal na sepse experimental e clínica pode fornecer dados valiosos quanto a novas intervenções e tratamentos altamente necessários para reduzir disfunção de múltiplos órgãos e mortalidade extremamente elevadas na sepse. Apresentamos nossa experiência com a tonometria a gás como monitor da adequação da perfusão da mucosa gastrointestinal na sepse clínica e experimental, e com o uso de drogas vasoativas no controle hemodinâmico em pacientes com choque séptico.

**DESCRITORES** – Choque séptico. Falência de múltiplos órgãos. Tonometria. Sepse. Catecolaminas. Mucosa intestinal.

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