

Research

Open Access

Effects of volume resuscitation on splanchnic perfusion in canine model of severe sepsis induced by live *Escherichia coli* infusionClaudio Esteves Lagoa¹, Luiz Francisco Poli de Figueiredo², Ruy Jorge Cruz Jr³, Eliézer Silva⁴ and Mauricio Rocha e Silva⁵¹DVM, Fellow, Division of Applied Physiology, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil²Associate Professor, Division of Applied Physiology, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil³Assistant Physician, Division of Applied Physiology, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil⁴Visiting Professor, Division of Applied Physiology, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil⁵Chairman, Division of Applied Physiology, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, BrazilCorresponding author: Luiz Francisco Poli de Figueiredo, lpoli@uol.com.br

Received: 30 October 2003

Revisions requested: 22 December 2003

Revisions received: 14 April 2004

Accepted: 21 April 2004

Published: 27 May 2004

Critical Care 2004, **8**:R221-R228 (DOI 10.1186/cc2871)This article is online at: <http://ccforum.com/content/8/4/R221>© 2004 Lagoa *et al.*; licensee BioMed Central Ltd. This is an Open Access article: verbatim copying and redistribution of this article are permitted in all media for any purpose, provided this notice is preserved along with the article's original URL.**Abstract****Introduction** We conducted the present study to investigate whether early large-volume crystalloid infusion can restore gut mucosal blood flow and mesenteric oxygen metabolism in severe sepsis.**Methods** Anesthetized and mechanically ventilated male mongrel dogs were challenged with intravenous injection of live *Escherichia coli* (6×10^9 colony-forming units/ml per kg over 15 min). After 90 min they were randomly assigned to one of two groups – control (no fluids; $n = 13$) or lactated Ringer's solution (32 ml/kg per hour; $n = 14$) – and followed for 60 min. Cardiac index, mesenteric blood flow, mean arterial pressure, systemic and mesenteric oxygen-derived variables, blood lactate and gastric carbon dioxide tension (PCO₂; by gas tonometry) were assessed throughout the study.**Results** *E. coli* infusion significantly decreased arterial pressure, cardiac index, mesenteric blood flow, and systemic and mesenteric oxygen delivery, and increased arterial and portal lactate, intramucosal PCO₂, PCO₂ gap (the difference between gastric mucosal and arterial PCO₂), and systemic and mesenteric oxygen extraction ratio in both groups. The Ringer's solution group had significantly higher cardiac index and systemic oxygen delivery, and lower oxygen extraction ratio and PCO₂ gap at 165 min as compared with control animals. However, infusion of lactated Ringer's solution was unable to restore the PCO₂ gap. There were no significant differences between groups in mesenteric oxygen delivery, oxygen extraction ratio, or portal lactate at the end of study.**Conclusion** Significant disturbances occur in the systemic and mesenteric beds during bacteremic severe sepsis. Although large-volume infusion of lactated Ringer's solution restored systemic hemodynamic parameters, it was unable to correct gut mucosal PCO₂ gap.**Keywords:** gas tonometry, live *E. coli*, mesenteric blood flow, oxygen metabolism, severe sepsis**Introduction**

Sepsis leads to endothelial damage, marked alterations in blood flow distribution and altered tissue oxygen metabolism, which are associated with high mortality rates among critically ill patients [1-3]. Although volume replacement is among the cornerstones of therapy for septic shock [4], studies conducted to elucidate the actual impact of fluid infusion on both

experimental and clinical sepsis with respect to systemic end-points of resuscitation and outcome are inconsistent [5-8]. This is largely because of the wide variety of experimental designs and fluid regimens employed.

Substantial clinical and animal evidence indicates that the mesenteric circulatory bed, particularly at the gut mucosa, is

highly vulnerable to reductions in oxygen supply and is prone to injury early in the course of shock [9-11]. Gut hypoxia or ischemia is one factor that possibly contributes to dysfunction of the gastrointestinal tract barrier, which may in turn contribute to the development of systemic inflammatory response and multiple organ dysfunction syndromes [12-15].

Although bolus injection of live bacteria has potential downsides [16], it may mimic the very early hemodynamic phase of severe sepsis, and serve to illustrate how systemic and regional blood flows react to aggressive and prompt fluid replacement. Interesting results have recently been reported in patients with sepsis resuscitated in the emergency room [17] based on central venous oxygen saturation. However, the disparity between systemic and regional variables has been well demonstrated, particularly in such a complex disease as sepsis, with a wide variety of clinical presentations and resuscitation protocols employed in clinical and experimental studies of shock. In the majority of experimental studies, fluid infusion did not restore intestinal mucosal perfusion, even though systemic and mesenteric parameters were improved [18,19]. In a recent clinical study conducted in patients with sepsis [20], a wide interindividual variability in carbon dioxide tension (PCO_2) gap in response to fluid loading was observed.

Our hypothesis is that, despite restoring systemic hemodynamic and oxygen derived variables, large-volume crystalloid infusion fails to restore gut mucosal blood flow and PCO_2 gap in animals challenged with infusion of live bacteria. Hence, we evaluated the impact of this early volume resuscitation on the systemic and splanchnic circulations in a model of severe sepsis.

Methods

The present study was approved by the Animal Care and Use Committee of the University of São Paulo Medical School, and was conducted in compliance with the guidelines of the National Regulations for the Care and Use of Laboratory Animals.

Animal preparation

Twenty-seven healthy male mongrel dogs (weight 17.2 ± 1.2 kg) were fasted for 12 hours before the start of the study and were given free access to water. Anesthesia was induced with an intravenous injection of 0.06 mg/kg morphine sulfate, followed by 25 mg/kg sodium pentobarbital. A cuffed endotracheal tube was placed into the trachea to allow mechanical ventilation with 100% oxygen, at a tidal volume of 20 ml/kg (Takaoka 2600, Takaoka Ltda, São Paulo, SP, Brazil). Respiratory rate was adjusted to maintain arterial PCO_2 at 35 ± 5 mmHg. A heating pad was used to maintain the core body temperature at $38.5 \pm 1.0^\circ C$. Additional doses of pentobarbital (2 mg/kg) were administered whenever required. A urinary catheter was placed for urine drainage. Each dog received an intravenous injection of 300 mg cimetidine.

The right common femoral artery was dissected and cannulated with a polyethylene catheter to measure mean arterial pressure at the abdominal aorta and to collect arterial blood samples for blood gas and lactate analysis. A catheter was introduced through the right common femoral vein for fluid infusion. Each animal received an infusion of lactated Ringer's solution (13 ml/kg) during the preparation period.

A 7.5-Fr flow-directed thermodilution fiberoptic pulmonary artery catheter (Edwards Swan-Ganz CCombo 744H7.5F; Baxter Edwards Critical Care, Irvine, CA, USA) was introduced through the right external jugular vein. The tip was placed in the pulmonary artery, guided by radioscopy and wave tracings, to measure pulmonary arterial pressures, continuous mixed venous oxygen saturation (SVO_2), and for mixed venous sampling for blood gas analysis. This catheter was connected to a cardiac computer (Vigilance™; Baxter Edwards Critical Care) to measure cardiac output using 3-ml bolus injections of isotonic saline at $20^\circ C$ every 10 min. All catheters were connected to disposable pressure transducers (P23XL; Viggo-Spectramed, Stathan, CA, USA) and to a computerized multichannel system for acquisition of biologic data (Acknowledge; Biopac Systems Inc., Goleta, CA, USA).

A left subcostal celiotomy was performed and an ultrasonic flow probe (Transonic Systems Inc., Ithaca, NY, USA) was placed around the origin of the superior mesenteric artery for measurement of transit time flow in this vessel (model T206; Transonic Systems Inc.). A P240 catheter was threaded into the portal system via the splenic vein for portal blood sampling. A large gastric polyethylene tube was introduced through the mouth and placed in the stomach, and a gastric lavage was performed with warm isotonic saline solution until a clear fluid was obtained at drainage. Then, a 16-Fr TRIP® tonometry catheter (TRIP® NGS, Tonometrics Division, Instrumentarium Copr., Helsinki, Finland.) was introduced orally and positioned at the large curvature of the stomach. The tonometry catheter was connected to a calibrated gas capnometer (Tonocap, model TC-200; Tonometrics, Datex-Engstrom, Finland) for gastric PCO_2 measurement.

Bacterial preparation

A strain of *Escherichia coli* O55B, provided by the Adolfo Lutz Institute of Infectious Diseases, originating from the stool of a patient with gastrointestinal sepsis, was used in the study. The bacteria were stored in gelose at room temperature, activated in trypticase soy broth, plated in trypticase soy agar and incubated at $36^\circ C$ for 24 hours. Aliquots were then suspended in sterile saline. The bacterial suspension was estimated turbidimetrically by comparing the newly grown bacterial suspension with known standards through spectrophotometry at a wavelength of 625 nm, in order to obtain a culture of the desired bacterial density. The same suspension was subsequently quantified by plating successive 10-fold dilutions onto trypticase soy agar plates and scoring visible colonies after 24

hours of incubation at 36°C. Our target dose, as calculated using the methods outlined above, was 3×10^9 cells/ml or 6×10^9 colony-forming units/ml per kg body weight.

Data collection and analysis

Mean arterial pressure, pulmonary artery and central venous pressures, heart rate and mesenteric blood flow were continuously recorded. Pulmonary artery occluded pressure was measured at every time point. Cardiac output was determined using thermodilution technique and expressed as cardiac index according to the dog's body surface area. Each determination was the arithmetic mean of three consecutive measurements when their differences did not exceed 10%.

Arterial, portal and mixed venous base deficit, pH, PCO₂, oxygen tension, oxygen saturation, hemoglobin, hematocrit, bicarbonate, and lactate levels were measured at baseline, and then at 15, 45, 75, 105, 135 and 165 min during the experimental protocol. All arterial, venous, and portal blood samples were analyzed by a Stat Profile Ultra Analyzer (Nova Biomedical, Waltham, MA, USA). Systemic and mesenteric oxygen delivery (DO₂) and systemic and mesenteric oxygen extraction ratio (O₂ER) were calculated using standard formulae.

Systemic venous–arterial PCO₂ gradient was calculated as the difference between mixed venous PCO₂ and arterial PCO₂. Portal–arterial PCO₂ gradient was calculated as the difference between portal vein PCO₂ and arterial PCO₂. Gastric mucosal PCO₂ was evaluated every 10 min. PCO₂ gap was calculated as the difference between gastric mucosal and arterial PCO₂.

Experimental protocol

After surgical preparation, animals were allowed to stabilize for 30 min. After baseline measurements (0 min), an infusion of *E. coli* at a dose of 6×10^9 colony-forming units/ml per kg was started and maintained for 15 min. At 90 min after bacterial infusion (S105), the animals were randomly assigned to two groups. Control animals ($n = 13$) received no fluids and were followed for 60 min with no additional intervention. Treated animals ($n = 14$) received lactated Ringer's solution (32 ml/kg per hour) and were also followed for 60 min. All animals were killed at the end of the experimental protocol (R165) by an overdose of anesthetic followed by injection of hypertonic potassium chloride.

Statistical analysis

Results are expressed as mean \pm standard error of the mean. Statistical analysis was performed using the Statistical Package for Social Sciences for Windows (version 6.0; SPSS Inc., Chicago, IL, USA). Two-way analysis of variance for repeated measures and *post hoc* Tukey's test were used to analyze differences between groups. Comparisons of values at different time points within groups were performed using analysis of

variance for repeated measures. $P < 0.05$ was considered statistically significant.

Results

Systemic effects of live *Escherichia coli* infusion and fluid replacement

The infusion of live *E. coli* promoted significant reductions in mean arterial pressure, cardiac index, DO₂, and SVO₂. In parallel, increases in oxygen extraction rate, venous–arterial PCO₂ gradient and arterial lactate were detected (Figs 1 and 2; Table 1).

In untreated control animals hemoglobin levels exhibited a sustained increase. Mean arterial pressure exhibited a spontaneous, partial, and progressive increase. No other systemic variable showed such a trend toward recovery within 150 min after the end of bacterial infusion (Figs 1 and 2; Table 1).

Fluid replacement was associated with an increase in mean arterial pressure, similar to that observed in untreated control animals. Other systemic variables (i.e. cardiac index, DO₂, and SVO₂) were restored to baseline values, and were significantly greater than those in control animals. Arterial lactate remained elevated after fluid infusion, at levels similar to those in control animals (Figs 1 and 2; Table 1).

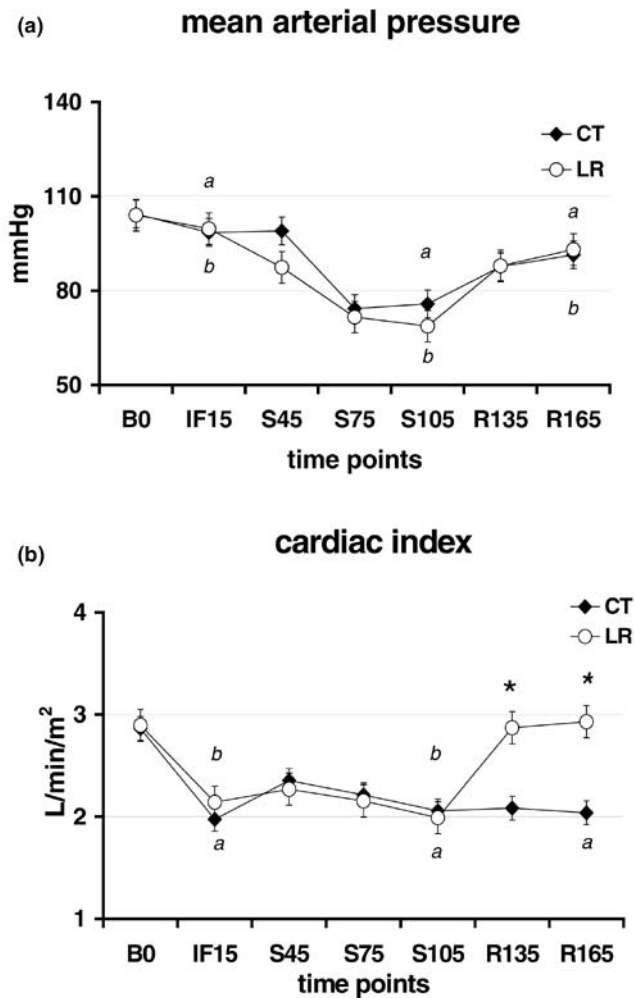
Regional effects of live *Escherichia coli* infusion and fluid replacement

Live *E. coli* infusion resulted in marked reductions in mesenteric blood flow, mesenteric DO₂ and portal SVO₂, whereas significant increases in mesenteric O₂ER, portal lactate and portal–arterial PCO₂ gradients were observed (Fig. 2; Table 2). Control animals exhibited a spontaneous increase in mesenteric blood flow and mesenteric DO₂, whereas portal lactate and portal oxygen saturation showed no significant changes. Treated animals exhibited only a partial increase in mesenteric blood flow. Fluid infusion was unable to restore the other regional variables. PCO₂ gap began to increase progressively after bacterial infusion. At 105 min the PCO₂ gap had increased by approximately 150% ($P < 0.0001$) in both groups (Fig. 2) and showed a sustained increase in control animals. Fluid replacement prevented further increases in the PCO₂ gap but was unable to reverse the increase, which remained significantly greater than at baseline but was lower than that in control animals.

Discussion

This model of severe sepsis satisfactorily matched the hemodynamic changes that are characteristic of a nonresuscitated, hypodynamic septic patient. Live *E. coli* injection promoted reductions in cardiac output, mean arterial pressure, and mesenteric blood flow. These alterations were paralleled by increases in systemic venous–arterial, portal–arterial and gastric mucosal–arterial PCO₂ gradients, thus reflecting the blood flow disturbances induced by the challenge with live bacteria.

Figure 1

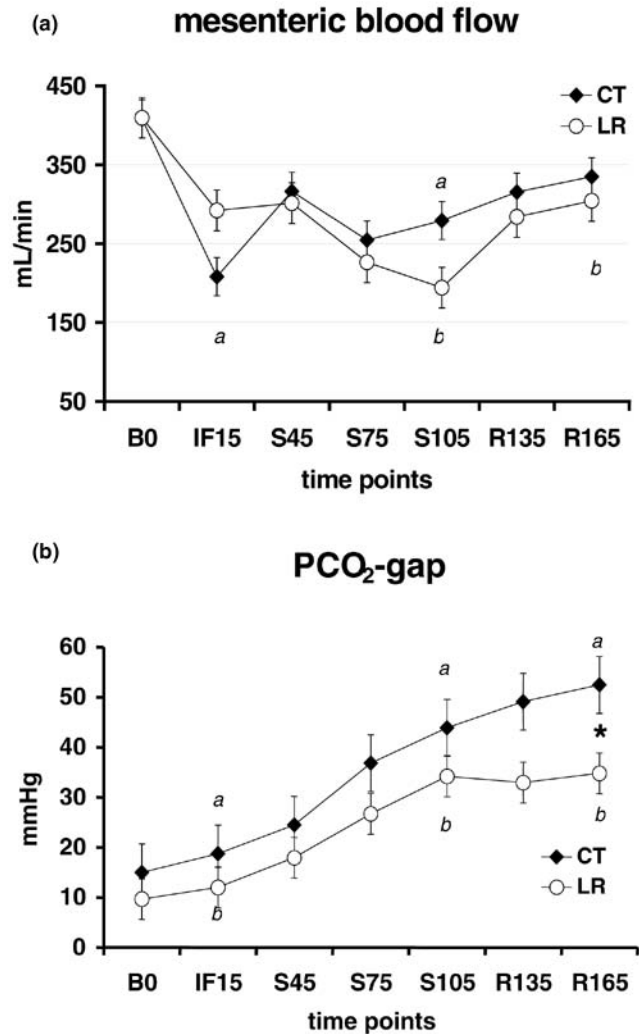


(a) Mean arterial pressure and (b) cardiac index. Data are expressed as mean \pm standard error of the mean. B0, baseline; IF15, 15 min after bacterial infusion; S45–S105, shock, 45–105 min after B0; R135–R165, resuscitation period. * $P < 0.05$ control (CT) versus baseline; † $P < 0.05$ lactated Ringer's solution (LR) versus baseline; * $P < 0.05$ CT versus LR.

The main finding in the study is that large-volume crystalloid resuscitation failed to correct the oxygen debt established in the mesenteric circulation, particularly gut mucosal blood flow, even though systemic hemodynamic and oxygen-derived parameters were restored.

Although several studies have shown that endotoxin infusion is associated with marked decreases in cardiac output and mesenteric blood flow, and with an increase in gastric mucosal PCO_2 [21–23], data from experiments involving infusion of live bacteria are scarce. In our model infusions of viable bacteria reproduced many of the features of early severe sepsis in humans, including hypotension, hyperlactatemia, and oliguria. The inflammatory response to infusion of viable bacteria can

Figure 2



(a) Superior mesenteric artery blood flow and (b) carbon dioxide tension (PCO_2) gap. Data are expressed as mean \pm standard error of the mean. B0, baseline; IF15, 15 min after bacterial infusion; S45–S105, shock, 45–105 min after B0; R135–R165, resuscitation period. * $P < 0.05$ control (CT) versus baseline; † $P < 0.05$ lactated Ringer's solution (LR) versus baseline; * $P < 0.05$ CT versus LR.

be more pronounced than that produced by endotoxin infusions [16]. This model is less expensive than endotoxin infusion in large animals, and it induces a more severe hemodynamic compromise with a low early mortality rate, mimicking severe sepsis after bacteremia. Hence, it is a very useful tool for improving our understanding of the earliest stages in bacteremic sepsis. Models that allow more prolonged observation of infection, such as intraperitoneal clot or cecum puncture and ligation, could better represent most clinical conditions. However, we aimed for a model that induces rapid and profound changes, such as those that are seen in bloodstream infections, thus allowing us to address the effects of

Table 1**Central venous and pulmonary artery occluded pressures, systemic oxygen-derived variables, arterial lactate, pH and hemoglobin**

Parameter	Baseline	Minutes after bacterial infusion			
		15	90	120	150
CVP (mmHg)					
Control	3.7 ± 0.4	4.0 ± 0.4	2.7 ± 0.5	2.4 ± 0.5	2.7 ± 0.5
Lactated Ringer's	3.3 ± 0.5	2.8 ± 0.5	2.4 ± 0.5	4.2 ± 0.8	4.9 ± 0.8
PAOP (mmHg)					
Control	6.1 ± 0.5	5.3 ± 0.8	4.0 ± 0.5	4.2 ± 0.6	4.3 ± 0.6
Lactated Ringer's	4.4 ± 0.5	4.1 ± 0.6	4.4 ± 0.6	5.0 ± 0.7	4.9 ± 0.5
pH					
Control	7.416 ± 0.01	7.416 ± 0.01	7.416 ± 0.01	7.416 ± 0.01	7.416 ± 0.01
Lactated Ringer's	7.424 ± 0.01	7.406 ± 0.01	7.384 ± 0.01	7.384 ± 0.01	7.408 ± 0.01
Hemoglobin (g/dl)					
Control	12.2 ± 0.5	12.5 ± 0.5	13.7 ± 0.3	14.0 ± 0.3**	14.2 ± 0.4**
Lactated Ringer's	12.6 ± 0.4	12.8 ± 0.5	13.8 ± 0.5	12.1 ± 0.5	11.5 ± 0.6
DO₂ (ml/min)					
Control	402.6 ± 27.3	284.9 ± 25.1*	321.7 ± 36.7*	328.7 ± 37*	325.3 ± 28.4*
Lactated Ringer's	432.8 ± 30.7	322.3 ± 25.1 [†]	320.9 ± 29.4 [†]	404.5 ± 21.8	395.4 ± 28.3
O₂ER (%)					
Control	23.9 ± 2.1	30.5 ± 2.5*	33.1 ± 3.0*	28.8 ± 2.8*	32.5 ± 2.8*
Lactated Ringer's	23.8 ± 3.0	26.9 ± 3.7	33.1 ± 5.6 [†]	26.7 ± 2.5	23.3 ± 2.3 [‡]
SVO₂ (%)					
Control	80.1 ± 2.3	69.7 ± 2.5*	67.4 ± 3.4*	71.6 ± 3.2*	67.6 ± 3.0*
Lactated Ringer's	78.6 ± 3.2	73.6 ± 3.8 [†]	66.8 ± 5.7 [†]	76.7 ± 2.6 [†]	77.2 ± 2.3 [‡]
Arterial lactate (mmol/l)					
Control	1.58 ± 0.49	1.62 ± 0.39	3.73 ± 0.34*	3.48 ± 0.29*	3.31 ± 0.25*
Lactated Ringer's	1.57 ± 0.24	1.85 ± 0.23	4.01 ± 0.65 [†]	4.22 ± 0.59 [†]	3.44 ± 0.51 [†]
Veno-arterial PCO₂ gradient (mmHg)					
Control	4.9 ± 1.0	8.4 ± 1.2	12.6 ± 2.0*	9.3 ± 1.7*	9.8 ± 2.0*
Lactated Ringer's	6.9 ± 1.0	8.8 ± 1.5	9.7 ± 1.5	5.8 ± 1.2	6.2 ± 0.8

Measurements were taken in control animals ($n = 13$) and animals treated with lactated Ringer's solution ($n = 14$). Data are expressed as mean ± standard error of the mean. CVP, central venous pressure; DO₂, systemic oxygen delivery; O₂ER, systemic oxygen extraction ratio; PAOP, pulmonary artery occluded pressure; PCO₂, carbon dioxide tension; SVO₂, mixed venous oxygen saturation. * $P < 0.05$, control versus baseline; [†] $P < 0.05$ lactated Ringer's versus baseline; [‡] $P < 0.05$ control versus lactated Ringer's.

early interventions (i.e. fluid infusion) in the absence of other confounding factors.

The observed increase in venous–arterial PCO₂ gradient reflected the reduction in cardiac output, whereas the increase in portal–arterial PCO₂ gradient paralleled mesenteric blood flow. However, the PCO₂ gap did not parallel systemic and regional blood flow trends. Hence, the distri-

bution of blood flow within the gut wall cannot be determined by following regional flow distribution.

The PCO₂ gap is often considered an index of splanchnic perfusion, but this has never been demonstrated conclusively. Some experimental and clinical studies have failed to demonstrate a linear correlation between gut mucosal PCO₂ and hepatosplanchnic blood flow [24,25]. The PCO₂ gap

Table 2**Regional oxygen-derived variables and portal vein lactate**

Parameter	Baseline	Minutes after bacterial infusion			
		15	90	120	150
Mesenteric DO ₂ (ml/min)					
Control	71.6 ± 8.5	37.7 ± 3.9*	54.4 ± 9.6*	61.7 ± 10.6	66.6 ± 11.2
Lactated Ringer's	74.3 ± 9.1	53.5 ± 7.1 [†]	37.9 ± 5.2 [†]	47.8 ± 4.2 [†]	48.2 ± 4.7 [†]
Mesenteric O ₂ ER (%)					
Control	15.1 ± 1.8	23.6 ± 3.1*	32.7 ± 3.7*	29.7 ± 4.5*	28.3 ± 3.5*
Lactated Ringer's	15.6 ± 2.8	19.8 ± 2.6 [†]	27.9 ± 2.8 [†]	22.3 ± 2.1 [†]	24.5 ± 2.3 [†]
SpO ₂ (%)					
Control	88.3 ± 1.6	75.9 ± 3.1*	67.5 ± 3.9*	71.9 ± 4.8*	71.7 ± 3.4*
Lactated Ringer's	87.9 ± 2.1	80.2 ± 1.9 [†]	72.4 ± 3.3 [†]	80.5 ± 2.1 [†]	77.4 ± 2.2 [†]
Portal vein lactate (mmol/l)					
Control	1.56 ± 0.44	1.67 ± 0.37*	3.65 ± 0.32*	3.31 ± 0.35*	3.32 ± 0.28*
Lactated Ringer's	1.58 ± 0.21	1.88 ± 0.22 [†]	3.97 ± 0.54 [†]	4.01 ± 0.52 [†]	3.55 ± 0.44 [†]
Portal-arterial PCO ₂ gradient (mmHg)					
Control	3.6 ± 1.0	7.9 ± 1.4*	11.1 ± 1.2*	9.3 ± 2.1*	9.6 ± 1.4*
Lactated Ringer's	4.9 ± 0.9	8.7 ± 1.4 [†]	11.1 ± 1.6 [†]	6.7 ± 1.7 [†]	7.5 ± 1.2 [†]

Measurements were taken in control animals ($n = 13$) and animals treated with lactated Ringer's solution ($n = 14$). Data are expressed as mean \pm standard error of the mean. DO₂, oxygen delivery; O₂ER, oxygen extraction ratio; PCO₂, carbon dioxide tension; SpO₂, portal vein oxygen saturation. * $P < 0.05$, control versus baseline; [†] $P < 0.05$ lactated Ringer's versus baseline.

merely reflects perfusion and/or oxygenation conditions of the gut mucosa. Therefore, we cannot extend gut mucosal carbon dioxide measurements to the entire splanchnic area, because blood flow distribution varies widely between and within organs, especially in sepsis. The peculiar microcirculatory system and its countercurrent exchange of oxygen and carbon dioxide within the mucosal villus could explain these findings. Because of these factors, techniques specially designed to assess mucosal blood flow, such as laser Doppler flowmetry [26], reflectance spectroscopy [27], and intravital microscopy [28], are the methods of choice for studying flow derangements associated with intramucosal acidosis. Also, gastric mucosal acidosis may not reflect blood flow reduction, but only oxygen impairment at the cellular level, which has been termed cytopathic hypoxia [29]. This may explain the coexistence of high tissue PCO₂ with adequate tissue oxygen tension and small intestine wall blood flow that has been observed by some authors [30]. In fact, a high gastric-arterial PCO₂ gradient could be a marker of dysoxia, irrespective of the causes of impaired oxygen utilization, although blood flow is always the major determinant of this gradient.

Our fluid challenge regimen efficiently restored cardiac index, systemic oxygen delivery, and SVO₂ to prechallenge measures. In the study, mesenteric O₂ER, portal lactate, and PCO₂ gap remained significantly elevated throughout the experiment

in both groups. As in the report by Baum and coworkers [31], our results also indicate that intravascular volume expansion alone was incapable of correcting gut mucosal acidosis. Our findings are in agreement with those from other clinical and experimental studies [32,33] that have demonstrated that gut hypoperfusion and acidosis occur rapidly after a septic challenge, despite normal mean arterial pressure, and elevated cardiac output and blood flow. From the therapeutic standpoint, though, it is surprising that large-volume crystalloid infusions had no major impact on total gut blood flow, DO₂, and mucosal acidosis as compared with controls. In fact, Drazenovic and coworkers [34] demonstrated that an endotoxin challenge can lead to a small but significant reduction in the density of perfused capillaries in the intestinal mucosal villi and crypts. This may explain the apparent loss of the relationship between oxygen availability and gut perfused capillary density found in that study. These data further demonstrate that variables of systemic cardiopulmonary function, and even the level of mesenteric DO₂, may be poor indicators of the intestinal mucosal perfusion status.

Changes in blood rheologic properties, derangement in the number of perfused capillaries, and alterations in microcirculatory blood flow to the gut mucosa may explain why large-volume crystalloid infusion was ineffective in correcting intramucosal PCO₂ gap and oxygen metabolism to preshock

values in the present study. Previously, Fink and coworkers [35] showed that intravascular volume expansion and massive doses of dobutamine ameliorate, but do not completely prevent, the development of mucosal acidosis in endotoxemic pigs.

Our data support the feasibility and usefulness of gastric PCO₂ monitoring for detecting gut mucosal malperfusion and ischemia, even in 'normodynamic, resuscitated' severe septic individuals. It also indicates that careful monitoring of mesenteric perfusion is of paramount importance in critically ill individuals. Failure to notice incomplete splanchnic resuscitation in critically ill patients has been correlated with multiple organ system dysfunction, prolonged length of stay in the intensive care unit, and death [36].

Conclusion

Significant disturbances occur in the systemic and mesenteric bed during bacteremic severe sepsis. Although large-volume lactated Ringer's infusion restored systemic hemodynamic parameters, it was unable to correct gut mucosal PCO₂ gap.

Competing interests

None declared.

Key messages

In dogs with bacteremic severe sepsis induced by intravenous live *E. coli*, early large-volume crystalloid infusion restored systemic and most regional hemodynamic parameters, but failed to correct increased arterial-gastric PCO₂-gap.

Acknowledgments

This study was supported by grants #98/06459-3 and #98/06458-7 from FAPESP – Fundação de Amparo à Pesquisa do Estado de São Paulo, Brazil.

References

1. McCuskey S, Urbaschek R, Urbaschek B: **The microcirculation during endotoxemia.** *Cardiovasc Res* 1996, **32**:752-763.
2. Hinshaw LB: **Sepsis/septic shock: participation of the microcirculation: an abbreviated review.** *Crit Care Med* 1996, **24**:1072-1078.
3. Friedman G, Silva E, Vincent JL: **Has the mortality of septic shock changed with time?** *Crit Care Med* 1998, **26**:2078-2086.
4. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine: **Practice parameters for hemodynamic support of sepsis in adult patients in sepsis.** *Crit Care Med* 1999, **27**:639-660.
5. Armistead CW Jr, Vincent JL, Preiser JC, De Backer D, Le Minh Thuc: **Hypertonic saline solution-hetastarch for fluid resuscitation in experimental septic shock.** *Anesth Analg* 1989, **69**:714-720.
6. Sakka SG, Meier-Hellmann A, Reinhart K: **Do fluid administration and reduction in norepinephrine dose improve global and splanchnic haemodynamics?** *Br J Anaesth* 2000, **84**:758-762.
7. Hayes MA, Timmins AC, Yau EHS, Palazzo M, Hinds CJ, Watson D: **Elevation of systemic oxygen delivery in the treatment of critically ill patients.** *N Engl J Med* 1994, **330**:1717-1722.
8. Gomersall CD, Joynt GM, Freebairn RC, Hung V, Buckley TA, Oh TE: **Resuscitation of critically ill patients based on the results of gastric tonometry: a prospective, randomized, controlled trial.** *Crit Care Med* 2000, **28**:607-614.
9. Schlichting E, Lyberg T: **Monitoring of tissue oxygenation in shock: an experimental study in pigs.** *Crit Care Med* 1995, **23**:1703-1710.
10. Knichwitz G, Rötter J, Möllhoff T, Richter KD, Brussel T: **Continuous intramucosal PCO₂ measurement allows the early detection of intestinal malperfusion.** *Crit Care Med* 1998, **16**:1550-1557.
11. Lebuffe G, Decoene C, Pol A, Prat A, Vallet B: **Regional capnometry with air-automated tonometry detects circulatory failure earlier than conventional hemodynamics after cardiac surgery.** *Anesth Analg* 1999, **89**:1084-1090.
12. Baker JW, Deitch EA, Li M, Berg RD, Specian RD: **Hemorrhagic shock induces bacterial translocation from the gut.** *J Trauma* 1988, **28**:896-906.
13. Deitch EA, XU D, Franko L, Ayala A, Chaudry IH: **Evidence favouring the role of gut as a cytokine-generating organ in rats subjected to hemorrhagic shock.** *Shock* 1994, **1**:141-146.
14. Doglio GR, Pusajo JF, Egorrola MA, Bonfigli GC, Parra C, Vetere L, Hernandez MS, Fernandez S, Palizas F, Gutierrez G: **Gastric mucosal pH as a prognostic index of mortality in critically ill patients.** *Crit Care Med* 1991, **19**:1037-1040.
15. Marik PE: **Gastric mucosal pH. A better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis.** *Chest* 1993, **104**:225-229.
16. Deitch EA: **Animal models of sepsis and shock: a review and lessons learned.** *Shock* 1998, **9**:1-11.
17. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: **Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345**:1368-1377.
18. Vallet B, Lund N, Curtis SE, Kelly D, Cain SM: **Gut and muscle tissue PO₂ in endotoxemic dogs during shock and resuscitation.** *J Appl Physiol* 1994, **76**:793-800.
19. De Backer D, Zhang H, Manikis P, Vincent JL: **Regional effects of dobutamine in endotoxic shock.** *J Surg Res* 1996, **65**:93-100.
20. Silva E, De Backer D, Creteur J, Vincent JL: **Effects of fluid challenge on gastric mucosal PCO₂ in septic patients.** *Intensive Care Med* 2004, **30**:423-429.
21. Guzman JA, Lacoma FJ, Kruse JA: **Gastric and esophageal intramucosal PCO₂ (PiCO₂) during endotoxemia: assessment of raw PiCO₂ and PCO₂ gradients as indicators of hypoperfusion in a canine model of septic shock.** *Chest* 1998, **113**:1078-1083.
22. Antonsson JB, Boyle CC III, Kruthoff KL, Wang HL, Sacristan E, Rothschild HR, Fink MP: **Validation of tonometric measurement of gut intramural pH during endotoxemia and mesenteric occlusion in pigs.** *Am J Physiol* 1990, **259**:G519-G523.
23. Nelson DP, Samsel RW, Wood LD, Schumacker PT: **Pathological supply dependence of systemic and intestinal O₂ uptake during endotoxemia.** *J Appl Physiol* 1988, **64**:2410-2419.
24. Kellum JA, Rico P, Garuba AK, Pinsky MR: **Accuracy of mucosal pH and mucosal-arterial carbon dioxide tension for detecting mesenteric hypoperfusion in acute canine endotoxemia.** *Crit Care Med* 2000, **28**:462-466.
25. Uusaro A, Russell JA, Walley KR, Takala J: **Gastric-arterial PCO₂ gradient does not reflect systemic and splanchnic hemodynamics or oxygen transport after cardiac surgery.** *Shock* 2000, **14**:13-17.
26. Duranteau J, Sitbon P, Teboul JL, Vicaut E, Anguel N, Richard C, Samii K: **Effects of epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock.** *Crit Care Med* 1999, **27**:893-900.
27. Tugtekin IF, Radermacher P, Theisen M, Matejovic M, Stehr A, Ploner F, Matura K, Ince C, Georgieff M, Trager K: **Increased ileal-mucosal-arterial PCO₂ gap is associated with impaired villus microcirculation in endotoxic pigs.** *Intensive Care Med* 2001, **27**:757-766.
28. Nakajima Y, Baudry N, Duranteau J, Vicaut E: **Microcirculation in intestinal villi: a comparison between hemorrhagic and endotoxin shock.** *Am J Respir Crit Care Med* 2001, **164**:1526-1530.
29. VanderMeer TJ, Wang H, Fink MP: **Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a nor-**

- modynamic porcine model of septic shock. *Crit Care Med* 1995, **23**:1217-1226.
30. Revelly JP, Ayuse T, Brienza N, Fessler HE, Robotham JL: **Endotoxic shock alters distribution of blood flow within the intestinal wall.** *Crit Care Med* 1996, **24**:1345-1351.
 31. Baum TD, Wang H, Rothschild HR, Gang D, Fink M: **Mesenteric oxygen metabolism, ileal mucosal hydrogen ion concentration, and tissue edema after crystalloid or colloid resuscitation in porcine endotoxic shock: comparison of Ringer's lactate and 6% Hetastarch.** *Circ Shock* 1990, **30**:385-397.
 32. Poli de Figueiredo LF, Cruz RJ Jr, Yada-Langui MM, Silva E, Rocha e Silva M: **Comparison of local and systemic markers of digestive tract dysoxia induced by hemorrhage and rapid resuscitation in dogs.** *Shock* 2001, **15**:47.
 33. Fink MP, Cohn SM, Lee PC, Rothschild HR, Deniz YF, Wang H, Fiddian-Green RG: **Effect of lipopolysaccharide on intestinal intramucosal hydrogen ion concentration in pigs: Evidence of gut ischemia in a normodynamic model of septic shock.** *Crit Care Med* 1989, **17**:641-646.
 34. Drazenovic R, Samsel RW, Wylan ME, Doerschuk CM, Schumacker PT: **Regulation of perfused capillary density in canine intestinal mucosa during endotoxemia.** *J Appl Physiol* 1992, **72**:259-265.
 35. Fink MP, Kaups KL, Wang HL, Rothschild HR: **Maintenance of superior mesenteric arterial perfusion prevents increased intestinal mucosal permeability in endotoxic pigs.** *Surgery* 1991, **110**:154-160.
 36. Kirton OC, Windsor J, Wedderburn R, Hudson-Civetta J, Shatz DV, Mataragas NR, Civetta JM: **Failure of splanchnic resuscitation in the acutely injured trauma patient correlates with multiple organ system failure and length of stay in the ICU.** *Chest* 1998, **113**:1064-1069.