**Gastric and Esophageal Intramucosal \( P_{\text{CO}_2} \) (PiCO\(_2\)) During Endotoxemia**

**Assessment of Raw PiCO\(_2\) and \( P_{\text{CO}_2}\) Gradients as Indicators of Hypoperfusion in a Canine Model of Septic Shock**

Jorge A. Guzman, MD; Felix J. Lacoma, MD; and James A. Kruse, MD

---

**Study objectives:** To validate capnometric recirculating gas tonometry (CRGT) for continuously monitoring gut intramucosal \( P_{\text{CO}_2} \) (PiCO\(_2\)) in a septic shock model, and to compare gastric vs esophageal \( P_{\text{CO}_2}\) vs intramucosal-arterial \( P_{\text{CO}_2}\) gradients.

**Interventions:** CRTG catheters were placed in the stomach and esophagus of six anesthetized dogs. A saline solution filled balloon tonometry (ST) catheter was also placed in the stomach. After equilibration, 3 mg/kg *Escherichia coli* lipopolysaccharide (LPS) was administered IV. PiCO\(_2\) measurements were made at 0, 45, and 90 min post-LPS by ST and continuously by CRGT.

**Results:** Baseline PiCO\(_2\) was 41.5±1.9 (±SE) in the stomach by CRGT, 38.0±1.0 by ST, and 43.0±4.4 mm Hg in the esophagus (p=not significant). Gastric PiCO\(_2\) by CRGT increased to 47.0±2.4 mm Hg by 25 min post-LPS (p<0.05), whereas gastric (ST) and esophageal PiCO\(_2\) increased significantly by 45 min post-LPS. Good agreement was observed between gastric CRGT and ST measurements (mean bias, 1.3 mm Hg). The PiCO\(_2\)-PaCO\(_2\) gradient increased post-LPS, but was significant only for gastric CRGT measurements 90 min post-LPS infusion.

**Conclusion:** CRGT provided continuous gastric PiCO\(_2\) measurements that were in close agreement with ST but detected changes earlier than the conventional technique. Continuous esophageal PiCO\(_2\) represents a valid alternative for assessing gastric PiCO\(_2\).

(CHEST 1998; 113:1078-83)

**Key words:** capnometry; endotoxemia; esophageal intramucosal \( P_{\text{CO}_2}\); gastric intramucosal \( P_{\text{CO}_2}\); gut-arterial \( P_{\text{CO}_2}\) gradient; monitoring; septic shock; tonometry

**Abbreviations:** ANOVA=analysis of variance; CO=cardiac output; CRGT=capnometric recirculating gas tonometry; \( DO_2\)=systemic oxygen delivery; LPS=lipopolysaccharide; NS=not significant, \( pH_i=intramucosal\ q pH; PiCO_2=intramucosal\ P_{\text{CO}_2}; PiCO_2-PaCO_2=intramucosal\ to\ arterial\ P_{\text{CO}_2}\) gradient; ST=saline solution-filled balloon tonometry; \( VO_2\)=systemic oxygen consumption

---

Sepsis remains one of the most common causes of the multiple organ dysfunction syndrome, in part as a consequence of sepsis-induced maldistribution of blood flow, resulting in hypoperfusion of regional vascular beds. Saline solution-filled balloon tonometry (ST) has evolved as a useful minimally invasive technique to monitor the adequacy of gut perfusion by indirectly measuring intramucosal \( P_{\text{CO}_2} \) (PiCO\(_2\)) and inferring intramucosal \( pH \) (\( pH_i \)).\(^5\)\(^6\) Gut mucosal acidosis has been associated with increased mortality in nonselected ICU patients\(^5\)\(^6\) and in patients with septic shock;\(^7\) however, the usefulness of the technique is eclipsed by several drawbacks. The procedure is cumbersome, personnel intensive, and time consuming. When used to assay carbon dioxide in saline solution, certain blood gas analyzers under-

---

1078

Laboratory and Animal Investigations

Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21763/ on 05/31/2017
estimate PCO₂ measurements by as much as 60%.8-10 Buffering of gastric acid may render pH estimates falsely low.11-13 Finally, poor reproducibility of individual measurements limits the accuracy of pH determinations using this conventional technique.14,15 Assessment of the gradient between gastric PiCO₂ and PaCO₂ has been proposed as a more reliable index of gastric perfusion,16 and measurement of esophageal PiCO₂ has been proposed as a means of obviating the effects of gastric acid buffering on pH.17,18

We recently reported a new method for continuously measuring gastric PiCO₂ using capnometric recirculating gas tonometry (CRGT).19 In brief, the device provides a continuous display of PiCO₂ using a modified balloon-tipped nasogastric tube that allows recirculation of gas through the balloon and an external closed circuit incorporating an infrared CO₂ analyzer. In experimental models, CRGT has been shown to be capable of detecting changes in gastric PiCO₂ shortly after inducing hypoxemia and hemorrhage,19,20 and the results compare favorably with values obtained using the conventional intermittent technique. The present study was performed to further validate the method in a different model of shock, to test whether continuous esophageal PiCO₂ could be used to infer gastric PiCO₂, and to assess raw gastric and esophageal PiCO₂ measurements in comparison to intramucosal to arterial PiCO₂ gradients (PiCO₂-PaCO₂) as indexes of perfusion failure during endotoxemia.

**Materials and Methods**

This protocol was approved by the Animal Investigation Committee of Wayne State University. Six mongrel dogs (12 to 30 kg) were anesthetized with IV sodium pentobarbital (20 to 30 mg/kg) and endotracheally intubated. Mechanical ventilation (MA-1; Puritan-Bennett Inc; Carlsbad, Calif) was instituted using an initial tidal volume of 15 mL/kg and a respiratory rate of 14 breaths/min. Ventilator settings were adjusted during the baseline period to maintain arterial pH >7.30. Femoral arterial and venous catheters were inserted by surgical cut-down for continuous BP monitoring, fluid and pentobarbital (0.056 µg/kg/min) administration, and arterial and venous blood sampling. Cimetidine (12.5 mg/kg bolus followed by 35 mg/h continuous infusion) was administered to suppress gastric acid secretion. A flow-directed, 8.0 Fr balloon-tipped thermistor tip catheter (Opticath; Abbott Laboratories; North Chicago, Ill) was inserted through the femoral vein with its tip positioned in the pulmonary artery as confirmed by waveform analysis. Two tonometry catheters, one conventional for intermittent gastric PiCO₂ measurements (TRIP NGS; Tonometrics Inc; Hopkinton, Mass) and one CRGT device for continuous gastric PiCO₂ readings, were positioned inside the stomach via the oral route. Correct position was confirmed by transabdominal auscultation of gas insufflated through the catheters into the stomach. A second CRGT catheter was placed with its balloon in the mid-lower esophagus for continuous monitoring of esophageal PiCO₂. After the surgical preparation and instrumentation were completed, the animals were left undisturbed for a baseline equilibration period of 90 min, aimed to achieve stable CRGT PiCO₂ readings.

**Systemic Hemodynamic and Oxygen Transport Measurements**

Arterial pressure was monitored continuously using fluid-filled pressure transducers (Transpac; Abbott Laboratories) driving an amplifier and monitor with digital and waveform display (78200 series, 78304A; Hewlett-Packard; Waltham, Mass). Cardiac output (CO) was measured by thermodilution using pulmonary artery catheterization (Oximetric 3 SO₂/CO Computer; Abbott Laboratories) and 10-mL aliquots of room-temperature saline solution as injectate. The mean of three CO determinations with <10% dispersion from each other was recorded. Systemic oxygen consumption (VO₂) was measured continuously by expired gas analysis (Deltatrac; SensorMedics; Yorba Linda, Calif). All blood gas measurements and derived hemoglobin saturations were obtained using an automated blood gas analyzer (ABL-2; Radiometer Inc; Westlake, Ohio). Systemic oxygen delivery (DO₂) was calculated by multiplying CO by arterial oxygen content. Oxygen extraction ratio was derived as the quotient of VO₂ and DO₂. Total peripheral vascular resistance was derived from mean arterial BP, CO, and body weight.

**PiCO₂ Measurements and Estimation of pH**

Gastric PiCO₂ was determined intermittently using ST following the standard technique as described elsewhere.3-7 Saline solution was assayed for PiCO₂ using the blood gas analyzer (ABL-2) and adjusted using the time-dependent equilibration correction factor supplied by the catheter manufacturer. Separate CRGT catheters and instruments were used to continuously monitor and record esophageal and gastric PiCO₂.19 Gastric and esophageal pH were determined from PiCO₂ using arterial bicarbonate concentration and the Henderson-Hasselbalch equation.3-7

**Experimental Protocol**

After the baseline stabilization period, the animals were infused with 3 mg/kg Escherichia coli lipopolysaccharide (LPS) (0111:B4; Difco; Detroit) over 5 to 10 min followed by initiation of fluid resuscitation using normal saline solution at a fixed rate of 1 mL/kg/min. Vital signs, arterial and mixed venous blood gas values, systemic hemodynamic and oxygen transport variables, and saline solution balloon PiCO₂ measurements were obtained immediately before LPS administration and every 45 min thereafter. Gastric and esophageal PiCO₂ were recorded continuously by CRGT throughout the experiment.

**Statistical Analysis**

Summary values are expressed as the mean±SE. For each method, one-way repeated measures analysis of variance was used to compare sequential PiCO₂ measurements during baseline and after infusion of LPS.

Two-way repeated measures analysis of variance (ANOVA) was used to compare esophageal and gastric PiCO₂ by CRGT. The same statistics was used to compare gastric PiCO₂ obtained by CRGT and by standard tonometry. Dunnett’s test was used to make multiple comparisons if ANOVA revealed significant differences. The control value for Dunnett’s test was designated as the last measurement obtained during the baseline equilibration period. Probability values (two-tailed) of <0.05 were considered statistically significant. Statistical calculations were performed.
using software (Excel version 5.0; Microsoft Corporation; Redmond, Wash; and SigmaStat version 1.0; Jandel Corporation; San Rafael, Calif).

**RESULTS**

Vital signs, systemic hemodynamics, and oxygen transport variables at the end of baseline period and at 45 and 90 min after infusing LPS are shown in Table 1. Baseline hemoglobin concentration was 9.1±0.4 g/dL. Gastric and esophageal PiCO₂ and pHı readings by CRGT were stable during the last part of the baseline equilibration period (41.5±1.9 vs 43.0±4.4 mm Hg and 7.20±0.03 vs 7.22±0.04, respectively; p=not significant [NS] between anatomic sites) and compared favorably with the results obtained by the conventional technique (38.0±1.0 mm Hg and 7.24±0.02; p=NS between methods). Gastric and esophageal PiCO₂ as well as POCO₂ and pH gradients at baseline and after administration of E.coli LPS for both techniques are shown in Table 2. Twenty-five minutes after LPS infusion, gastric PiCO₂ by CRGT rose to 47.0±2.4 mm Hg (p<0.05 compared with baseline). Gastric and esophageal hypercarbia continued to develop throughout the experiment despite resuscitative measures. Esophageal PiCO₂ reached statistical significance at 45 min after LPS administration (50.3±5.2 mm Hg; p<0.05 compared with baseline). Similarly, PiCO₂ measurements provided by the conventional method were statistically significant 45 min after E.coli LPS infusion (49.4±3.7; p<0.01). The pattern of PiCO₂ measurements obtained by the two techniques compared favorably (Fig 1). ANOVA did not demonstrate statistically significant differences between methods of PiCO₂ assessment (CRGT vs ST) over the three main experimental points (end of the baseline and 45 and 90 min post-LPS infusion). No difference was found when gastric and esophageal PiCO₂ were compared. Gastric and esophageal PiCO₂ and pHı as well as intramucosal-arterial POCO₂ and pH gradients at baseline and after administration of E.coli LPS for both techniques are shown in Table 2. Mean bias between the two methods was 1.3±1.8 mm Hg (95% confidence interval, −3.4 to 6.0 mm Hg).

**DISCUSSION**

Impairment of tissue oxygen extraction and loss of autoregulatory mechanisms that leads to maldistribution of blood flow are thought to be responsible for the regional dysoxia observed during sepsis.1 Administration of endotoxin has been shown to significantly decrease splanchnic DO₂ and concomitantly increase PiCO₂ and lead to the development of intramucosal acidosis in several animal models.3,21-23 In the clinical setting, gastric intramucosal acidosis has been associated with adverse outcome among various ICU populations, and its ability to predict outcome and development of multiple organ dysfunction syndrome has been increasingly appreciated.5,7,24-27 To date, ST has been the most commonly used method to indirectly measure PiCO₂ and derive pHı. The technique has been validated in endotoxemia with excellent agreement using measurements obtained by tissue pH microelectrodes implanted directly into the gut wall.3 However, some inherent disadvantages of the conventional method preclude its widespread clinical use.8-10,14,15

<table>
<thead>
<tr>
<th>Physiologic Variable*</th>
<th>Baseline</th>
<th>45 min Post-LPS Infusion</th>
<th>90 min Post-LPS Infusion</th>
<th>p Value by ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>146±5</td>
<td>120±5</td>
<td>136±10</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial BP, mm Hg</td>
<td>115±7</td>
<td>60±38†</td>
<td>51±5†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CO₂, mL/kg/min</td>
<td>170±50</td>
<td>82±10†</td>
<td>94±14†</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>Total peripheral vascular resistance, dynem/kg·cm⁻²</td>
<td>778±144</td>
<td>784±111</td>
<td>586±83</td>
<td>NS</td>
</tr>
<tr>
<td>Mixed venous oxyhemoglobin saturation, %</td>
<td>70±6</td>
<td>37±7†</td>
<td>33±4†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pHı</td>
<td>7.36±0.02</td>
<td>7.14±0.04†</td>
<td>7.07±0.03†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>25.5±1.1</td>
<td>31.6±6.0</td>
<td>33.9±6.3</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.33±0.01</td>
<td>7.11±0.04†</td>
<td>7.04±0.03†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCO₂, mm Hg</td>
<td>30.6±3.1</td>
<td>35.5±5.1</td>
<td>40.6±3.7</td>
<td>NS</td>
</tr>
<tr>
<td>DO₂, mL/kg/min</td>
<td>24.6±3.6</td>
<td>11.1±1.4†</td>
<td>12.9±1.7†</td>
<td>0.001</td>
</tr>
<tr>
<td>VO₂, mL/kg/min</td>
<td>5.7±0.4</td>
<td>4.9±0.4</td>
<td>4.9±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic oxygen extraction ratio, %</td>
<td>25±3</td>
<td>45±3†</td>
<td>40±5†</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

*pHı=arterial pH; pH=mixed venous pH; PiCO₂=mixed venous PiCO₂.

†p<0.01 compared with baseline.

*p<0.05 compared with baseline.
Table 2—Mean (±SE) PiCO₂ and pH and Corresponding PiCO₂-PaCO₂ and pH-pHi Gradients for Stomach and Esophagus Obtained by CRGT and ST at Major Experimental Time Points*

<table>
<thead>
<tr>
<th>Physiologic Variable</th>
<th>Location of Measurement</th>
<th>Measurement Method</th>
<th>Baseline</th>
<th>45 min Post-LPS Infusion</th>
<th>90 min Post-LPS Infusion</th>
<th>p Value by ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PiCO₂, mm Hg</td>
<td>Esophagus</td>
<td>CRGT</td>
<td>43.0±4.4</td>
<td>50.3±5.2</td>
<td>61.1±7.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PiCO₂, mm Hg</td>
<td>Stomach</td>
<td>CRGT</td>
<td>41.5±1.9</td>
<td>50.6±2.5</td>
<td>62.3±2.9</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>PiCO₂, mm Hg</td>
<td>Stomach</td>
<td>ST</td>
<td>38.0±1.0</td>
<td>49.4±3.7</td>
<td>59.0±6.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>pHi</td>
<td>Esophagus</td>
<td>CRGT</td>
<td>7.22±0.04</td>
<td>7.00±0.03</td>
<td>6.86±0.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>pHi</td>
<td>Stomach</td>
<td>CRGT</td>
<td>7.20±0.03</td>
<td>6.97±0.03</td>
<td>6.83±0.04</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>pHi</td>
<td>Stomach</td>
<td>ST</td>
<td>7.24±0.02</td>
<td>6.98±0.02</td>
<td>6.87±0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PiCO₂-PaCO₂, mm Hg</td>
<td>Esophagus</td>
<td>CRGT</td>
<td>14.4±4.0</td>
<td>18.6±7.1</td>
<td>27.2±9.3</td>
<td>NS</td>
</tr>
<tr>
<td>PiCO₂-PaCO₂, mm Hg</td>
<td>Stomach</td>
<td>CRGT</td>
<td>13.3±2.2</td>
<td>18.6±6.2</td>
<td>27.7±6.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PiCO₂-PaCO₂, mm Hg</td>
<td>Stomach</td>
<td>ST</td>
<td>9.8±1.1</td>
<td>17.3±5.8</td>
<td>24.3±7.8</td>
<td>NS</td>
</tr>
<tr>
<td>pH-pHi</td>
<td>Esophagus</td>
<td>CRGT</td>
<td>0.13±0.03</td>
<td>0.14±0.04</td>
<td>0.20±0.06</td>
<td>NS</td>
</tr>
<tr>
<td>pH-pHi</td>
<td>Stomach</td>
<td>CRGT</td>
<td>0.15±0.02</td>
<td>0.17±0.05</td>
<td>0.23±0.05</td>
<td>NS</td>
</tr>
<tr>
<td>pH-pHi</td>
<td>Stomach</td>
<td>ST</td>
<td>0.12±0.01</td>
<td>0.16±0.05</td>
<td>0.20±0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

*pH=arterial pH.

*p<0.05 compared with baseline.

*p<0.01 compared with baseline.

Recently reported, CRGT is an attractive alternative method that, in addition to providing continuous on-line measurements of gastric PiCO₂, obviates many of the inconveniences of the conventional technique. Continuous CRGT can detect significant changes in PiCO₂ within minutes of inducing hypoxemia or hemorrhage. In addition, a preliminary report using this technique showed that the degree of induced hemorrhage correlated with the magnitude of PiCO₂ rise. The present study was conducted for further validation of CRGT in a different model of shock. ST was used as the reference method.
method based on the excellent correlation between the conventional technique and those obtained using tissue pH electrodes during endotoxemia.3

The hemodynamic response to IV administration of LPS depends on the host species, the dose of LPS, the method of its administration (bolus vs slow infusion), and the extent of resuscitation.21 In the present study, systemic hypotension and decreased CO followed LPS administration, and these systemic hemodynamic effects could not be reversed with vigorous isotonic fluid administration. The rather low baseline pH values observed in our experiments may be due in part to the long equilibration period employed to achieve stable PiCO2 measurements and to the effects of pentobarbital anesthesia on the splanchnic circulation.29,30 Gastric PiCO2 measured by CRGT rose shortly after finishing E. coli endotoxin administration and reached statistical significance within 25 min. A similar pattern was observed in esophageal PiCO2, although the rise did not occur immediately after infusing LPS, and therefore statistical significance was delayed compared with gastric PiCO2. PiCO2 measurements obtained by standard ST followed a similar trend to those obtained by CRGT. The study design and intermittent nature of the conventional technique precluded demonstration of a precise point at which statistical significance was reached by the standard method. However, findings from other investigations suggest that CRGT may be more sensitive for detecting changes in PiCO2 compared with the saline solution balloon technique.19,20 This improved sensitivity may be due to the continuous recirculation of gas already in equilibrium with PiCO2 immediately prior to LPS administration, and possibly due to greater accuracy and reproducibility of CRGT compared with the conventional method.31

Raw esophageal and gastric PiCO2 measurements were almost identical during the baseline period. However, after LPS administration, gastric PiCO2 increased more rapidly than esophageal PiCO2. The differential sensitivity of gastric vs esophageal monitoring for detecting physiologic changes associated with endotoxemia might be due to differences in blood supply to the organs (the esophagus receiving additional flow from the aorta) and lack of esophageal countercurrent mucosal circulation; however, more specific research is needed to confirm this hypothesis. Nevertheless, esophageal PiCO2 reliably provided a similar trend to gastric PiCO2 measurements. In addition, esophageal PiCO2 measurements are not influenced by acid secretion and therefore may represent an alternative way of assessing splanchnic perfusion while avoiding the necessity of H2-receptor blockade.

The gradient between tissue and arterial PCO2 has been postulated as a more specific marker of gut ischemia than raw PiCO2 measurements. The rationale is that this gradient should not be influenced by the effects of systemic hypercarbia on GI PiCO2.16,32 Our baseline PCO2 gradients were higher than expected, a consequence of arterial hypocapnia apparently not paralleled by changes in esophageal and gastric PiCO2. Only at the terminal phase of these experiments were we able to show using CRGT a significant change in PCO2 gradient. However, neither gastric PiCO2-PaCO2 by ST nor esophageal PiCO2-PaCO2 by CRGT reached statistical significance after 90 min of endotoxemia. This apparent lack of sensitivity of tissue-arterial PiCO2 gradient might be attributable to the mild upward trend observed in PaCO2 on gut PiCO2. That the gradient was significant only when PiCO2 was measured by CRGT could be due to the increased accuracy and precision provided by CRGT compared with the conventional method,29 and by poor in vivo reproducibility found with ST.14

In this model of endotoxin-induced shock, CRGT provided continuous measurements of PiCO2 that closely agreed with intermittent measurements obtained by the conventional ST. In addition, CRGT detected changes in PiCO2 sooner than the traditional method. Continuous esophageal PiCO2 monitoring using CRGT was feasible and, although apparently less sensitive, provided information similar to gastric PiCO2. It may represent an alternative approach to the clinical assessment of splanchnic perfusion. Although intramucosal-arterial PiCO2 and pH gradients might provide more specific information on GI perfusion by correcting for the effects of systemic PiCO2 and pH on gut PiCO2, significant changes in these derived measures were observed later in our experiments than raw PiCO2 and pH.

REFERENCES
1 Schumacker PT, Cain SM. The concept of a critical oxygen delivery. Intensive Care Med 1987; 13:223-29
7 Marik PE. Gastric intramucosal pH: a better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. Chest 1993; 104: 225-29


16 Schlichtig R, Mehta N, Gayowski TJ. Tissue-arterial Pco2 difference is a better indicator of ischemia than intramural pH (PiH) or arterial pH-PHi difference. J Crit Care 1996; 11:51-56


28 Guzman JA, Kruse JA. Assessment of splanchnic perfusion by continuous recirculating gas tonometry during different degrees of hemorrhage [abstract]. Am J Respir Crit Care Med 1996; 153(suppl):A660

29 Guzman JA, Kruse JA. Accuracy and precision of two methods for measuring gastric intramucosal Pco2 (PiC02): comparison between standard saline tonometry (SST) and capnometric recirculating gas tonometry (CRGT) [abstract]. Chest 1996; 110:74S

