Lingual, splanchnic, and systemic hemodynamic and carbon dioxide tension changes during endotoxic shock and resuscitation

Jorge A. Guzman, Mathew S. Dikin, and James A. Kruse
Division of Pulmonary, Critical Care, and Sleep Medicine, Wayne State University School of Medicine, Detroit, Michigan
Submitted 4 March 2004; accepted in final form 28 July 2004

Guzman, Jorge A., Mathew S. Dikin, and James A. Kruse. Lingual, splanchnic, and systemic hemodynamic and carbon dioxide tension changes during endotoxic shock and resuscitation. J Appl Physiol 98: 108–113, 2005. First published July 30, 2004; doi: 10.1152/japplphysiol.00243.2004.—Sublingual and intestinal mucosal blood flow and P$_{CO_2}$ were studied in a canine model of endotoxin-induced circulatory shock and resuscitation. Sublingual P$_{CO_2}$ ($P_{SCO_2}$) was measured by using a novel fluorescent optrode-based technique and compared with lingual measurements obtained by using a Stowe-Severinghaus electrode [lingual P$_{CO_2}$ ($P_{LCO_2}$)]. Endotoxin caused parallel changes in cardiac output, and in portal, intestinal mucosal, and sublingual blood flow ($Q_s$). Different blood flow patterns were observed during resuscitation: intestinal mucosal blood flow returned to near baseline levels postfluid resuscitation and decreased by 21% after vasopressor resuscitation, whereas $Q_s$ rose to twice that of the pre-shock level and was maintained throughout the resuscitation period. Electrochemical and fluorescent P$_{CO_2}$ measurements showed similar changes throughout the experiments. The shock-induced increases in $P_{SCO_2}$ and $P_{LCO_2}$ were nearly reversed after fluid resuscitation, despite persistent systemic arterial hypotension. Vasopressor administration induced a rebound of $P_{SCO_2}$ and $P_{LCO_2}$ to shock levels, despite higher cardiac output and $Q_s$, possibly due to blood flow redistribution and shunting. Changes in $P_{LCO_2}$ and $P_{SCO_2}$ paralleled gastric and intestinal P$_{CO_2}$ changes during shock but not during resuscitation. We found that the lingual, splanchnic, and systemic circulations follow similar patterns of blood flow variations in response to endotoxin shock, although discrepancies were observed during resuscitation. Restoration of systemic, splanchnic, and lingual perfusion can be accompanied by persistent tissue hypercarbia, mainly lingual and intestinal, more so when a vasopressor agent is used to normalize systemic hemodynamic variables.

sublingual circulation; endotoxic shock; vasopressors

ALTHOUGH ASSESSMENT of the adequacy of tissue perfusion and oxygenation has been a major focus in the clinical management of critically ill patients, conventional hemodynamic and oxygen-derived physiological variables have been shown to be insensitive and may even be normal in the early stages of circulatory shock (3, 8). Recognition that tissue hypoxia may still be present in certain regional tissues, such as the gut and kidneys, despite normal or even elevated cardiac output ($Q_{s}$), and that inadequate organ perfusion due to hemorrhage or other causes results in tissue hypercarbia, has shifted attention to examining tissue $P_{CO_2}$ as a marker for the presence or severity of perfusion failure (10, 14, 16, 17, 21, 23).

The architecture of gut mucosal microvasculature, a higher critical oxygen delivery compared with other organs and the body as a whole, and disproportionately greater vasoconstriction than other vascular territories in response to decreased $Q_{s}$, make the gastrointestinal (GI) tract a highly sensitive target organ for detecting early or occult tissue dysxia (12, 28, 30).

Various anatomic sites for monitoring GI P$_{CO_2}$ have been examined, and, although gastric ($P_{GCO_2}$), intestinal ($P_{ICO_2}$), esophageal, and rectal P$_{CO_2}$ have been studied as indicators of hypoperfusion in the experimental setting, the stomach is currently the preferred site for clinical use (5, 11, 27). Recently, sublingual P$_{CO_2}$ ($P_{SCO_2}$) has been proposed as an indicator of systemic or gut hypoperfusion (17, 23, 32, 34). $P_{SCO_2}$ paralleled changes in $P_{GCO_2}$ during experimental hemorrhage and also clinically. Because sublingual capnometry is disarrayingly facile, is noninvasive, does not require administration of H$_2$-receptor-blocking drugs, and has the potential to be less costly than conventional tonometry, it may emerge as a valid clinical alternative for monitoring tissue perfusion in the intensive care setting (19, 23).

However, although correlation between $P_{SCO_2}$ and $P_{GCO_2}$ has been shown to be acceptable, marked heterogeneity of regional splanchnic blood flow appears to be the rule during endotoxin-induced circulatory shock (11, 24). Additionally, recent evidence suggests that the stomach may not represent the most accurate GI site for detecting splanchnic ischemia (33). Furthermore, a large discrepancy between $P_{GCO_2}$ and $P_{SCO_2}$, was reported in one patient with bowel ischemia, suggesting that sublingual blood flow ($Q_{s}$) may not parallel gut perfusion in all clinical conditions (19). To our knowledge, comparisons between $Q_{s}$ and splanchnic blood flow have only been reported in hemorrhagic shock models but not in models of septic shock, where peripheral blood flow redistribution and shunting are even more striking. All of the above considerations question the validity of $P_{SCO_2}$ as a surrogate marker of mucosal $P_{ICO_2}$ during endotoxin or septic shock.

We hypothesize that the sublingual and the intestinal mucosal circulations do not always correlate during different phases of endotoxin-induced circulatory shock and resuscitation. Using a canine model of endotoxin shock, we performed the following investigation to test whether the sublingual and intestinal mucosal circulations follow similar patterns of change during endotoxin-induced circulatory shock and resuscitation, and whether measurements of lingual P$_{CO_2}$ ($P_{LCO_2}$) or $P_{SCO_2}$ can be used to infer $P_{GCO_2}$ and $P_{ICO_2}$. The investigation also evaluated a novel, fluorescent optrode-based technique for assessing $P_{SCO_2}$.

MATERIALS AND METHODS

Surgical preparation. This protocol was approved by the Animal Investigation Committee of Wayne State University. Mongrel dogs

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
stabilize for 45 min, during which time minute ventilation was
into the intestinal lumen for continuous measurement of PiCO2, and the
mucosal perfusion (26). Through a second antimesenteric ileostomy,
previously as a reliable means of estimating relative changes in
microvascular perfusion in absolute terms, but it has been validated
through the femoral vein and guided into the pulmonary artery by
balloon-tipped, multilumen, thermodilution pulmonary artery catheter
mittent blood sampling for blood-gas and hemoglobin assays. A
ballooned, multilumen, thermodilution pulmonary artery catheter
(Opticath; Abbott Laboratories, Morgan Hill, CA) was advanced
through the femoral vein and guided into the pulmonary artery by
pressure waveform analysis for measurement of Q; and pulmonary
artery occlusion pressure (Ppao). Following a midline laparotomy, the
duodenum and small intestine were displaced to expose the portal
vein. After careful dissection, an 8-mm ultrasonic transit-time flow
probe (model 8RS; Transonic Systems) was affixed to the floor of the
duodenum and rendered insensitive to changes in pH. The light is launched into an optical fiber and
delivered to the tip of the disposable sensor. The green fluorescent
light generated in the optode is directed back to the N-80 instrument
through an optical fiber. The light is then radiometrically quantitated
and directly correlated to PCO2. Immediately following calibration,
the optode sensors (SLS-1; Nellcor) were manually positioned within
the oral cavity with the optical windows held firmly in place against
1) the ventral paramedian surface of the tongue near its root (fluores-
cence PCO2), and 2) the floor of the mouth (fluorescence PSCO2)
approximately midway between the incisors and the root of the
tongue. Measurements were rejected if they could not be completed
within 3 min of calibration or in the case of a calibration error. PCO2
was monitored continuously by way of the balloon-tipped ileal cath-
eter by using capnometric recirculating gas tonometry (9, 10). PSCO2
was monitored intermittently by automated reciprocal aspiration
(Tonocap; Datex-Ohmeda) from the balloon-tipped gastric catheter.
Both tonometry measurement techniques employ infrared spectros-
copy calibrated to a precision CO2 source.

Experimental procedure. After two consecutive sets of baseline measurements (hemodynamic values; arterial, mixed-venous, and portal
gas blood, acid-base, and lactate values; Qs, Qv, Qh, and Qc; and
electrochemical PCO2, fluorescence PCO2, fluorescence PSCO2, PCO2,
and PSCO2) were obtained, maintenance intravenous fluids were dis-
continued, and endotoxic shock was induced by intravenous injection
of 3 mg/kg E. coli LPS (serotype 0111:B4; Sigma-Aldrich, St. Louis,
MO) over 5 min. Resuscitation was started 20 min after commence-
ment of LPS. This resuscitation lasted 45 min and was divided into
two phases. During the first 15 min, an intravenous infusion of
isolotic saline solution was administered to target and maintain a
Ppao similar to baseline. During the subsequent 30 min of the
resuscitation period, an intravenous infusion of norepinephrine was
initiated and titrated to achieve the baseline MABP level, if that goal
could not be reached by intravascular volume expansion alone. Mea-
surements were obtained at 10-min intervals before, during, and
immediately after the LPS injection was initiated, and at 15-min
intervals thereafter. Timing for LPS infusion was chosen based on
previous experience at our laboratory and others, aiming to induce a
decrease in systemic hemodynamic parameters of a magnitude com-
parable to that observed in a similar clinical scenario (11, 35).
Similarly, the resuscitation pattern was intended to reflect a response
pattern comparable clinically. Animals were then euthanized by in-
jection of a saturated solution of potassium chloride through the right
heart catheter.

Statistical analysis. Summary values are expressed as means ± SE.
One-factor repeated-measures ANOVA was used to compare sequen-
tial measurements for each tested variable obtained between baseline
and subsequent experimental time points. Dunnett’s test was used to
make further comparisons if ANOVA revealed significant differences.
The control value for Dunnett’s test was designated as the last
measurement obtained at the end of the baseline period. Two-way
repeated-measures ANOVA was used for comparisons of changes
between Qs and Qv, between Qs and Qh, between electrochemical
PCO2 and fluorescence PCO2, and between electrochemical PCO2 and
fluorescence PSCO2 over the experimental time points. Correlations
were examined by using the Pearson product-moment statistic. Agree-
ment analysis was performed by the method of Bland and Altman by
using electrochemical measurements as the criterion standard (1).
Probability values (two-tailed) of <0.05 were considered statistically
significant. Statistical calculations were performed by using Excel
(version 7.0; Microsoft, Redmond, WA) and SigmaStat (version 2.0;
Jandel, San Rafael, CA) software.

RESULTS

Seven animals were studied (18 ± 1 kg). Systemic hemo-
dynamic variables, venous PO2, and venoarterial carbon diox-
ide differences are shown in Table 1. In agreement with
previous reports, endotoxin infusion induced a decrease in
heart rate followed by a return to near baseline levels after fluid resuscitation and then a tachycardic response during vasopressor resuscitation (3, 8, 13). MABP dropped by almost 50% 10 min post-LPS infusion. Although MABP improved with intravascular volume expansion, it did not reach preendotoxin levels. By protocol design, MABP at the end of the resuscitation period was comparable to baseline levels. Mixed-venous and portal venous Po2 followed a similar pattern throughout the experimental time points: both decreased significantly post-LPS, whereas Q˙s rose to twice that of the preshock level and was maintained at baseline levels throughout the resuscitation period. Baseline blood lactate level was 1.7 mmol/l. It increased to 3.5 ± 0.7 mmol/l at the end of resuscitation and decreased to 2.5 ± 0.3 mmol/l at the end of experiments (P < 0.05). The mean volume of isotonic saline infused during the resuscitation period was 79 ml/kg, of which 44% was administered during the first 15 min of resuscitation. The total dose of norepinephrine required to achieve baseline MABP levels during the last 30 min of the resuscitation period was 0.20 ± 0.08 mg/kg.

Changes in blood flow are shown in Fig. 1. Qp paralleled Qt, except at the final measurement period, at which point there was divergence: Qt continuing to increase and Qp, showing a downward trend. Qm mirrored Qs during LPS-induced shock (r = 0.49, P < 0.05), but a different pattern emerged during resuscitation: Qm returned to near baseline levels postfluid resuscitation and decreased by 21% after vasopressor resuscitation, whereas Qs rose to twice that of the preshock level and was maintained throughout the resuscitation period.

Changes in tissue Pco2 are shown in Fig. 2. Figure 2, top, shows changes in PgcO2 and Pico2. Both variables had a similar pattern of change; however, in accordance with previous reports, the change in Pco2 was more striking at the intestinal mucosa (1, 14). Thus only Pico2 reached statistical significance. Electrochemical Pico2, and fluorescent Psco2 changed comparably throughout the experiments. Changes in fluorescent Pico2 followed a pattern similar to both electrochemical Pico2, and fluorescent Psco2, but they did not achieve statistical significance. The shock-induced increases in fluorescent Psco2 and electrochemical Pico2 were nearly reversed after fluid resuscitation, despite a MABP that remained below the baseline level. However, after initiation of the vasopressor, fluorescent Psco2, and electrochemical Pico2 rebounded and remained at shock levels, despite normalization of MABP and a higher Qs and Qm. The mean bias between Pico2 by the Severinghaus electrode criterion standard method and the fluorescent optode method was 38.8 ± 3.7 Torr on the glossal surface and 44.0 ± 3.2 Torr at the sublingual position.

Table 2 shows Pco2 gaps (tissue minus arterial blood values) at various monitoring sites. Baseline Pico2 was 32.2 ± 1.1 Torr, 32.2 ± 1.5 Torr post-LPS, 35.2 ± 2.2 Torr post-fluid resuscitation, and 39.9 ± 2.5 Torr at the end of resuscitation (P = not significant), probably reflecting increased ventilation-perfusion mismatch induced by the hyperdynamic status in sepsis. A significant correction factor was noted for the sublingual site (P < 0.05 between groups by 2-way repeated-measures ANOVA).

### Table 1. Systemic hemodynamic variables, venous oxygen tension, and venoarterial carbon dioxide tension gradients at major experimental time points

<table>
<thead>
<tr>
<th>Time</th>
<th>Heart rate, beats/min</th>
<th>Cardiac output, ml·kg⁻¹·min⁻¹</th>
<th>MAP, mmHg</th>
<th>Ppao, mmHg</th>
<th>Pico2-Torr</th>
<th>Ppico2-Torr</th>
<th>Pico2-Paco2-Torr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>160 ± 10</td>
<td>150 ± 10</td>
<td>106 ± 5</td>
<td>5.2 ± 0.8</td>
<td>47 ± 3</td>
<td>52 ± 2</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>10 min Post-LPS</td>
<td>128 ± 5†</td>
<td>70 ± 10</td>
<td>50 ± 5†</td>
<td>5.0 ± 1.3</td>
<td>34 ± 5†</td>
<td>37 ± 3†</td>
<td>14 ± 3†</td>
</tr>
<tr>
<td>20 min Post-LPS</td>
<td>42 ± 9</td>
<td>110 ± 10</td>
<td>66 ± 5†</td>
<td>4.0 ± 1.0</td>
<td>41 ± 6</td>
<td>44 ± 4</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>15 min Postresuscitation (Fluids)</td>
<td>158 ± 7</td>
<td>220 ± 40</td>
<td>75 ± 5†</td>
<td>7.0 ± 1.7</td>
<td>54 ± 5</td>
<td>57 ± 4</td>
<td>5 ± 3</td>
</tr>
<tr>
<td>45 min Postresuscitation (Fluids + Vasopressor)</td>
<td>194 ± 14†</td>
<td>220 ± 40</td>
<td>112 ± 5</td>
<td>7.4 ± 1.6</td>
<td>59 ± 5</td>
<td>61 ± 5</td>
<td>2 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. LPS, E. coli lipopolysaccharide; MAP, mean arterial blood pressure; Ppao, pulmonary artery occlusion pressure; Pico2, mixed-venous Po2; Ppico2, portal venous Po2; Paco2, arterial Po2; Ppico2-Paco2, mixed-venous Po2-arterial Po2 difference; Pico2-Paco2, portal venous Po2-Paco2 difference. *P < 0.001 by repeated-measures ANOVA. †P < 0.05 compared with baseline by Dunnett’s multiple-comparison statistic.
achieved during resuscitation. Differences in baseline Pco₂ and Pco₂ gap at various levels of the GI tract were observed and have been described previously (11, 33). At the level of the tongue, electrochemical PICO₂-Paco₂ was considerably higher than the other CO₂ gaps, and this may be explained by the differences in measurement methodology (Severinghaus electrode vs. fluorescent optode). All CO₂ gaps increased after LPS infusion. At the end of resuscitation, CO₂ gaps (by either measurement technique) returned to near-baseline levels; however, in accordance with Qi, PICO₂-Paco₂ remained at near shock levels.

**DISCUSSION**

Although measurement of gut mucosal Pco₂ has proven to be a useful marker for hypoperfusion and for assessing the adequacy of resuscitation, the optimal site for clinical monitoring remains unclear (4, 5, 11, 17, 27). Our data show that changes in the tongue and sublingual territory in response to shock are almost indistinguishable from splanchnic changes; however, notable differences are apparent during resuscitation.

Endotoxin administration induced a drop in MABP of >50% and comparable decreases in systemic blood flow, splanchnic blood flow, and Qs. These findings are in accordance with previously reported data from our laboratory and by others (13, 17, 27). However, a different pattern was observed during resuscitation, depending on the territory monitored and the phase of resuscitation. After 15 min of aggressive fluid resuscitation, rebound to a hyperdynamic status was observed at the level of the large-vessel circulation, Qi and Qp. This rebound occurred, despite a mean arterial pressure that was almost 25% lower than the baseline level. After norepinephrine administration was initiated during the second phase of resuscitation, MABP returned to baseline levels and Qi continued to increase; however, Qp showed a sharp change to a downward trend, even though it remained higher than baseline levels. Concordant with previously reported decreases in Qp and jejunal blood flow observed when norepinephrine was administered to increase MABP to 20 mmHg above shock levels (32), these findings suggest a more selective vasoconstrictive effect of norepinephrine at the splanchnic vasculature.

At the level of the small-vessel circulations under study, a different response to resuscitative efforts was noted between the lingual and the ileal mucosal territories. Qi returned to baseline levels after fluid resuscitation but decreased by 20% after norepinephrine was initiated. This reduction could be secondary to a relatively selective splanchnic vasoconstrictive effect of norepinephrine with redistribution of blood flow away from the gut (13, 16). On the other hand, Qi reached and maintained values twice higher than baseline throughout resuscitation. Explanations for this observation can only be hypothetical, because few investigations have examined the lingual or sublingual circulation during endotoxic shock. However, a study using orthogonal polarization of spectral imaging to assess the number of perfused sublingual vessels by size demonstrated that the normal (1.5:1) ratio of small-to-large vessel perfusion is reversed in sepsis (6). Therefore, it is possible that resuscitation increased shunting by enhancing flow to larger sublingual vessels rather than increasing capillary perfusion. This hypothesis is supported by our measurements of lingual and PSCO₂, which demonstrated rebound increases during resuscitation with norepinephrine.

### Table 2. Tissue-arterial Pco₂ gradients at various monitoring sites during major experimental time points

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>10 min Post-LPS</th>
<th>20 min Post-LPS</th>
<th>15 min Postresuscitation (Fluids)</th>
<th>45 min Postresuscitation (Fluids + Vasopressor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescence PSCO₂-Paco₂ * Torr</td>
<td>10.9 ± 2.5</td>
<td>26.2 ± 4.2†</td>
<td>16.0 ± 4.2</td>
<td>5.0 ± 1.7</td>
<td>11.1 ± 4.7</td>
</tr>
<tr>
<td>Fluorescence PlCO₂-Paco₂ * Torr</td>
<td>13.5 ± 1.9</td>
<td>23.9 ± 2.1†</td>
<td>20.6 ± 0.7</td>
<td>13.9 ± 1.2</td>
<td>15.8 ± 3.5</td>
</tr>
<tr>
<td>Electrochemical PlCO₂-Paco₂ * Torr</td>
<td>44.9 ± 4.3</td>
<td>70.3 ± 7.9†</td>
<td>66.8 ± 7.7†</td>
<td>51.4 ± 7.9</td>
<td>59.0 ± 8.9</td>
</tr>
<tr>
<td>PlSCO₂-Paco₂ * Torr</td>
<td>24.9 ± 4.6</td>
<td>34.8 ± 6.2</td>
<td>39.8 ± 7.3†</td>
<td>41.2 ± 8.9†</td>
<td>37.1 ± 8.7†</td>
</tr>
<tr>
<td>PSCO₂-Paco₂ * Torr</td>
<td>6.9 ± 3.1</td>
<td>12.6 ± 2.7</td>
<td>11.3 ± 2.3</td>
<td>10.4 ± 3.1</td>
<td>3.1 ± 4.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. PSCO₂, PlSCO₂, PICO₂, and PSCO₂: sublingual, lingual, intestinal, and gastric Pco₂, respectively; fluorescence PSCO₂-Paco₂, PlSCO₂, (fluorescent method)-Paco₂ gradient; fluorescence PlCO₂-Paco₂, PlCO₂ (fluorescent method)-Paco₂ gradient; electrochemical PlCO₂-Paco₂, PlCO₂ (electrochemical method)-Paco₂ gradient; PlSCO₂-Paco₂, PlSCO₂-Paco₂ gradient; PSCO₂-Paco₂, PSCO₂-Paco₂ gradient. *P < 0.001 by repeated-measures ANOVA; †P < 0.05 compared with baseline by Dunnett’s multiple-comparison statistic.
Both electrochemical $P_l\text{CO}_2$ and fluorescence $P_s\text{CO}_2$ followed a similar pattern throughout the experiments, and, despite the differences in methodology and anatomic positioning, the percent change was almost identical for both techniques. As noted above, lingual $P\text{CO}_2$ and $P_s\text{CO}_2$ decreased to near-baseline levels during the initial phase of resuscitation (isotonic saline infusion) but rebounded to shock levels once the vasopressor infusion was started to achieve normalization of MABP. Whether this rise in tissue $P\text{CO}_2$ was a consequence of increased infusion was started to achieve normalization of MABP. (sission) but rebounded to shock levels once the vasopressor during the initial phase of resuscitation (isotonic saline infusion)

whether increased

increased

hypoperfusion results in lingual and sublingual tissue hypercarbia that parallels changes in tissue $P\text{CO}_2$ observed at the levels of the gastric and intestinal mucosa. However, the most striking finding of our study was that restoration of systemic, splanchnic, and lingual perfusion can be accompanied by persistent tissue hypercarbia, more so when norepinephrine is used to normalize systemic hemodynamic variables. Our data support the notion that monitoring efforts directed at restoration of systemic hemodynamic variables may be misleading and that concomitant measurements of tissue $P\text{CO}_2$ provide helpful additional information.

DISCLOSURES

This study was funded in part by a grant from Nellcor Puritan Bennett.

REFERENCES


