Lactic acidosis in the rectal lumen of patients with septic shock measured by luminal equilibrium dialysis

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Background. Gut ischaemia may contribute to morbidity in sepsis, but little is known about the metabolic state of the gut mucosa in such patients.

Methods. Nine patients with abdominal septic shock treated with norepinephrine, and ten healthy subjects, were subjected to equilibrium dialysis with a rectal balloon. pH, P\textsubscript{CO\textsubscript{2}} and concentrations of L-lactate were measured by auto-analyser.

Results. In rectal dialysis fluid from patients with septic shock, acidosis was present (pH 7.23, 95% CI 7.11–7.36) and concentrations of L-lactate were approximately five times greater than controls (2.5–5.8 vs 0.5–1.2 mmol litre\textsuperscript{−1}). The lactate concentration was related to the dose of norepinephrine (P<0.001). In contrast, values of dialysate P\textsubscript{CO\textsubscript{2}} did not differ significantly between patients and controls (6.4–11.0 vs 8.9–13.8 kPa).

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Conclusions. The results suggest that, either lactic acidosis in rectal mucosa is related to shock severity, or that norepinephrine causes mucosal ischaemia. In any case, metabolic dysfunction is present in the rectal mucosa in patients with abdominal septic shock treated with norepinephrine.

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In septic shock, gut ischaemia may contribute to morbidity and this feature may be remediable in septic patients. However, very little is known about the metabolism of the gut in human septic shock.

We set out to measure pH, PCO₂ and concentrations of L-lactate in the gut of patients with septic shock and healthy subjects. Luminal equilibrium dialysis is a valid, non-invasive method for the estimation of extracellular concentrations of small molecules (<12 kDa) in rectal mucosa. Animal studies show that measurement of mucosal lactate by luminal microdialysis is a valid method by which to assess intestinal ischaemia.

Methods and results

Participants

After approval by the regional ethics committee and with informed written consent, we studied nine patients with peritonitis (six had intestinal perforation and three acute pancreatitis) and established septic shock (>24 h), and ten healthy volunteers.

Septic shock was defined as the presence of a positive bacterial culture from the blood or the peritoneal cavity and the need for infusion of norepinephrine (>0.04 μg kg⁻¹ min⁻¹) to maintain a mean arterial pressure (MAP) >70 mm Hg. We did not include patients with any of the following conditions: (i) any changes in cardiovascular treatment in the preceding 2 h, (ii) systemic hypoxia (PaO₂ <8 kPa), (iii) abnormal rectum or left colon, (iv) active gastrointestinal bleeding, or (v) an intra-abdominal pressure >20 mm Hg. All patients had been resuscitated with i.v. fluids before the study using Dextran 60 (Macrodex; Pharmacia-Upjohn, Uppsala, Sweden) and isotonic saline until the arterial pressure was stable, after which another 1000–2000 ml of fluid were given. Blood was given if the haemoglobin concentration was <5 g dl⁻¹. If oliguria was present, dopamine was infused at 4 μg kg⁻¹ min⁻¹ (four patients). All patients received systemic antibiotics, selective digestive decontamination (except three patients) and enteral nutrition (except one). Three patients had a pulmonary artery catheter in place during the study. All of these patients had a cardiac index >3 litre min⁻¹ m⁻², a pulmonary capillary wedge pressure >16 mm Hg and a systemic vascular resistance index <1000 dyn s cm⁻⁵ m⁻².

Luminal equilibrium dialysis

pH, PCO₂ and concentrations of L-lactate in rectal mucosa were measured by luminal equilibrium dialysis as previously described. Bags of dialysis tubing (semipermeable cellulose, cut-off 12 kDa; Sigma, St Louis, MO, USA) were closed over 5 cm of Tygon tube (Cole-Parmer Instruments Company, Vernon Hills, IL, USA) with a three-way stopcock at the distal end for airtight sampling. Bags were filled with 4 ml of Dextran 40 10% in isotonic saline (Rheomacrodex; Pharmacia-Upjohn) and placed in the rectal lumen for 4 h, which was the time required for 100% equilibrium of eicosanoids in vivo. Incubation of dialysis bags for 2 h in a saline bath containing 1 mmol litre⁻¹ L-lactate (Sigma) at 37°C was sufficient for 100% equilibrium of L-lactate. pH, PCO₂ and L-lactate were measured by auto-analyser (ABL 625, Radiometer, Copenhagen, Denmark). As D-lactate may be produced by luminal bacteria, saline solutions containing 1, 10 and 100 mmol litre⁻¹ D-lactate (Sigma) were analysed in the ABL 625, but D-lactate was undetectable (n=3).

Statistics

Normal distribution of the variables was tested with the Kolmogorov–Smirnov statistics and the Levine test was used to test for equal variance. Data were analysed by Student’s t-test for unpaired or paired variables, or linear regression analysis where appropriate. P-values <0.05 (2-tailed) were considered significant.

Results

In dialysis fluid from the patients with septic shock, acidosis and increased concentrations of L-lactate were observed compared with values in fluid from healthy subjects (Table 1). In septic patients, the mean concentration of L-lactate in dialysis fluid was 70% greater than in arterial blood (P=0.03, Table 1), and there was no correlation between the two values (P=0.27). In contrast, dialysate
concentrations of L-lactate correlated with the dose of nor-
epinephrine (Fig. 1, \( r^2=0.89; P=0.0001 \)). The dose of
norepinephrine was not related to systemic values of
L-lactate (\( P=0.48 \)).

Comment

Our results show lactic acidosis in the rectal lumen of
patients with abdominal septic shock. Lactic acidosis may
represent anaerobic glycolysis from hypoperfusion of rectal
mucosa. Although sympatomimetics can cause systemic
lactic acidosis through aerobic glycolysis, this has not been
seen during infusion of norepinephrine,\(^5\) as was used in the
present study. In support of this, systemic values of L-lactate
were not related to norepinephrine dose in our patients, but
the regression analyses of the present study have a high risk
of a type II error. In addition to being markers of
metabolism, acidosis\(^6\) as well as lactate\(^7\) can cause cellular
dysfunction leading to increased intestinal permeability and
increased morbidity in septic shock.

Rectal equilibrium dialysis may be a simple, non-invasive
method to measure markers of metabolism in gut mucosa in
critically ill patients. The 4 h of equilibration used in the
present study may hamper its clinical use. However, it is
possible that equilibrium can be obtained earlier or that non-
equilibrium dialysis with a shorter time of exposure can
detect clinically relevant differences. Future studies should
address these questions as well as the effects of age,
dopamine, antibiotics, enteral nutrition and fluid manage-
ment.

The high values of \( P_{CO_2} \) observed in the rectal lumen of
both patients and healthy subjects suggest that carbon
dioxide may come from bacterial metabolism. Alternatively, weak acids in faeces may be buffered by
\( HCO_3^- \), which is secreted into the lumen by rectal epithelial
cells. Consequently, any change in bacterial number or
metabolism or epithelial secretion of \( HCO_3^- \) could affect
\( P_{CO_2} \), pH, or both and complicate the interpretation of these
values. In the gastric mucosa, an increased luminal–arterial
\( P_{CO_2} \) gap may indicate regional hypoperfusion. We did not
determine arterial \( P_{CO_2} \) in the healthy subjects, so com-
parison between the groups is not possible. Bacterial
metabolism may also generate D-lactate, but this was not
detectable by the auto-analyser used in the present study.
This suggests that bacterial metabolism did not contribute to
the high dialysate lactate observed in septic patients.

The observed relationship between dialysate L-lactate and
norepinephrine dose suggests that mucosal L-lactate is
related to shock severity, which may be indicated by the
dose of norepinephrine. Alternatively, norepinephrine treat-
ment may itself cause mucosal ischaemia. In any case,
metabolic dysfunction is present at the rectal–mucosal
barrier in patients with abdominal septic shock treated with
norepinephrine.

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**Table 1** Characteristics and metabolic values in arterial blood and rectal dialysis fluid in patients with abdominal septic shock and healthy subjects. Data are
mean (SD or range) or number of patients (%). *Values from seven patients, as air-contamination occurred in dialysates from two patients

<table>
<thead>
<tr>
<th></th>
<th>Septic patients ((n=9))</th>
<th>Healthy subjects ((n=10))</th>
<th>( t )-test</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56 (38–72)</td>
<td>26 (23–32)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>45</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>SAPS II</td>
<td>43 (9)</td>
<td>--</td>
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<tr>
<td>MAP (mm H(_2))</td>
<td>80 (9)</td>
<td>--</td>
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<td></td>
</tr>
<tr>
<td>HR (beat min(^{-1}))</td>
<td>103 (19)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Arterial blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.34 (0.05)</td>
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<td></td>
</tr>
<tr>
<td>( P_{CO_2} ) (kPa)</td>
<td>5.8 (0.8)</td>
<td>--</td>
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<td></td>
</tr>
<tr>
<td>( P_{O_2} ) (kPa)</td>
<td>11.9 (1.4)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>L-lactate (mmol litre(^{-1}))</td>
<td>2.4 (1.3)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Rectal dialysate</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>pH</td>
<td>7.23 (0.15)*</td>
<td>7.46 (0.15)</td>
<td>0.01</td>
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</tr>
<tr>
<td>( P_{CO_2} ) (kPa)</td>
<td>8.7 (2.8)*</td>
<td>1.3 (3.2)</td>
<td>0.34</td>
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</tr>
<tr>
<td>L-lactate (mmol litre(^{-1}))</td>
<td>4.1 (2.2)</td>
<td>0.8 (0.5)</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

HR=heart rate; MAP=mean arterial pressure; SAPS II=simplified acute physiology score II.

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**Fig 1** Relationship between rectal dialysis fluid concentration of L-lactate
and the dose of norepinephrine in patients with abdominal septic shock.
\( r^2=0.89; P=0.0001 \) by linear regression analysis.
References