Gastric Tonometry in Patients with Sepsis*
Effects of Dobutamine Infusions and Packed Red Blood Cell Transfusions

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We wanted to determine the efficacy of dobutamine infusions and Prbc transfusions on splanchnic tissue oxygen utilization by measuring gastric pH\textsubscript{i}. Physiologic parameters and pH\textsubscript{i} measurements via the use of a gastric tonometer were obtained in 21 septic patients before and after the administration of a dobutamine infusion (5 µg/kg/min) or the transfusion of two units of Prbc. Subsets of measurements with normal (>7.32) and with low (<7.32) pH\textsubscript{i} were separately analyzed for each intervention. In the dobutamine low pH\textsubscript{i} group, pH\textsubscript{i} increased significantly from 7.16±0.03 to 7.24±0.03 (n=9, p<0.05). In contrast, pH\textsubscript{i} failed to increase in the Prbc low pH\textsubscript{i} subgroup (7.16±0.05 to 7.17±0.04 [n=10, p>0.80]). We conclude that dobutamine rather than Prbc transfusions should be administered to reverse gastric intramucosal acidosis.

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\textbf{T}issue hypoxia, caused by an imbalance between the oxygen demand and the oxygen uptake of the peripheral tissues, is considered an important contributing factor to the morbidity and mortality observed in sepsis and critical illness.\textsuperscript{1,2} Controversy, however, surrounds the proper assessment of tissue oxygenation, since techniques for directly monitoring the adequacy of tissue oxygenation are not available in the clinical setting.\textsuperscript{3}

Much interest has focused on measurements of systemic DO\textsubscript{2} and systemic VO\textsubscript{2}, but these global measurements do not provide information about oxygen utilization by tissues as related to their needs. Mixed venous oxygen saturation also is a poor marker of tissue oxygenation in sepsis, because maldistribution of blood flow and shunting can cause elevated values in the setting of tissue hypoxia in individual organs.

Investigators have considered lactate levels to be a marker of oxygen debt in patients with sepsis, since several studies have demonstrated this parameter to be predictive of outcome\textsuperscript{4,5} as well as predictive of oxygen-supply dependency.\textsuperscript{6,7} These measurements, however, may not be a specific marker of tissue hypoxia. This may be so because the serum lactate level is the net effect of both the production and elimination of lactate. Therefore, it may be elevated in conditions associated with increased lactate production\textsuperscript{6,9} or with decreased clearance, eg, liver failure\textsuperscript{10} or sepsis.\textsuperscript{11} Furthermore, the lactate level represents a global index and hence, may not be an optimal measure of the adequacy of regional or microvascular perfusion in specific organ systems. Finally, lactate levels may transiently rise during therapeutic maneuvers due to a “washout” phenomenon,\textsuperscript{12,13} which may prevent immediate feedback on the efficiency of interventions.

Recently, experimental studies have shown that pH\textsubscript{i} measured by tonometers placed in the intestines is a good indicator of gut ischemia\textsuperscript{14-18} and several clinical studies have demonstrated the potential utility of intestinal\textsuperscript{19-22} and gastric\textsuperscript{23,24} tonometry in identifying patients at risk for developing complications attributable to mucosal disruption in a variety of critical illnesses. These measurements are attractive because they are minimally invasive and attempt to assess the adequacy of tissue oxygenation in an organ system that may play a pivotal role in sepsis.\textsuperscript{25} Indeed, commentators have hypothesized that ischemia-induced mucosal injury may promote bacterial translocation from the lumen of the gut into the vasculature, thereby initiating and/or perpetuating the septic process.\textsuperscript{26}

Since low pH\textsubscript{i} measurements may reflect deficient splanchnic tissue oxygenation and hence inadequacy of resuscitative measures, we wanted to determine the efficacy of therapeutic interventions on gut oxygen utilization by observing their effects on gastric tonometric pH values.

\textbf{METHODS}

\textbf{Patient Population}

Data from 21 patients were retrospectively reviewed. All patients met criteria for the sepsis syndrome, as defined by Bone and colleagues:\textsuperscript{27} (1) positive blood cultures or clinical evidence of

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infection or both, (2) rectal temperature >38.5°C or <35.5°C, (3) tachycardia (HR greater than 90 beats per minute), and (4) tachypnea (respiratory rate >20 breaths per minute while spontaneously breathing).

Hemodynamic Monitoring

All intravascular pressures were measured with the patient in the supine position using the midaxillary level as the zero reference point. The MAP was obtained from an indwelling arterial catheter. The HR was obtained from the ECG. Values for PAWP were obtained from a percutaneously placed pulmonary artery catheter and measured at end-expiration from a strip chart recorder.

Cardiac output was measured by the thermodilution technique using cold (<8°C) 5 percent dextrose in water and a closed system (CO-set system, Marquette Laboratories). Three to five measurements were averaged to obtain each cardiac output value. All values were within 10 percent of each other.

Arterial and mixed venous blood samples were obtained for determination of blood gas values (ABL3; Radiometer, Copenhagen, Denmark), hemoglobin saturation, and hemoglobin concentration. Arterial lactate samples were placed on ice and immediately measured by reflectance spectrophotometry (Ektachem 700, Eastman Kodak, Rochester, NY); normal arterial values ranged from 4.5 to 14.4 mg/dl.

The Do2 (ml/min/m²) and VO2 (ml/min/m²) were calculated as:

\[ CI \times Hb \times SaO2 \times 1.39 \times 10 \quad \text{and} \quad CI \times Hb \times (SaO2 - SVo2) \times 1.39 \times 10 \]

respectively, where the CI is measured in liters per minute per square meter, the hemoglobin concentration is given in grams, and SaO2 and SVo2 are given as percentages.

Gastric Tonometry

A nasogastric tube with a silicone rubber balloon (Tonometer, Tonometrics, Worcester, Mass) was used to measure pH. Satisfactory placement of the tube was confirmed roentgenographically. Normal saline solution (2.5 ml) was used to fill the balloon of the tonometer. After an equilibration time of 90 min, the first 1 ml of fluid obtained from the balloon was discarded to account for the dead space of the conduit, whereas the remaining 1.5 ml was sent for determination of PCO2. At the same time, samples of arterial blood were obtained for measurement of HCO3 and lactate.

Gastric pH was calculated using the Henderson-Hasselbalch equation:

\[ pH = 6.1 + \log_{10} \left( \frac{HCO3^- \times 1.14 \times PCO2 \times 0.03}{PCO2} \right) \]

where HCO3 is the bicarbonate concentration in arterial blood, PCO2 is the partial pressure of CO2 in the saline within the balloon of the tonometer, and 1.14 is a correction factor determined by previous investigators to account for the incomplete equilibration of CO2 between gastric juice and the saline in the balloon within the 90-min time frame.

Protocol

Increases in Do2 were achieved by either dobutamine infusions (5 μg/kg/min) or the administration of two units of Prbc. Initiation of therapeutic maneuvers depended on the decision of the primary physician directly managing the patient. Because physiologic measurements both before and after major interventions routinely are performed in the intensive care unit participating in this study, physiologic parameters, gastric tonometry, and lactate levels could be obtained before (within 1 h) and after the completion of each intervention. Data on the effects of dobutamine infusions and Prbc transfusions on pH were obtained from the same patient on 14 occasions. However, all 16 patients who received dobutamine had previously received Prbc transfusions. Furthermore, patients given Prbc transfusions were not receiving dobutamine at the time of the transfusions.

During the intervention period, no changes in therapy, including the infusion rate of adrenergic agents, level of inspired oxygen concentrations, or magnitude of PEEP were allowed. Data were excluded if body temperatures varied by more than 1.0°C.

Subsets of measurements with normal (>7.32) and with low (<7.32) pH were separately analyzed for each intervention. The pH value of 7.32 represents the lower limit of normal derived from previous investigators.

Statistical Analysis

A paired t test was used to compare differences within groups. Linear regression analysis was performed using the least squares method. A probability value less than 0.05 was considered significant. All data are expressed as mean ± SEM.

RESULTS

Data were obtained from 21 patients, 11 women and 10 men. The average age was 47 ± 4.1 years (range: 21 to 88 years) and the mortality rate was 38 percent. Blood cultures were positive in 48 percent of the patients. The source of infection was lung in ten patients, kidney in five, and an empyema, catheter-related infection, endocarditis, epidural abscess, peritonitis, and osteomyelitis in the other six patients. The infecting organisms were Gram-negative bacteria in ten patients, Gram-positive bacteria in five, *Pneumocystis carinii* in three, and fungus in one; cultures were negative in the remaining two patients. Liver failure, defined by a serum bilirubin level twice the upper limit of normal (0.9 mg/dl) was present in three of the patients. Intravenous ranitidine was administered to 18 of 21 patients.

The interval between initial and final physiologic measurements was 3.1 ± 0.4 and 7.1 ± 0.8 h for dobutamine infusions and Prbc transfusions, respectively. The baseline hemoglobin for patients receiving dobutamine infusions was 10.3 ± 1.4 g/100 ml, which was significantly greater than the baseline hemoglobin value in patients who received Prbc transfusions (8.5 ± 0.5 g/100 ml; p<0.0001).

The changes in physiologic parameters associated with dobutamine and Prbc transfusions are shown in Tables 1 and 2 for subsets of normal and low pH measurements. A significant increase in pH was observed in the dobutamine low pH subgroup, whereas the mean pH value remained virtually unchanged in the Prbc low pH subgroup. Systemic pH remained unchanged in both these subgroups. The pH decreased in the Prbc normal pH subgroup and tended to decrease in the dobutamine normal pH subgroup (p = 0.07).

Significant increases in Do2 occurred in all subgroups. Dobutamine infusions produced significant elevations in CI in both subgroups, whereas Prbc transfusions failed to significantly increase the CI in both subgroups. In the Prbc low pH subgroup, the SVo2 increased significantly.

Correlations between systemic pH and pH and between changes in systemic pH and changes in pH were poor (y = 1.8 + 0.74x, r = 0.39; y = 0.008 – 0.19x, r = .08, respectively). A poor correlation also

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was observed between the pH and lactate levels obtained prior to the interventions (y = 7.31 – 0.002x, r = 0.25).

**DISCUSSION**

This study demonstrates that dobutamine increases low gastric tonometric pH values in septic patients, suggesting that this agent may improve splanchic tissue oxygenation in this disease state. In contrast, Prbc transfusions failed to improve gastric intramucosal acidosis.

The mechanism of dobutamine’s effect on restoring the balance between oxygen demand and oxygen uptake in the splanchic circulation remains undefined; but enhancement of mesenteric blood flow warrants consideration occurring either from the effects of an increase in systemic flow or a direct vasodilatory action on splanchic vessels. In healthy animals, investigators have demonstrated increases in blood flow to the mesenteric bed with dobutamine, but this effect was moderate and only occurred at high doses. In vitro studies, however, have demonstrated alpha-antagonistic effects of dobutamine, and therefore, dobutamine’s direct vasodilatory actions on the splanchic circulation may be more pronounced when splanchic vascular tone is increased under conditions of enhanced sympathetic stimulation. Indeed, MacCannell and co-workers demonstrated that dobutamine at 5 µg/kg/min produced significant increases in blood flow to the splanchic organs in a dog model of heart failure, whereas Fleisch and Spaethe observed dobutamine-induced relaxation of norepinephrine-perfused rat mesenteric artery strips. These observations suggest that dobutamine’s ability to vasodilate the splanchic bed may be enhanced in sepsis, where there is a relative or absolute decrease in splanchic perfusion caused by the vasoconstrictor effects of the catecholamines released in this shock state. A low pH, therefore, may be indicative of increased vascular tone in the splanchic bed.

The failure of Prbc transfusions to improve splanchic tissue oxygenation may have been due to a decrease in organ blood flow caused by the effect of enhanced blood viscosity or vasomotor changes, or both, that occur with increases in the hematocrit level. A decrease in organ blood flow may therefore oppose the increased arterial oxygen content sufficiently to cause capillary oxygen delivery to remain constant. Indeed, one study demonstrated that the oxygen

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### Table 1—Physiologic Parameters before and after Dobutamine Infusions

<table>
<thead>
<tr>
<th></th>
<th>Normal pH (n = 7)</th>
<th>Low pH (n = 9)</th>
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<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>HR (beats per minute)</td>
<td>109 ± 5</td>
<td>124 ± 7*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>87 ± 5</td>
<td>90 ± 6</td>
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<tr>
<td>PAWP (mm Hg)</td>
<td>11.3 ± 1.5</td>
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<td>CI (L/min/m²)</td>
<td>4.1 ± 0.7</td>
<td>4.5 ± 0.7*</td>
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<tr>
<td>SVO₂ (%)</td>
<td>71.4 ± 3.5</td>
<td>75 ± 2.5</td>
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<tr>
<td>D₀ₓ (ml/min/m²)</td>
<td>577 ± 102</td>
<td>682 ± 98*</td>
</tr>
<tr>
<td>V₀ₓ (ml/min/m²)</td>
<td>144 ± 20</td>
<td>147 ± 22</td>
</tr>
<tr>
<td>Lactate (mg/dl)</td>
<td>18.0 ± 2.4</td>
<td>16.7 ± 2.8</td>
</tr>
<tr>
<td>pHa</td>
<td>7.40 ± 0.04</td>
<td>7.38 ± 0.03</td>
</tr>
<tr>
<td>pH</td>
<td>7.43 ± 0.03</td>
<td>7.35 ± 0.01</td>
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*p<0.00001, initial to final.

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### Table 2—Physiologic Parameters before and after Packed Red Blood Cell Transfusions

<table>
<thead>
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<th></th>
<th>Normal pH (n = 9)</th>
<th>Low pH (n = 10)</th>
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<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>HR (beats per minute)</td>
<td>106 ± 5</td>
<td>110 ± 5</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>82 ± 7</td>
<td>85 ± 7</td>
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<tr>
<td>PAWP (mm Hg)</td>
<td>13.2 ± 2.5</td>
<td>13.1 ± 1.6</td>
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<tr>
<td>CI (L/min/m²)</td>
<td>5.4 ± 0.7</td>
<td>5.5 ± 0.9</td>
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<tr>
<td>Hemoglobin (g/100 ml)</td>
<td>8.4 ± 0.5</td>
<td>10.6 ± 0.5*</td>
</tr>
<tr>
<td>SVO₂ (%)</td>
<td>72.4 ± 1.7</td>
<td>73.5 ± 1.5</td>
</tr>
<tr>
<td>D₀ₓ (ml/min/m²)</td>
<td>617 ± 99</td>
<td>793 ± 144†</td>
</tr>
<tr>
<td>V₀ₓ (ml/min/m²)</td>
<td>156 ± 22</td>
<td>178 ± 22</td>
</tr>
<tr>
<td>Lactate (mg/dl)</td>
<td>24.8 ± 9.3</td>
<td>28.4 ± 9.3</td>
</tr>
<tr>
<td>pHa</td>
<td>7.39 ± 0.03</td>
<td>7.38 ± 0.03</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.02</td>
<td>7.31 ± 0.05†</td>
</tr>
</tbody>
</table>

*p<.000001, initial to final.

†p<0.05, initial to final.
transport to the intestines remained unchanged within a hematocrit range of 30 to 55 percent. In sepsis, viscosity effects may be even more pronounced due to decreased red cell deformability and enhanced red cell aggregation.  

This study also demonstrates that a reduction in pH from a normal value may occur with therapeutic maneuvers. Decreases in pH occurred with Prbc transfusions, while the decreases in pH with dobutamine infusions approached statistical significance. Further studies are needed to confirm whether hyperresuscitation in the setting of a normal pH can promote splanchnic ischemia and, if so, the mechanisms by which dobutamine and Prbc transfusions can cause this phenomenon.

Findings from this study also suggest that lactate levels may not be a sensitive or a specific marker of splanchnic tissue oxygenation, since the correlation between lactate levels and pH measurements were poor.

Although there is a conceptual basis for the use of tonometry in critically ill patients, several factors, may limit the ability of gastric pH to accurately reflect the oxygenation status of the splanchnic organs. Gastric intramucosal acidosis can occur from hypoperfusion as well as from the back-diffusion of CO\textsubscript{2} generated within the stomach by the reaction of secreted H\textsuperscript{+} with secreted HCO\textsubscript{3}\. The extramural production of CO\textsubscript{2}, therefore, may limit the accuracy of the gastric tonometer in reflecting intramucosal acidosis due to inadequate oxygen uptake alone. Recently, Heard and colleagues\textsuperscript{9} demonstrated higher gastric fluid PCO\textsubscript{2} values in healthy subjects with acid-secreting stomachs compared with subjects treated with an H\textsubscript{2} antagonist to block acid secretion. Hence, previous investigations\textsuperscript{14-18} demonstrating the sensitivity of pH as an indicator of splanchnic ischemia with the use of tonometers placed in the intestines may not be applicable to gastric tonometers. Indeed, Hartmann and colleagues\textsuperscript{19} observed a poor correlation between gastric and intestinal pH in a porcine model of hemorrhagic shock. In our study, the contribution of intraluminal CO\textsubscript{2} production to gastric intramucosal acidosis was probably minimal because ranitidine was administered to a large majority of our patients, thus minimizing the occurrence of hydrogen ion secretion.

A second limiting factor in the use of tonometry derives from experimental studies demonstrating the inaccuracy of tonometrically derived pH in low flow states,\textsuperscript{17} which may promote a dissociation between arterial and tissue HCO\textsubscript{3} values. This effect, however, was not observed in endotoxemia, and hence, may not be relevant to patients with sepsis.

Finally, the influence of metabolic acidosis from nonanaerobic causes or systemically produced lactic acid on the pH\textsubscript{i} is unknown. However, our study involved following the effects of interventions on changes in pH\textsubscript{i} over narrow time intervals, at which time the systemic pH\textsubscript{a} remained relatively constant. Furthermore, we found a poor correlation between the absolute values as well as the changes in systemic pH\textsubscript{a} and pH\textsubscript{i}. Finally, the magnitude of systemic acidosis or lactate acidosis in our study was modest and therefore probably had a minimal effect on pH\textsubscript{i}. Further investigations, however, are needed to assess the effects of severe acidosis on the pH\textsubscript{i}.

In summary, this study demonstrates the effectiveness of dobutamine in improving gastric intramucosal acidosis as measured by tonometry, as well as the utility of gastric tonometry in providing immediate feedback on the efficacy of interventions on restoring the balance between oxygen uptake and oxygen demand. Further studies are required to determine if increasing pH\textsubscript{i} improves survival in patients with sepsis.

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REFERENCES


28 Bobie NW, Goldberg LI. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine. Am Heart J 1975; 89:340-45
30 Liang CS, Hood WB. Dobutamine infusion in conscious dogs with and without autonomic nervous system inhibition: effects on systemic hemodynamics, regional blood flows and cardiac metabolism. J Pharm Exp Ther 1979; 211:696-705
33 MacCannell KL, Giraud GD, Groves HG. Haemodynamic responses to dopamine and dobutamine infusions as a function of duration of infusion. Pharmacology 1983; 26:29-30
38 Fan FC, Chen RY, Schuessler GB, Chien S. Effects of hematocrit variations on regional hemodynamics and oxygen transport in the dog. Am J Physiol 1990; 258:H545-52
39 Effrey DJ, Blaisdell FW, McIntyre KE, Graziano CJ. The relationship between sepsis and intravascular coagulation. J Trauma 1978; 18:689-95