Gastric mucosal acidosis and cytokine release in patients with septic shock

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Objective: **It has been postulated that in critically ill patients, splanchnic hypoperfusion may lead to cytokine release into the systemic circulation. The presence of cytokines could trigger an inflammatory response and cause multiple organ dysfunction syndrome. Although experimental studies support this hypothesis, humans studies remain controversial. The aim of the study was to determine the relationship between splanchnic hypoperfusion and cytokine release during septic shock.**

Design: **Human prospective study.**

Setting: **Medical intensive care unit at a university hospital.**

Patients: **A total of 30 patients with mean arterial pressure of <60 mm Hg after volume loading with either oliguria or hyperlactatemia.**

Measurements: **Gastric intramucosal measurements as an indicator of splanchnic hypoperfusion and blood samples were obtained at admission to the medical intensive care unit and repeated during 48 hrs. Cytokine (tumor necrosis factor-α and interleukin-6) values were evaluated by enzyme-linked immunoassays at the following periods: at the time of admission and 2, 4, 8, 12, 24, 36, and 48 hrs later.**

Main Results: **High levels of interleukin-6 and tumor necrosis factor-α were observed at admission in survivors and nonsurvivors, without significant difference. At 48 hrs, cytokine levels were significantly higher in patients who died compared with the survivors (tumor necrosis factor: 163 ± 16 for nonsurvivors vs. 34 ± 9 ng/mL for survivors; interleukin-6: 2814 ± 485 for nonsurvivors vs. 469 ± 107 ng/mL for survivors). At 48 hrs, the P_{CO_2} gap was significantly higher in the nonsurvivors compared with survivors (25.87 ± 2.73 vs. 11.35 ± 2.25 mm Hg), despite systemic hemodynamic variables in the normal range. A positive relationship was demonstrated between plasma levels of tumor necrosis factor-α and interleukin-6 and the P_{CO_2} gap throughout the study. The P_{CO_2} gap was not correlated with hemodynamic variables.**

Conclusions: **Our data suggest a relationship between gastric mucosal acidosis, as assessed by P_{CO_2} gap, and cytokine levels in critically ill patients with septic shock. Gut injury may be a contributor of the inflammatory response in patients with septic shock. (Crit Care Med 2003; 31:2137–2143)**

Key Words: **humans; septic shock; cytokine; tumor necrosis factor-α; interleukin-6; splanchnic hypoperfusion; gastric tonometry; P_{CO_2} gap; lactate; hemodynamic variables**

Cytokine release is known to trigger systemic inflammatory response syndrome and mediates the development of multiple organ dysfunction syndrome in critically ill patients (1). The role of the gut in the pathogenesis of systemic inflammatory response syndrome still remains controversial. It has been suggested that splanchnic hypoperfusion could result in loss of barrier function of the intestine and lead to a translocation of bacteria or endotoxin into the systemic circulation (2). Although there is compelling experimental evidence to support this theory, results in humans are still unclear (3–5). In an experimental hemorrhagic shock model, we previously demonstrated that intestinal ischemia-reperfusion may be a major trigger for cytokine gene expression in the absence of endotoxin (6). Hynninen et al. (7) have demonstrated that patients with severe pancreatitis often have splanchnic hypoperfusion and produce major cytokine response, despite a rare occurrence of endotoxemia. In this study, both increased concentrations of cytokines and low intramucosal gastric pH were found to be correlated to the development of multiple organ failure. In abdominal aortic surgery, the degree and duration of intramucosal acidosis is often predictive of the severity of ischemic colitis (8). The development of gastric intramucosal acidosis has been found to be a good predictor of outcome in major abdominal surgery and correlated with IL-6 plasma levels (9). In a model of hemorrhagic shock, the restoration of systemic arterial pressure fails to prevent progression of gastric intramucosal acidosis (10). This finding may be related to persistent splanchnic reperfusion injury, even with normal mean arterial pressure.

These different data in experimental studies raise the question of, in humans, whether splanchnic hypoperfusion may be related to cytokine release, which results in systemic inflammatory response syndrome with poor patient outcome. The main goal of this study was to define the relationship between gastric mucosal

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acidosis, as assessed by P_{CO_2} gap, and cytokine release in critically ill patients with septic shock.

MATERIALS AND METHODS

Patients. This study was approved by the hospital ethics committee, and written informed consent was obtained from each patient's closest relative. The present study included 30 consecutive patients with septic shock as defined by the ACCP/SCCM Consensus Conference Committee between December 1998 and December 1999 (1). The severity of illness was assessed according to the Simplified Acute Physiology Scale II score within 24 hrs after the admission to the medical intensive care unit. Multiple organ system failure score was calculated as described by Knaus et al (11). Multiple organ system failure score is defined as the sum of the failing organ systems. Patients were followed for 28 days after the start of the study or until death. The clinical characteristics are summarized in Table 1.

Patients were eligible for entry into study if they had a definable source of infection or positive blood cultures. To be included in the study, after the optimal volume resuscitation and treatment with dopamine, up to a dose of 20 μg/kg per min, patients had to meet the following criteria: 1) mean arterial pressure of <60 mm Hg, 2) signs of altered perfusion (i.e., oliguria [<30 mL/hr] or an increased lactate level [>2 mmol/L]) (12). Large-volume fluid resuscitation was instituted. Optimal cardiac filling had been guided by pulmonary artery occlusion pressure of >12 mm Hg and was no longer accompanied by an increase in cardiac index after infusion of additional fluids (13, 14). If the patient remained hypotensive after adequate volume resuscitation had been established, vasopressor agents were instituted (15). Epinephrine and norepinephrine were started at 0.3 μg/kg per min. Their infusion rate was titrated on mean arterial pressure at 5-min intervals to obtain a mean arterial pressure of >80 mm Hg with a stable or increased cardiac index. After the first hour, the titration of vasopressor agent was increased to obtain the same mean arterial pressure, if necessary. Epinephrine was administered to 17 patients at doses ranging from 0.5 to 3 μg/kg per min. Norepinephrine-dobutamine was administered to eight patients at doses ranging from 0.5 to 3 μg/kg per min for norepinephrine, and dobutamine was infused at a fixed dose of 5 μg/kg per min. Dopamine was administered alone to five patients at doses of 20 μg/kg per min.

Procalcitonin has been suggested as an excellent marker of bacteria-associated sepsis in patients (16). Procalcitonin was measured by an immunoluminometric assay (Lumitest, procalcitonin, Brahms, Diagnostica GmbH, Berlin, Germany) and obtained at the time of admission and at 24 and 48 hrs after admission.

Table 1. Patient characteristics at admission

	Survivors (n = 16)	Nonsurvivors (n = 14)	*p* Value
Age, yrs	64 ± 20	60 ± 15	NS
Sex, M/F	13/3	13/1	NS
SAPS II	58 ± 11	64 ± 12	NS
OSF	3.3 (2–4)	3.5 (2–4)	NS
Primary illness	16 medical	14 medical	
Source of infection	Pulmonary, 10 Renal, 2 Septicemia, 4	Pulmonary, 8 Abdominal, 2 Septicemia, 4	
Pa_{O_2}/F_2, mm Hg	157 ± 102	105 ± 9	NS
Oliguria, n	12	11	NS
Hyperlactatemia, n	16	14	NS

NS, not significant; SAPS, Simplified Acute Physiology Score; OSF, organ system failure.
[a]Median values with interquartile ranges given in parentheses. Values expressed as mean ± SD.

Hemodynamic and Metabolic Variables. Hemodynamic variables, tonometric variables, and blood samples were obtained at the following periods: at time of admission and 2, 4, 8, 12, 24, 36, and 48 hrs later. Heart rate was monitored continuously. Routine clinical monitoring of patients included a thermodilution pulmonary artery catheter with fiberoptic continuous monitoring of mixed venous oxygen saturation (Swan Ganz, Baxter, Irvine, CA) and a radial or a femoral artery catheter. The zero reference level for the supine position was the midchest level, and pressure was measured at the end of expiration. Serial measurements of heart rate, mean arterial pressure, pulmonary arterial pressure, pulmonary artery occlusion pressure, right atrial pressure, cardiac output, and arterial and mixed venous hemoglobin saturation were performed. Arterial and mixed venous blood gases were analyzed immediately thereafter using an automated blood gas analyzer. There was no additional volume loading and no change in ventilator variables or catecholamine during the first hour of the study.

Tonometric Measurements. The tonometer (catheter TRIP NGS, Tonometrics, Plastimed, France) was inserted nasally, and its position was confirmed by auscultation over the epigastrium after injection of 50 mL of air into the lumen. The tonometer and the airway sampling catheter attached to the patient's airway were connected to an automated gas analyzer (Tonocap, Datex, Helsinki, Finland). After the tonometer balloon was filled with the air and allowed to equilibrate for 15 mins, the gas was automatically sampled and measured by infrared spectroscopy. Arterial blood samples were obtained simultaneously with measurement of Pa_{CO_2} to calculate the gastric-to-arterial P_{CO_2} difference or P_{CO_2} gap. Blood gas values were entered via the Tonocap keyboard for the calculation of gastric intramucosal pH. Gastric intramucosal pH can be indirectly calculated by substituting, in the Henderson-Hasselbalch equation, the steady-state adjusted P_{CO_2} and the arterial blood bicarbonate concentration, assuming that gastric mucosal and blood HCO_3 are equivalent (17). However, this method relies on unjustified assumptions concerning tissue Hco_3^- (18, 19). It is possible that low gastric intramucosal pH may simply be an indicator of systemic acidosis rather than splanchnic ischemia (20). Given these potential difficulties, the gastric-to-arterial CO_2 gap ($Pr_{CO_2} - Pa_{CO_2}$), which is independent of the systemic acid-base status, has become more widely used (21–23).

All patients received histamine receptor (H2) blocking agent by a continuous infusion (ranitidine, 150 mg/day). During the study, nasogastric tubes were not on continuous aspiration, and intravenous sodium bicarbonate and enteral feedings were not administrated.

Metabolic Measurement. For lactate measurements, arterial blood samples were collected in fluoride oxalate–containing tubes and placed on ice. Lactate was measured by an enzymatic colorimetric method adapted to automatic analyzer (Biochem Systems, Paris, France), and the higher normal limit was considered as 2 mmol/L.

Cytokine Measurement. Tumor necrosis factor-α (TNFα) and interleukin (IL)-6 were determined in duplicate by an immunoenzymatic assay (Beckman Coulter France, Coultronics France, Margency, France). Blood specimens were collected into plastic tubes with EDTA, and plasma was separated by centrifugation at 10,000 × *g* for 10 mins and at 4°C before analysis. The limits of assay detection were 5 pg/mL for TNFα and 6 pg/mL for IL-6.

Statistical Analysis. Characteristics of patients and hemodynamic data are represented as mean ± SD and compared by using Student's *t*-test. IL-6 and TNFα levels, P_{CO_2} gap values, and arterial lactate concentration were calculated for all patients at all points and are expressed as mean ± SEM. Analysis of variance with repeated measure was used to compare mean values between the groups. Spearman's correlations were used to assess any associations between two variables concerning cytokines levels, P_{CO_2} gap values, lactate concentration, and cardiac index. To analyze the

accuracy of the variables of lactate, IL-6, TNFα, P_{CO_2} gap to predict mortality, we used Fisher's exact test. A p of $<.05$ was considered statistically significant.

RESULTS

Patient Characteristics. The patients were divided in two groups: survivors or nonsurvivors. There were 16 patients in the survivor group and 14 patients in the nonsurvivor group. All patients were studied for 48 hrs, except for two who died after 1 day. Among the nonsurvivors, patients died due to irreversible shock and multiple organ failure. Clinical data for the survivors and nonsurvivors are shown in Table 1.

Hemodynamic measurements and oxygen-derived variables are listed in Table 2. No statistical difference in systemic hemodynamic measurements were found between survivor or nonsurvivor patients. The different catecholamine regimes (dopamine vs. epinephrine vs. norepinephrine-dobutamine) induced no significant difference in terms of systemic hemodynamic variables (pulmonary arterial pressure, central venous pressure, mean pulmonary artery pressure, pulmonary artery occlusion pressure, cardiac index). The P_{CO_2} gap increased if the epinephrine regime was transient, and returned to normal within 24 hrs. No statistical difference in survivors and nonsurvivors were found between the dopamine and epinephrine and norepinephrine-dobutamine infusions.

Procalcitonin concentrations were markedly increased during the acute phase of septic shock, and this increase was not significantly different between survivors and nonsurvivors (survivors, 135 ± 174 mg/mL; nonsurvivors, 130 ± 170 mg/mL; $p = .3$). At the 48th hour, procalcitonin concentration greatly decreased (survivors, 70 ± 47 mg/mL; nonsurvivors, 82 ± 57 mg/mL; $p = .1$). We observed no significant difference between survivor and nonsurvivor patients at any time.

Lactate Measurement. In the two groups of patients, lactate concentration significantly increased when compared with normal range (<2 mmol/L) (Table 3). The initial concentration was significantly more elevated in the nonsurvivor patients than in the survivor patients (nonsurvivors, 7.18 [range 2–21 mmol/L]; survivors, 4.7 [range 2–12 mmol/L]). At 48 hrs, lactate concentration was significantly higher in the nonsurvivor patients than in the survivor patients (nonsurvivors, 5.2 ± 0.6 mmol/L; survivors, 3.02 ± 0.6 mmol/L; $p = .0004$).

Tonometry Results. At the admission, all patients presented an elevated P_{CO_2} gap, without a significant difference between survivors and nonsurvivors (survivors, 19.84 ± 2.25 mm Hg; nonsurvivors, 18 ± 2.25 mm Hg; $p = .5$) (Table 3). The initial P_{CO_2} gap value did not discriminate nonsurvivor and survivor patients (Fig. 1). After 24 hrs, the P_{CO_2} gap increased in the nonsurvivor group, and the value was 25.87 ± 2.73 mm Hg at 48 hrs. In the survivor patients, the P_{CO_2} gap returned to the normal values at the 48 hrs (11.35 ± 2.25 mm Hg). At 48 hrs, the P_{CO_2} gap was significantly higher in the nonsurvivor patients compared with survivor patients.

Indeed, we analyzed the difference in catecholamine regime with respect P_{CO_2} gap, and we observed that P_{CO_2} gap increased more significantly in the epinephrine group compared with the norepinephrine-dobutamine group or

Table 2. Systemic and pulmonary hemodynamic data

Group	Admission	2 hrs	4 hrs	8 hrs	12 hrs	24 hrs	48 hrs
MAP, mm Hg							
S	60 ± 8	77 ± 10[a]	78 ± 13[a]	89 ± 10[a]	93 ± 8[a]	96 ± 8[a]	90 ± 8[a]
NS	60 ± 8	74 ± 14[a]	67 ± 10[a]	87 ± 11[a]	86 ± 8[a]	90 ± 8[a]	81 ± 15[a]
HR, beats/min							
S	120 ± 21	125 ± 18	124 ± 22	117 ± 17	112 ± 28	105 ± 19	108 ± 19
NS	125 ± 14	126 ± 20	121 ± 14	118 ± 24	115 ± 14	117 ± 18	120 ± 15
CVP, mm Hg							
S	11 ± 3.6	12 ± 5	12 ± 4	12 ± 3.7	12 ± 4.4	11 ± 5.1	12 ± 4
NS	12 ± 4	12 ± 4.8	11 ± 4.2	12 ± 4	12 ± 5.1	11 ± 4.1	12 ± 3.7
MPAP, mm Hg							
S	25 ± 7	31 ± 8[a]	29 ± 7	27 ± 10	28 ± 8	26 ± 9	30 ± 8
NS	26 ± 7	30 ± 7[a]	27 ± 8	27 ± 12	25 ± 7	27 ± 10	28 ± 7
PAOP, mm Hg							
S	13 ± 7	13 ± 4	12 ± 6	11 ± 5	13 ± 6	13 ± 7	12 ± 6
NS	13 ± 7	9 ± 4	10 ± 5	10 ± 5	12 ± 3	10 ± 7	11 ± 5
CI, $L \cdot min^{-1} \cdot m^{-2}$							
S	4 ± 1	3.1 ± 0.9[a]	3 ± 0.8[a]	4.1 ± 0.8	4.1 ± 1	3.7 ± 0.8[a]	4 ± 0.9
NS	4 ± 1	2.9 ± 0.8[a]	3.1 ± 0.7[a]	3.5 ± 0.7[a]	3.5 ± 0.9[a]	3.6 ± 0.6[a]	3.8 ± 1.1
Sv_{O_2}, %							
S	74 ± 18	75 ± 15	76 ± 12	71 ± 10	73 ± 13	73 ± 9	72 ± 8
NS	75 ± 12	61 ± 9	57 ± 13	64 ± 12	63 ± 10	71 ± 9	68 ± 10
$\dot{D}_{O_2}I$, $L \cdot min^{-1} \cdot m^{-2}$							
S	491 ± 152	642 ± 140[a]	652 ± 148[a]	618 ± 144[a]	620 ± 150[a]	622 ± 160[a]	632 ± 154[a]
NS	530 ± 150	652 ± 150[a]	665 ± 145[a]	610 ± 140[a]	610 ± 143[a]	612 ± 150[a]	622 ± 147[a]
$V_{O_2}I$, $L \cdot min^{-1} \cdot m^{-2}$							
S	131 ± 38	149 ± 52	150 ± 42	146 ± 50	143 ± 35	141 ± 30	147 ± 41
NS	141 ± 31	147 ± 42	151 ± 42	146 ± 51	149 ± 31	143 ± 28	149 ± 31

MAP, mean arterial pressure; S, survivors; NS, nonsurvivors; HR, heart rate; CVP, central venous pressure; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; Sv_{O_2}, mixed venous oxygen saturation; $\dot{D}_{O_2}I$, oxygen delivery index; $V_{O_2}I$, oxygen consumption index.

[a] $p < .05$ vs. baseline. Values expressed as mean ± SD.

Table 3. Metabolic and tonometric values

Group	Admission	2 hrs	4 hrs	8 hrs	12 hrs	24 hrs	36 hrs	48 hrs
Lactate, mmol/L								
S	4.8 ± 0.9	5.12 ± 1.03	5.4 ± 1.06	5.3 ± 1.5	2.8 ± 0.3	4.38 ± 0.9	3.7 ± 1	3 ± 0.6
NS	7.2 ± 1.3[a]	7.4 ± 1.0[a]	7.6 ± 1.4[a]	6.9 ± 1.07[a]	5.8 ± 1.01[a]	6.3 ± 0.9[a]	5.8 ± 0.5[a]	5.2 ± 0.64[a]
Arterial pH								
S	7.35 ± 0.07	7.3 ± 0.07	7.26 ± 0.11	7.26 ± 0.11	7.32 ± 0.08	7.35 ± 0.11	7.34 ± 0.12	7.38 ± 0.08
NS	7.32 ± 0.08	7.29 ± 0.07	7.3 ± 0.07	7.35 ± 0.11	7.30 ± 0.09	7.35 ± 0.11	7.32 ± 0.11	7.36 ± 0.09
$Paco_2$, mm Hg								
S	35 ± 2	39 ± 3	40 ± 2	42 ± 3.1	41 ± 3	39 ± 2.5	40 ± 4	43 ± 2.5
NS	36 ± 2	40 ± 3	41 ± 2.5	42 ± 2.9	42 ± 2.9	41 ± 2.8	41 ± 3.2	45 ± 2.9
Pco_2 gap, mm Hg								
S	19.8 ± 0.28	27.4 ± 0.5	29 ± 0.51	28.6 ± 0.47	22.9 ± 11.5	22 ± 0.36	14.9 ± 2.4	11 ± 0.29
NS	18 ± 2.3	19.2 ± 0.29	26 ± 0.35	26.9 ± 034	26.8 ± 0.35	25.8 ± 0.36	27.1 ± 0.3	28 ± 0.13[a]

S, survivors; NS, nonsurvivors, Pco_2 gap, gastric to arterial Pco_2.
[a] $p < .05$ difference between S and NS. Values expressed as mean± SEM.

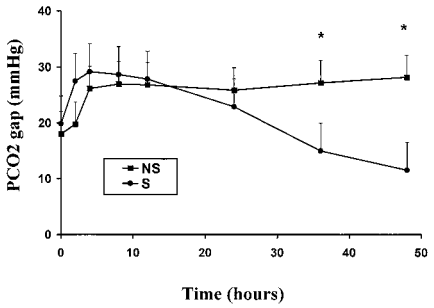

Figure 1. Time course of Pco_2 gap in survivors (*S; circles*) and nonsurvivors (*NS; squares*). Values are mean ± SEM. *$p < .05$ between groups.

dopamine group. The difference in Pco_2 gap in the epinephrine group was transient and observed from the fourth hour to the 12th hour.

Cytokine Release. At admission, there was no difference between survivor and nonsurvivor patients in IL-6 concentrations (survivors, 1322 ± 303 ng/mL; nonsurvivors, 1974 ± 521 ng/mL; $p = .09$) (Table 4). At 48 hrs, the IL-6 concentrations were significantly higher in patients who died from refractory shock compared with the survivors (nonsurvivors, 2814 ± 485 ng/mL; survivors, 469 ± 107 ng/mL; $p = .03$). TNFα concentrations increased in nonsurvivors and progressively decreased in survivors from the 48th hour, and this difference was significant (nonsurvivors, 163 ± 16; survivors, 34 ± 9 ng/mL; $p = .001$) (Table 4).

Correlation Between Indices. Spearman's correlation analysis showed a significant correlation between Pco_2 gap and TNFα values ($r = .94$, $p < 10^{-6}$) and more slight correlation between Pco_2 gap and IL-6 values ($r = .58$, $p < 10^{-6}$) at any time (Fig. 2). When we considered three different catecholamine regimes, Spearman's correlation analysis showed a significant correlation between Pco_2 gap and TNF values in three groups of catecholamine therapy (dopamine group: $r = .88$, $p < 10^{-6}$; epinephrine group: $r = .92$, $p < 10^{-6}$; norepinephrine-dobutamine group: $r = .90$, $p < 10^{-6}$) (data not shown). This association was stronger with TNF than IL-6 in the three groups. No statistical correlation was demonstrated between Pco_2 gap and arterial lactate concentration. Spearman's correlation analysis showed a significant correlation between TNFα values and IL-6 values ($r = .6$, $p < 10^{-6}$).

At all times, there was a significant but slight correlation between IL-6 values and arterial lactate concentration ($r = .23$, $p < .002$) and between IL-6 values and cardiac index ($r = -.34$, $p < 10^{-6}$). No significant relationship was observed between hemodynamic variables (cardiac index) and Pco_2 gap.

DISCUSSION

Multiple organ failure is the major cause of death in patients admitted to the intensive care unit (24). It has been hypothesized that splanchnic ischemia may play a major role in the development of multiple organ dysfunction syndrome (25). In humans, the consequence of the gut injury in the systemic inflammatory response remains controversial. We have measured concomitantly Pco_2 gap and cytokine levels: TNFα and IL-6 in critically ill patients with severe septic shock during 48 hrs. We observed that gastric mucosal acidosis develops and persists after restoration of routine hemodynamic variables. We found that increases in Pco_2 gap are common and that increases in Pco_2 gap at the 48th hour correlate with mortality. For the first time, we have demonstrated that increases in Pco_2 gap values were associated with high values of TNFα and IL-6 in critically ill patients with septic shock. The time course levels of TNFα and Pco_2 gap curves were remarkably parallel, and the relationship was strongest with TNFα compared with IL-6 values (Fig. 2). We did not observe such a significant relationship between the cytokine levels and conventional hemodynamic variables or lactate concentration.

Splanchnic ischemia seems difficult to assess in humans, and gastric tonometry has been proposed to detect regional splanchnic hypoperfusion by the measurement of partial gastric mucosal CO_2 pressure and gastric intramucosal pH (26, 27). Gastric tonometry is a relative noninvasive monitoring technique that can measure gastric intramucosal acidosis and provides useful information on the adequacy of splanchnic perfusion (28). The normal value for Pco_2 gap has been established in normal volunteers to be approximately 7 mm Hg (29). The increase in intestinal tissue Pco_2 during ischemia correlated with the histologic grade of intestinal injury. Increased Pco_2 gap during a decrease in oxygen delivery can be explained by several mechanisms (30). When $\dot{D}o_2$ is above its critical value, ensuring a constant CO_2 production by oxidative phosphorylation, increased $Prco_2$ reflects a decrease CO_2 washout secondary to decreased gastric blood flow. When $\dot{D}o_2$ is below its critical value, cell dysoxia occurs and $Prco_2$ results from an imbalance between decreased aerobic CO_2 production and increased anaerobic CO_2 production due to H^+ buffering by bicarbonates. An increased Pco_2 gap means decreased flow, not necessarily

Table 4. Tumor necrosis factor (TNF)α and interleukin (IL)-6 values in patients

Group	Admission	2 hrs	4 hrs	8 hrs	12 hrs	24 hrs	36 hrs	48 hrs
TNFα, pg/mL								
S	72.93 ± 15.65	222.66 ± 94.74	185.12 ± 72.86	227.5 ± 74.55	257.12 ± 74.55	124.06 ± 18.21	68.56 ± 18.21	34.68 ± 9.02
NS	63.05 ± 17.04	79.5 ± 17.62	129.35 ± 29.75	150.07 ± 27.92	132.58 ± 32.86	144.08 ± 49.92	155.25 ± 43.9[a]	163.08 ± 16.1[a]
IL-6, pg/mL								
S	1322.9 ± 303.4	1370.0 ± 54.6	1731.5 ± 369.2	1389.4 ± 313.0	1381.6 ± 313.0	881.1 ± 260.5	944.5 ± 446.5	469.7 ± 107.3
NS	1974.2 ± 521.7	2023.7 ± 572.9	2634.1 ± 665.1	2357.1 ± 665.1[a]	2357.9 ± 468.9	1945.1 ± 484.7	1993.1 ± 484.7	2814.5 ± 485.2[a]

TNFα, tumor necrosis factor; S, survivors; NS, nonsurvivors; IL-6, interleukin-6.
[a]$p < .05$ difference between S and NS. Values expressed as mean ± SEM.

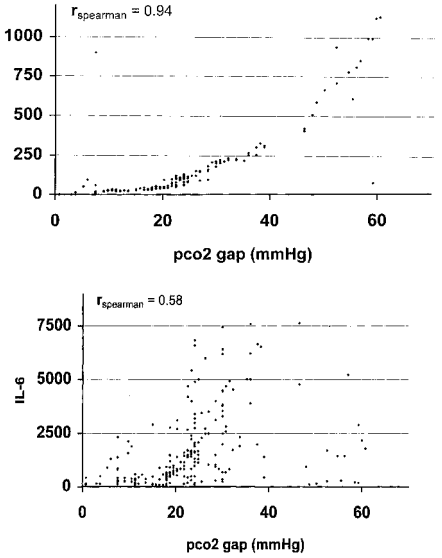

Figure 2. *Top panel*, correlation analysis between P_{CO_2} gap and tumor necrosis factor (*TNF*). Spearman's correlation was statistically significant ($r = .94$, $p < 10^{-6}$). *Bottom panel*, correlation analysis between P_{CO_2} gap and interleuking (*IL*)-6. Spearman's correlation was statistically significant ($r = .58$, $p < 10^{-6}$).

critically decreased flow (31). Therefore, it has been assumed that small changes in P_{CO_2} gap indicate mesenteric hypoperfusion (12, 29). Schlichtig and Bowles (32) found that intestinal anaerobiosis began only when the CO_2 gradient was ≥40 mm Hg. Kellum et al. (33), directly studying portal blood flow in a resuscitated endotoxic dog model, found that increases in the P_{CO_2} gap (<50 mm Hg) were neither sensitive nor specific for mesenteric hypoperfusion. The discrepancy between these studies may be explained by different experimental models and by using saline rather that gas tonometry to obtain P_{CO_2} gap. In this condition, the relationship between splanchnic hypoperfusion and tonometric data are still debatable. P_{CO_2} gap measurements in our experiment were increased, but none of them exceeded 30 mm Hg. Indeed, we observed a significant increase in lactate levels. However, an increase in lactate levels does not always result from tissue hypoxia (34). In this context, values of P_{CO_2} gap in our experiment are compatible with a certain degree of mesenteric hypoperfusion without necessarily corresponding to the occurrence of hypoxia at the level of the gastric mucosa. Our data support the hypothesis that gastric mucosal acidosis, as assessed by P_{CO_2} gap, is associated with systemic inflammatory response in septic shock. This striking relationship between immunologic data and P_{CO_2} gap does not prove a cause-and-effect relationship but is nevertheless an interesting finding, linking cytokine release and gut dysfunction. These findings suggest both that gastric mucosal acidosis increases systemic inflammatory response and that inflammatory mediators like cytokines induce gut injury.

Insufficient evidence exists to support goal-directed therapy with catecholamine in the treatment of sepsis syndrome (35). In this condition, no definitive recommendations can be made regarding the best of vasopressor or inotropic agents. Also, three different catecholamine regimes were administered in our study. When we compared systemic hemodynamic variables, dopamine or epinephrine or norepinephrine-dobutamine induced no significant difference. It has been shown that during septic shock, inotropic agents may result in increased P_{CO_2} gap (12, 36). In agreement with previous results, we found that the results obtained in epinephrine-treated patients are consistent with a transient increase in gastric mucosal acidosis. The increase in P_{CO_2} gap returned to normal within 24 hrs. The exact immunologic role of these transient changes remain to be determined. Nevertheless, the relationship between gastric mucosal acidosis and cytokine release was observed in three different regimes of catecholamine therapy.

Gut dysfunction occurs frequently among critically ill patients and is postulated to be of major importance in the development of multiple organ failure (37). Evidence is that gastrointestinal function, particularly splanchnic bed perfusion and the integrity of the gut mucosa, may have a major role in the pathogenesis of multiple organ failure. Hynninen et al. (7) demonstrated that patients with severe pancreatitis have splanchnic hypoperfusion, assessed by increase in gastric intramucosal pH, and produce a wide array of cytokines, despite a rare occurrence of endotoxemia. They concluded that gut ischemia result in the production of molecules that may harm distant tissues. In patients with severe hemorrhagic shock, a relationship was observed between P_{CO_2} gap and cytokine release (38). Such a relation could confirm the pivotal role of the gut injury as a trigger of systemic inflammatory response syndrome during hemorrhagic shock. It has been suggested that restoration of blood flow to the splanchnic area is associated with reperfusion injury (39). This can result from local generation of oxygen-derived free radicals that are capable of stimulating release of humoral inflammatory mediators such as cytokine and trigger leukocyte attraction and activation (40). Release of inflammatory mediators and leukocyte activation can lead to mechanical trapping of leukocytes within capillaries, thereby obstructing time blood flow, despite reperfusion through larger vessels. In an experimental model of hemorrhagic shock, we have demonstrated that intestinal reperfusion induces an increased production of reactive oxygen species that results in cytokine expression leading to lung injury (41). These experimental findings suggest a role of intestinal ischemia-reperfusion in systemic production of cytokines.

In summary, this study shows that patients with septic shock display an increase in P_{CO_2} gap. We found a relation-

Data suggest a relationship between gastric mucosal acidosis, as assessed by P_{CO_2} gap, and cytokine levels in critically ill patients with septic shock.

ship between the systemic inflammatory response and P_{CO_2} gap in critically ill patients with septic shock. Such a relation suggests the participation of gut injury in systemic inflammatory response in shock. The exact mechanisms of this relationship remain to be elucidated. Despite aggressive management of septic shock, mortality rate remains high. Also, it may be interesting that future studies propose differential therapeutic concepts and new diagnostic tools to improve outcome in patients with septic shock.

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