Failure of Splanchnic Resuscitation in the Acutely Injured Trauma Patient Correlates With Multiple Organ System Failure and Length of Stay in the ICU*

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Introduction: **The purpose of our study was to evaluate the relationship between the state of splanchnic perfusion and morbidity and mortality in the hemodynamically unstable trauma patient acutely resuscitated in the ICU.**
Methods: **Gastric intramucosal pH (pHi) was monitored in a blinded fashion in 19 consecutive critically ill trauma patients with evidence of systemic hypoperfusion (arterial pH [pHa] <7.35, base excess >2.3 mmol/L, lactic acid >2.3 mEq/L) who received right heart catheters to guide resuscitation and subsequent hemodynamic monitoring.**
Design: **Prospective randomized consecutive series with retrospective analysis of data.**
Setting: **University hospital, surgical ICU.**
Results: **The mean values of APACHE II (acute physiology and chronic health evaluation) Injury Severity Score, pHa, arterial base excess, cardiac index, oxygen delivery index, and oxygen consumption index by 24 h were similar (Student's *t* test, $p>0.1$) between survivors and nonsurvivors and between those who developed at most a single (SOF) vs multiple organ system failure (MOSF). Supranormal oxygen delivery and utilization parameters were evenly distributed among survivors and nonsurvivors and patients with SOF and MOSF (χ^2, $p>0.5$). Ten patients had a pHi <7.32 and nine patients had a pHi ≥7.32 by 24 h. Fifty percent of patients with a pHi <7.32 died, compared with 11% of patients with a pH ≥7.32 (χ^2, $p=0.07$). Sixty percent of patients with a pHi <7.32 developed MOSF compared with 11% of patients with a pHi ≥7.32 (χ^2, $p=0.03$). The one patient who developed MOSF and died in the pHi ≥7.32 cohort suffered from massive head trauma and had all futile medical interventions halted. No other patients who achieved a pH ≥7.32 by hour 24 developed MOSF. Survivors with a pHi <7.32 at hour 24 had an increased ICU stay (pHi <7.32=46±15 days, pHi ≥7.32=13±9 days; $p<0.01$). A pHi <7.32 carried a relative risk of 4.5 for death and 5.4 for the occurrence of MOSF.**
Conclusion: **Attainment of a pHi ≥7.32 at hour 24 carried a significantly reduced likelihood of MOSF. Being an inference of the state of regional perfusion, in a high-risk microvascular bed, gastric intraluminal tonometry should identify perfusion states of compensated or uncompensated shock during hemodynamic resuscitation of the critically ill injury patient. A low pHi appears to be a marker of postresuscitative morbidity and subsequent increased length of stay.**
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Key words: critical illness; hemodynamic monitoring; intensive care unit, surgical; multiple organ system failure; right heart catheter; tonometry, gastric shock

Abbreviations: APACHE=acute physiology and chronic health evaluation; BE=base excess; CI=cardiac index; Do_2=oxygen delivery; ISS=Injury Severity Score; MOSF=multiple organ system failure; NPV=negative predictive value; pHa=arterial pH; pHi=intramucosal pH; PPV=positive predictive value; RR=relative risk; SOF=single organ (system) failure; $\dot{V}o_2$=oxygen consumption

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Incomplete splanchnic cellular resuscitation has been associated with the development of multiple organ system failure (MOSF) and increased mortality in the critically ill patient.[1,2] There is convincing evidence that systemic hemodynamic and oxygen transport variables fail to portray accurately the complex interaction between energy requirements and the energy supply at the tissue level,[3-5] and that achieving supranormal cardiovascular oxygen transport and utilization indexes does not reliably confer improved outcome (*ie*, decreased mortality rates and

diminished MOSF) in a number of clinical conditions (sepsis, ARDS, etc).[6-9] These findings have led to the search for better monitoring techniques. Gastric or intestinal tonometry has been proposed as a relatively noninvasive monitor of the adequacy of aerobic metabolism in an organ system whose superficial mucosal lining is extremely vulnerable to low flow and hypoxemia, and in which blood flow is sacrificed first in both shock and the cytokine milieu of the systemic inflammatory response.[1,10,11]

The purpose of this study was to evaluate the relationship between the state of splanchnic perfusion and mortality and morbidity in the critically ill, hemodynamically unstable trauma patient with signs of tissue hypoperfusion who is receiving a right heart catheter to guide resuscitation.

Materials and Methods

Consecutive critically ill trauma patients (APACHE II [acute physiology and chronic health evaluation] ≥15, Abbreviated Injury Score ≥15) with hemodynamic instability and evidence of microcirculatory hypoperfusion (arterial pH [pHa] ≤7.35, base excess [BE] ≥2 mmol/L, arterial lactic acid ≥2.3 mEq/L) in whom right heart catheters were inserted to guide resuscitation and subsequent hemodynamic management were evaluated over a 6-month period.[12,13] The protocol was approved by the Medical Sciences Subcommittee for the Protection of Human Subjects in Research. Right heart catheters and tonometric nasogastric sump tubes were placed on arrival of patients to the ICU. Patients were excluded if placement or manipulation of a nasogastric tube was contraindicated (*eg*, major stomach reconstruction or pyloric ablation, nasopharyngeal or esophageal obstruction), active upper GI tract bleeding (proximal to ligament of Treitz), death occurred within 24 h, or Glascow Coma Scale was ≤8 on hospital admission. Measurement of P_{CO_2} from saline solution in the tonometric balloon was conducted at 1, 3, 6, 18, and 24 h following the placement of the tonometer, and it was continued every 12 h for the next 48 h, once daily until the right heart catheter was discontinued, and during episodes of hemodynamic instability. Prior to sampling, enteral feedings were discontinued for 1 h, nasogastric suctioning was discontinued for 30 min, and treatment with antacids per nasogastric tube was discontinued for 2 h. In addition, any IV bicarbonate infusions were completed 1 h prior to saline solution sampling. The P_{CO_2} value from the saline solution sample was then entered into the Henderson-Hasselbach equation along with the arterial bicarbonate measurement from an arterial blood gas sample to calculate intramucosal pH (pHi). Based on gastric tonometric measurements in healthy volunteers pretreated with a histamine receptor type 2 blockade (pHi=7.39±0.03), a pHi ≥7.32 (representing 2 SDs) was considered normal for the purposes of this study.[14] This indirect method of measuring the pH within the intestinal mucosa is based both on the fact that CO_2 is a highly permeable gas and on the assumption that this generated CO_2 is the end result of adenosine triphosphate hydrolysis, with neutralization of generated hydrogen ions by intestinal mucosal bicarbonate.[15] Concurrent with gastric tonometry sampling, oxygen transport (cardiac index [CI] and oxygen delivery [D_{O_2}]), oxygen utilization (oxygen consumption [$\dot{V}_{O_2}$]), and metabolic parameters (pHa, BE, arterial lactic acid) were also measured.

All caregivers (physicians and nurses) were blinded to the calculated pHi values. Management of the patient's resuscitation and ICU care was left to the direction of the critical care fellow and attending physician on duty. Every patient received our typical resuscitation protocol that focused on the rapid correction of systemic and microvascular hypoperfusion by optimizing the components of oxygen transport (*ie*, preload, contractility, afterload, maintaining hemoglobin ≥11 g/dL).

Gathered patient outcome data included length of ICU and hospital stay and incidence of death and MOSF (≥2 system failure).[16] A patient was considered to be completely resuscitated if the last recorded value for pHi and pHa within the initial 24 h of observation were each ≥7.32; otherwise, the patient was deemed incompletely resuscitated.

Data were analyzed by one- and two-way analysis of variance, χ^2 analysis using Fisher's Exact Tests for small sample size, and Student's *t* test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the relative risk of death (RR=PPV/1-NPV) were calculated.[17] The RR ratio implies the likelihood of nonsurvival among incompletely resuscitated patients (*ie*, pHi <7.32) as compared with the likelihood of death among completely resuscitated patients (*ie*, pHi ≥7.32).

Results

Nineteen patients were accrued, 14 male and 5 female. Mean admission pHi, D_{O_2} and utilization indexes, BE, and serum lactate level are shown in Table 1. Ten patients suffered blunt trauma and 9 had penetrating trauma. There were six deaths, and seven patients developed MOSF. The times (in minutes) from hospital to ICU admission (290+86 min, 245+44 min; p=0.52), from ICU admission to placement of a right heart catheter (155+116 min, 167+99 min; p=0.52), and a gastric tonometer (238+256 min, 311+216 min; p=0.46) were not significantly different between survivors and nonsurvivors and those who developed single organ failure (SOF) vs MOSF. Patients with SOF vs MOSF and survivors vs nonsurvivors were statistically similar

Table 1—*ICU Admission Measurements and Calculations*

D_{O_2}	Oxygen Utilization	Metabolic Parameters
CI (L/min/m^2): 3.23±1.0	$\dot{V}_{O_2}$ (mL/min/m^2): 115±42	pHa: 7.34±0.07
D_{O_2} (mL/min/m^2): 461±191		BE (mmol/L): 4.3±3.3
		Arterial lactate (mEq/L): 4.7±2.4
		pHi: 7.26±0.12

based on mean Injury Severity Score (ISS), APACHE II scores, as well as average pHa and base deficit at 24 h (Table 2).

Multivariate regression demonstrated 24-h pHi as predictive of the development of MOSF when compared with other time intervals after admission to the ICU (*ie,* 6 h, 24 h, 72 h). Indexes of normal or supranormal oxygen transport and utilization (CI, Do_2, $\dot{V}o_2$) did not identify survivors from nonsurvivors or SOF vs MOSF (Tables 2-4). There was a statistically similar distribution of patients with hypodynamic and normodynamic to hyperdynamic cardiac performance (CI, Do_2, $\dot{V}o_2$) at hour 24 following tonometer placement, regardless of whether they survived, died, or developed SOF vs MOSF (Table 2). Most patients who died or suffered MOSF achieved supranormal Do_2 and utilization parameters (CI>3.5 L/min/m^2; Do_2>550 mL/min/m^2; $\dot{V}o_2$>140 mL/min/m^2) by the 24th hour (Table 3) of resuscitation and hemodynamic monitoring.

Half of the patients (5/10) with a pHi <7.32 at 24 h died, compared with 11% (1/9) mortality if pHi ≥7.32 (p=0.07). Sixty percent of patients with a pHi <7.32 developed MOSF, compared to a 12% incidence when 24-h pHi ≥7.32 (p=0.03). The one patient with a pHi ≥7.32, who developed MOSF and died, suffered an unheralded intracranial hemorrhage on ICU day 4 and had therapy withdrawn. No other patients who achieved a pHi ≥7.32 by 24 h developed MOSF or died. Survivors with a 24-h pHi <7.32 had a significantly greater number of mean ICU and total hospital days (ICU stay: pHi <7.32=46±15 days; pHi ≥7.32=13±9 days; total hospital stay: pHi <7.32=70±12 days; pHi ≥7.32=22±11 days; p<0.01). The patients who died had a mean ICU stay of 13±22 days (range, 1 to 57 days). All deaths were related to progressive MOSF. A pHi <7.32 carried 83% sensitivity and 61% specificity in predicting nonsurvival and 86% sensitivity and 66% specificity in predicting the development of MOSF (Table 4). A pHi <7.32 at 24 h carried an RR of 5.4 for occurrence of MOSF and 4.5 for death (p<0.01), compared with achievement of supranormal Do_2 and utilization parameters (RR, 1.4 and 1.1, respectively). Arterial lactic acid, but not BE, correlated with nonsurvival and incidence of MOSF (Table 5). The RR of death and development of MOSF associated with an abnormal arterial lactic acid (*ie,* ≥2.3 mmol/L) were 3.0 and 3.6, respectively.

Table 3—*Percent Achieving Supranormal Do_2 and Utilization at 24 h of ICU Care and Outcome*

Status at 24 h of ICU Care	SOF, %	MOSF, %	Survivors, %	Deaths, %
CI, >3.5 L/min/m^2	75	71	77	67
Do_2, >550 mL/min/m^2	75	71	77	67
$\dot{V}o_2$, >140 mL/min/m^2	83	86	83	86

Table 2—*Status at 24 h of ICU Care*

	Survivors	Nonsurvivors	p Value (χ^2 or Student's *t* Test)
ISS < (mean±SD)	22±4	29±7	0.41
APACHE II (mean±SD)	17±2	21±2	0.11
CI <2.8 L/min/m^2	2	1	
CI ≥2.8 L/min/m^2	11	5	0.94
Do_2/BSA* <400 mL/min/m^2	0	1	
Do_2/BSA >400 mL/min/m^2	13	5	0.13
$\dot{V}o_2$/BSA <120 mL/min/m^2	1	1	
$\dot{V}o_2$/BSA >120 mL/min/m^2	12	5	0.55
pHa	7.38±0.03	7.39±0.03	0.79
BE	0.7±1.1	−2.7±1.7	0.12
	SOF	MSOF	p Value (χ^2 or Student's *t* Test)
ISS (mean±SD)	22±5	29±5	0.39
APACHE II (mean±SD)	18±2	21±3	0.47
CI <2.8 L/min/m^2	2	1	
CI ≥2.8 L/min/m^2	10	6	0.89
Do_2/BSA <400 mL/min/m^2	0	1	
Do_2/BSA >400 mL/min/m^2	12	6	0.18
$\dot{V}o_2$/BSA <120 mL/min/m^2	1	1	
$\dot{V}o_2$/BSA >120 mL/min/m^2	11	6	0.68
pHa (mean+SD)	7.38±0.02	7.39±0.02	0.84
BE (mean+SD)	0.5±1.3	−1.8±1.5	0.26

*BSA=body surface area.

Table 4—*Sensitivity, Specificity, PPV, and NPV and RR Based on 24-h pHi Hemodynamic Measurements and Calculations*

Status at 24 h of ICU Care	pHi (≥7.32)	CI (Supranormal: >3.5 L/min/m^2)	Do_2 (Supranormal: >550 mL/min/m^2)	$\dot{V}o_2$ (Supranormal: >140 mL/min/m^2)
Survival				
Sensitivity, %	83	33	33	17
Specificity, %	61	77	77	85
RR	4.5	1.4	1.4	1.1
PPV, %	50	40	40	33
NPV, %	89	71	71	69
MOSF				
Sensitivity, %	86	29	29	14
Specificity, %	66	75	75	83
RR	5.4	1.1	1.1	0.9
PPV, %	60	40	40	33
NPV, %	89	64	64	62

Discussion

The Ryder Trauma Center at the University of Miami evaluates approximately 3,500 level I trauma cases a year of which 1,000 are admitted to the Trauma ICU. The overwhelming majority of these admissions do not require placement of a pulmonary artery catheter for fluid management. The 19 patients in this report, accumulated over 3 months, represent a select subgroup who had significant deficits in systemic and peripheral perfusion as characterized by metabolic acidosis and elevated arterial lactic acid levels, despite initial agressive fluid resuscitation. A pulmonary artery catheter was placed in the ICU to determine cardiovascular performance and intravascular volume status. Patients who met this criteria but died within 24 h were excluded. This select subgroup of very ill ICU patients in need of cardiovascular optimization represented one to two patients a week. The purpose of this study was to determine if gastric intramucosal acidosis, as a reflection of regional hypoperfusion, provided a better prediction of MOSF, mortality, and length of ICU stay in a subset of critically ill injured victims of trauma. This study was not designed to compare pHi vs non-pHi driven resuscitation. Gastric pHi measurements were collected in a blinded fashion and reviewed retrospectively. In this study, pHi appeared to be a better predictor of outcome compared with indexes of oxygen transport and consumption.

Attainment of a pHi ≥7.32 by hour 24 was associated with a reduced incidence of MOSF. More importantly, in survivors, the failure to normalize pHi by 24 h in survivors was associated with increased intensive care and overall hospital length of stay. The RR of death in patients whose pHi was <7.32 was 4.5 and the RR of developing MOSF was 5.4, compared with those with a pHi ≥7.32. Global parameters of oxygen transport utilization did not distinguish survivors from nonsurvivors nor those patients who developed MOSF from those who did not.

We evaluated all outcome parameters at 0, 6, 12, 18, 24, 36, and 72 h from ICU admission and found no correlation to outcome between any of the hemodynamic variables (CI, Do_2, $\dot{V}o_2$) at any of these time points. Consistent with other published reports, we found gastric pHi at the 24-h time point to be most predictive of outcome ($p \leq 0.01$).

Doglio and associates[18] measured gastric pHi in a heterogeneous group of 80 patients at the time of ICU admission and at 12 h later. A pHi ≥7.35 was considered normal. The group admitted with a low pHi had greater ICU mortality rate, 65% vs 44%

Table 5—*Sensitivity, Predictability, and RR Based on 24-h BE and Arterial Lactic Acid Levels*

	Survival		MOSF	
Status at 24 h of ICU Care	BE, mmol/L	Lactate, mEq/L	BE, mmol/L	Lactate, mEq/L
Sensitivity, %	67	83	43	86
Specificity, %	46	46	33	50
RR	1.4	3.0	0.5	3.6
PPV, %	36	42	27	50
NPV, %	75	86	50	86

($p<0.04$). Furthermore, patients with persistently low pHi at 12 h after ICU admission had the highest mortality rate (87%). The prevalence of sepsis was also greater in the low pHi group, 59% vs 26% ($p<0.01$). The study was repeated in patients with acute circulatory failure by Maynard and colleagues,[17] who found remarkably similar outcomes. In addition to gastric pHi, Maynard et al measured hemodynamic oxygen transport and metabolic variables on admission and again at 24 h. Prediction of outcome was assessed by sensitivity, specificity, and logistic regression. In this study by Maynard and colleagues,[17] there were significant differences in mean gastric pHi between survivors and nonsurvivors on admission and at 24 h (7.40 vs 7.28, 7.40 vs 7.24, respectively; $p<0.001$). There was no difference in CI, Do_2, and $\dot{V}o_2$ between survivors and nonsurvivors. Gastric pHi had a sensitivity of 88% predicting death and an odds ratio of 2.32, much higher than indexes of Do_2 and utilization.

In 35 patients undergoing orthotopic liver transplantation, gastric pHi was evaluated as an indicator of graft survival and liver function.[19] The only patient whose pHi remained lower than 7.3 for >3 h after reperfusion underwent retransplantation the following day for graft failure. In a level I Trauma Center, Chang and colleagues[20] conducted a prospective study of 20 critically ill patients that compared pHi with base deficit, lactate, Do_2 and $\dot{V}o_2$, mixed venous oxygen saturation, the oxygen utilization coefficient, and pHa. Patients with pHi <7.32 on admission, who did not correct within the initial 24 h, had a higher mortality than those whose pHi corrected (50% vs 0%; $p=0.03$) and a higher incidence of MOSF (2.6 organs per patient vs 0.62 organs per patient; $p=0.02$). Rouman and associates[21] performed gastric tonometry prospectively in 15 multiple trauma patients. A pHi <7.32 was considered abnormal. Three of eight patients who developed a low pHi ≥6 h developed major complications, and two subsequently died. The seven patients who never had an abnormal pHi measurement experienced an uneventful recovery.

To our knowledge, there have been only two prospective controlled interventional studies in which therapy was instituted because the pHi was low. Neither of these studies, however, attempted to normalize the pHi, but rather focused on increasing Do_2 and utilization. Gutierrez and associates[22] observed that the hospital mortality rate was significantly greater in control patients whose pHi was normal on admission (*ie,* pHi≥7.35) and then became abnormal during their ICU stay, compared with those whose abnormal pHi prompted interventions to increase Do_2. Unfortunately, if admission pHi was low, the mortality rates were the same in both treatment and control groups. The authors chose to increase Do_2 rather than restore pHi to normal values. In addition, they limited the prescribed interventions to three fluid boluses (750 mL total), mean posttreatment hemoglobin levels to 11 g/dL, and dobutamine was limited to a maximum of 10 μg/kg/min.

Ivatury and others[23] randomized critically ill trauma patients into the following: group 1, an end point of pHi ≥7.3, 11 patients; and group 2, supranormal Do_2 parameters (as defined by Shoemaker et al[24]), 16 patients. In the pHi group, goals were met by 24 h in 10 of 11 patients—9 survived. The incidence of multiple organ dysfunction was 18% and the death rate was 9%. In the supranormal Do_2 group, goals were met in 14 patients—10 survived. In the 10 surviving patients, pHi values were also ≥7.3. The incidence of MOSF was 38%; death was 31%. Seventy-five percent of the patients who developed MOSF had pHi <7.3. In group 2, four of the five patients who died did achieve supranormal Do_2 and consumption goals, but had pHi <7.3 at 24 h. Moreover, they observed that a late fall in pHi was often associated with a physiologic catastrophe (*eg,* intestinal leak, gangrene, bacteremia).

A counter-current blood flow exchange system exists within the superficial mucosal layer between the arterial and venous circulation, rendering the GI tract particularly sensitive to neuronal and systemic vasoconstrictors.[25] This is compounded by the high concentration of receptors for systemically released vasoconstrictors within the splanchnic microvascular bed. The peptides, angiotensin II and vasopressin, are the most potent splanchnic vasoconstrictors.[10] The intestinal tract possesses a lower capillary density and is unable to recruit capillaries to augment local blood flow to match increases in metabolic needs. This results in low perfusion-to-oxygen demand ratios and subsequent tissue hypoxia *(the trickle down economy of systemic oxygenation).*[11]

The GI tract was once considered an organ system of quiescence and inactivity. Recent experimental and clinical studies have solidly positioned this organ system squarely in the pathogenesis of MOSF; it is associated with regional ischemia-reperfusion injury and generation of oxygen radicals, numerous cytokines and arachidonic acid metabolites, as well as promoting bacterial translocation and local polymorphonuclear cell priming and their systemic activation.[26-29] Monitoring all patients likely to have had activation of the neurohumoral response and decreased splanchnic blood flow is probably beneficial, because they are at risk for a reperfusion injury, MOSF, and a higher mortality rate.[30] Should pHi be used to initiate therapy or to represent an end point?

Restoration of a normal pHi could be valuable as a marker for the restoration of oxidative metabolism. We believe that the use of an index of regional hypoperfusion in a high-risk microvascular bed will allow the clinician to identify states of compensated shock when adenosine triphosphate hydrolysis predominates associated with intramucosal acidosis.

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