**SUMMARY**

**Introduction.** This prospective non-interventional study intended to assess the prognostic value of gastric intramucosal acidosis in patients with severe trauma admitted to a medical/surgical ICU.

**Methods.** Gastric tonometer catheters were introduced to measure air PCO₂ level (Tonocap device) in forty consecutive critically ill trauma patients. Gastric intramucosal pH, air PCO₂ gradient, lactate and acid-base parameters were measured at admission and at 6, 12 and 24 h thereafter.

**Results.** The median age, mean APACHE II and SOFA scores were higher in nonsurvivors than in survivors (p<0.05). There were significant differences in the PCO₂ gradient between survivors and nonsurvivors at 12 and 24 hours (10–7 vs. 24–19 mmHg, 13–16 vs. 29–25 mmHg; p<0.05). Gastric intramucosal pH values were lower in nonsurvivors than in survivors, on admission and after 12 or 24 hours (p<0.05). Arterial pH and bicarbonate were lower, lactate concentration higher, and base excess more negative in nonsurvivors. Prediction of outcome (mortality and MODS) at 24 hours of ICU assessed by their ROC curves was similar (p=NS). At 24 hours, air PCO₂ gradient > 18 mmHg carried a relative risk of 4.6 for death, slightly higher than a HCO₃<sub>-</sub> < 20 mEq/L (RR=4.29) or base excess of <-2 mmol/L (RR=3.65).

**Conclusion.** Bicarbonate, base deficit, lactate, gastric intramucosal pH and PCO₂ gradient discriminate survivors from nonsurvivors of major trauma. A critical air PCO₂ gradient carried the greatest relative risk for death at 24 hours of ICU. Inadequate regional blood flow as detected by a critical PCO₂ gradient seems to contribute to morbidity and mortality of severe trauma patients.

**Key Words:** Trauma. Mortality. Splanchnic perfusion. Gastric tonometry. Outcome prediction.

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**INTRODUCTION**

In Brazil, traumatic injury is the leading cause of loss of life before 50 years of age. As in other critically ill patients admitted to an intensive care unit (ICU), multiple organ dysfunction syndrome (MODS) is the most common cause of death. Incomplete resuscitation has been associated to development of MODS and death. There is conclusive evidence that global parameters fail to accurately address the adequacy of resuscitation in a number of clinical conditions, including trauma patients. Significant splanchnic ischemia can be present despite apparently complete global resuscitation and may ultimately result in the development of MODS.

Previous studies have shown that blood lactate and base deficit are good predictors of mortality even in a context of normalized vital signs, such as blood pressure, urine output, and heart rate. Both indices of resuscitation are however representative of an overall condition, some degree of regional inadequate perfusion or oxygenation that may persist in the splanchnic bed. Gastric intramucosal pH (pHi), calculated from the gastric tonometer was developed to assess the degree of perfusion of the gut mucosa, which is particularly sensitive to a blood flow reduction. Several clinical studies have associated intramucosal pH values with morbidity and mortality rates of critically ill and trauma patients.

Although pHi is a good prognostic marker, apparently it is not a useful monitoring variable to follow the effect of treatment on gastric perfusion because it is encumbered by technical problems and influenced by the systemic acid-base status. Therefore, air-tonometry is a more precise technique, furthermore there are no records of a study that evaluated PCO₂ gradient using this technology in trauma patients.

The primary purpose of this study was to evaluate the relationship between the state of splanchnic perfusion and mortality and morbidity in critically ill trauma patients. Thus, this study prospectively investigated the prognostic value of PCO₂ gradient in a group of severely traumatized patients and compared it with metabolic markers of tissue hypoperfusion.

**METHODS**

**Study design**

Prospective, descriptive study in the interdisciplinary ICU of a university hospital.
Patient population

Inclusion Criteria

Forty consecutive traumatized patients with hemodynamic instability, admitted at a medical/surgical intensive care unit, in whom central venous catheters had been inserted to guide resuscitation, were evaluated over a period of one year. The Ethics Committee of Hospital São Vicente de Paulo approved the study.

Exclusion criteria

Patients were excluded if placement or manipulation of a nasogastric tube was contraindicated (e.g., Major stomach reconstruction or nasopharyngeal or esophageal obstruction and active upper gastrointestinal tract bleeding).

Measurements

Central venous catheters and tonometric nasogastric tubes were placed on patients’ arrival at the ICU. Arterial blood gases, arterial blood lactate and intramucosal PCO₂ were simultaneously obtained upon study admission, and 6, 12 and 24 h later. A gastric tonometer (Tonometrics, Hopkinton, MA, USA) was introduced and the correct position confirmed by injecting air through the tube and auscultating a gurgling sound in the stomach and aspirating a small amount of gastric fluid. Subsequently, the gastric tonometer was connected to an automated gas analyzer (Tonocap, TC-200; Datex, Helsinki, Finland). Before use, the Tonocap monitor was calibrated (Quick Cal Calibration Gas). Prior to air sampling from the balloon catheter, enteral feeding was discontinued for 1 h and nasogastric suction was discontinued for 30 min. All patients received ranitidine (150 mg/day) intravenously. The gastric PCO₂ gap was calculated by subtracting the temperature-corrected arterial PCO₂ from gastric CO₂. Blood-gas values were entered via the Tonocap keyboard for calculation of gastric pH, with pH = pHa - log (gastric tonometered PCO₂/PaCO₂). Concentration of arterial blood lactate was measured enzymatically (Cobas Mira Plus, Roche). Development of organ dysfunction was evaluated using the Sequential Organ Failure Assessment score (SOFA) at admission and 3, 7, 10, 14, 21 and 28 days thereafter26. Patients were followed up until death or discharge from the hospital. The clinical diagnosis of MODS was established on the basis of the SOFA score, with a minimum score of 3 and more than two organs affected.

Statistical analysis

An unpaired Student’s t-test for normally distributed variables or a Mann-Whitney test for non-normally distributed variables were used to compare differences within groups at study admission. Changes over time were analyzed using a two-way analysis of variance for repeated measurements. A Newman-Keuls test was used for post-hoc comparisons.

Receiving operating characteristics (ROC) curves were constructed to analyze the discriminating power of each variable to predict mortality and development of MODS at 24 hours of ICU. Based on previous studies, a pH < 7.32, PCO₂ gradient > 18 mmHg, arterial Base Deficit > 2 mmol/L, arterial HCO₃ < 20 mEq/L and an arterial lactate > 2.2 mmol/L were considered critical for the purpose of this study (11-25). The one-tailed Fisher exact test was used to determine significant differences in the proportions for survival in each variable. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the relative risk of death (RR=PPV/1-NPV) were calculated for each variable. The RR ratio implies the likelihood of nonsurvival among patients with critical values as compared with the likelihood of death among patients with normal values. A p<0.05 was considered significant. Data are reported as mean±SD for normally distributed variables and median (25–75th percentiles) for non-normally distributed variables.

Based on previous studies about the prognostic value of gastric tonometry, we expected to recruit 43 patients (significance level 0.05, power 80%).

Results

The clinical characteristics of survivors and nonsurvivors are listed in Table 1. Forty patients were enrolled in the study. Patients had a median age of 35 (14-79) years and a mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 16±7 (2). Thirty-six were male (90%). Hospital mortality rate was 38% (15/40) and 22 patients developed multiple organ dysfunction syndrome (MODS). Median ICU stay was of 5 (2-12) days. Fourteen patients died in the intensive care unit (five in less than 24 hours) and 25 were discharged alive from the hospital. Nonsurvivors APACHE II and SOFA scores substantially exceeded those of survivors indicating a more significantly injured population.

Time courses of the analyzed variables are shown in Table 2 and Figures 1 and 2. Nonsurvivors were more tachycardic and had a lower mean arterial pressure than survivors but differences were only significant after 24 hours. Urine output was the same for survivors and nonsurvivors during the 24 hours period (2910±1419 vs. 2171±1546, p=0.05). Upon study admission, 29 (73%) patients had an increased blood lactate concentration. However, blood lactate levels remained high in nonsurvivors and progressively decreased in survivors, so that differences became significant at 6, 12 and 24 h after (Figure 1). Blood lactate levels were not measured in 10 patients at 24 h (3 survivors and 7 nonsurvivors). Arterial bicarbonate and base excess had a course similar to blood lactate and differences became significant at 6, 12 and 24 h (Figure 1). Nonsurvivors were more acidic and arterial pH did not show any improvement after 24 h. During the first 24 h pH values were significantly higher in survivors than in nonsurvivors. In addition, PCO₂ gradient values were lower in survivors than in nonsurvivors and the differences became significant at 12 and 24 h (Figure 2).

The ability of each metabolic variable to predict mortality and MODS at 24 hours was tested. Accuracy (area under the curve) of the receiver operating curves for mortality and MODS was similar (p=NS) for all studied variables Sensitivity, specificity and best cutoff point for mortality are shown in Table 3. A critical PCO₂ of 18 mmHg gradient had a 67% sensitivity and an 83% specificity to predict nonsurvival with a 4.6 RR for death, greater than any other variable evaluated, but similar to arterial bicarbonate (Table 4).

Discussion

The Hospital São Vicente de Paulo at the University of Passo Fundo evaluates approximately 1000 trauma cases per year of which 90 are admitted to the ICU. The aim of this study was to determine if gastric intramucosal acidosis measured by gastric tonometry, as a reflection of regional hypoperfusion, provided a better predictor of mortality in a subset of 40 very ill traumatized patients. In this study, gastric intramucosal acidosis appeared as a good predictor of mortality or MODS, together
Table 1 - Descriptive characteristics of survivors and nonsurvivors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>P value (Fischer’s test or Student’s t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>25</td>
<td>15</td>
<td>0.002</td>
</tr>
<tr>
<td>Age, years</td>
<td>27 [19-36]</td>
<td>45 [28-64]</td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td>13 ±5</td>
<td>21 ±7</td>
<td>0.001</td>
</tr>
<tr>
<td>RTS</td>
<td>5.7 ±1.6</td>
<td>4.7 ±1.7</td>
<td>0.058</td>
</tr>
<tr>
<td>Duration of ICU stay, days</td>
<td>7 [3-15]</td>
<td>4 [1-7]</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of Hospital stay, days</td>
<td>24 [11-11]</td>
<td>4 [2-8]</td>
<td>0.002</td>
</tr>
<tr>
<td>SOFA</td>
<td>5.5 ±4</td>
<td>12 ±6</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8 [0.7-1.0]</td>
<td>1.3 [1.1-1.9]</td>
<td>0.001</td>
</tr>
<tr>
<td>Automobile vs. pedestrian, No</td>
<td>3</td>
<td>3</td>
<td>0.666</td>
</tr>
<tr>
<td>Automobile vs. automobile</td>
<td>12</td>
<td>6</td>
<td>1.000</td>
</tr>
<tr>
<td>Motorcycle accident</td>
<td>3</td>
<td>4</td>
<td>0.417</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>2</td>
<td>0.467</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or median (percentiles 25%-75%)

Acute physiology and chronic health evaluation II = APACHE II. Revised trauma score = RTS. Sequential organ failure assessment score = SOFA.

Table 2 - Time-course of hemodynamic and metabolic variables

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>6 hours</th>
<th>12 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>102±28</td>
<td>104±24*</td>
<td>102±27</td>
<td>97±20*</td>
</tr>
<tr>
<td>NS</td>
<td>112±27</td>
<td>123±21</td>
<td>117±22</td>
<td>116±24</td>
</tr>
<tr>
<td><strong>MAP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>92±16</td>
<td>87±12</td>
<td>93±23</td>
<td>92±13*</td>
</tr>
<tr>
<td>NS</td>
<td>92±21</td>
<td>86±23</td>
<td>81±20</td>
<td>76±20</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>7.36±0.07*</td>
<td>7.40±0.08*</td>
<td>7.40±0.05</td>
<td>7.41±0.07*#</td>
</tr>
<tr>
<td>NS</td>
<td>7.31±0.10</td>
<td>7.31±0.12</td>
<td>7.35±0.13</td>
<td>7.34±0.12</td>
</tr>
<tr>
<td><strong>PCO₂ (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>38.4±5.2</td>
<td>37.0±5.7</td>
<td>38.8±4.8</td>
<td>38.7±5.8</td>
</tr>
<tr>
<td>NS</td>
<td>39.2±8.2</td>
<td>37.7±7.9</td>
<td>33.8±6.8</td>
<td>35.7±6.7</td>
</tr>
<tr>
<td><strong>PO₂ (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S, survivors; NS, nonsurvivors.

Data are expressed as mean±SD or median (percentiles 25%-75%).

*p<0.05 and **p<0.01 between groups

#p<0.01 vs. admission

with other metabolic markers of hypoperfusion. A critical PCO₂ gradient after 24 hours of ICU carried the highest relative risk of death in comparison with other markers of acid-base derangement, and indicates that splanchnic hypoperfusion contributes to excessive death in this particular population of severe trauma patients.

All metabolic markers of acidosis indicating hypoperfusion showed improvement in survivors after 24 h. All outcome parameters were evaluated at 0, 6, 12, and 24 h after ICU admission. Global parameters of metabolic hypoperfusion showed differences between survivors and nonsurvivors. Although upon admission the mean value of PCO₂ gradient was rather low, both for survivors and nonsurvivors, it became higher than 18 mmHg after 6 hours for 47% (7/15) of nonsurvivors, but for only 28% (7/25) of survivors. While we expected that at ICU admission, a higher degree of gastric hypoperfusion would be present in most nonsurvivors, we speculated that fluid resuscitation was properly performed in the emergency room and transient regional perfusion was adequate but rapidly deteriorated.

Our data support earlier studies that a significantly deranged pH, BE, bicarbonate, lactate and intramucosal pH or gastric PCO₂ gradient correlates with poor outcome(15). Several studies showed that systemic hemodynamic or even metabolic variables were worse predictors of outcome than gastric acidosis(4-6;10-12). Vital signs such as mean arterial
pressure and heart rate became different only after 24 hours, while the other variables identified survival after 12 and even 6 hours. In addition, only 3 (8%) of the patients were hypotensive (PAM>65 mmHg) at 24 hours. In our study, a critical PCO$_2$ gradient carried the highest relative risk for mortality at 24 hours, similar to bicarbonate. However, when looking at the ROC curves, systemic metabolic measurements (particularly base excess and bicarbonate) discriminated nonsurvival or development of MODS as well as the PCO$_2$ gradient.

These results display the multifactorial nature of the acid load that occurs with critical illness, even if the initial component is mainly hemorrhagic shock as in trauma patients. These patients were evaluated after significant fluid resuscitation with normal saline solution so that the impact of chloride loading on the outcome cannot be ruled out.

Nevertheless, this study addresses a concern of the importance of hypoperfusion to discriminate survivors and nonsurvivors. Our data confirms that metabolic parameters can identify patients that will die even after global resuscitation is achieved. Our patients were aggressively resuscitated in the emergency room and even at ICU admission and, particularly, after 12-24 hours, however, several patients continued to show evidence of hypoperfusion. Further our data suggested a strong relationship between a higher PCO$_2$ gradient and death or MODS. Several studies in the decade of the 90’s addressed the importance of gastric acidosis using saline tonometry in trauma patients. Studies that targeted a PH$_i$ <7.32 as a...
cutoff value showed that patients with pH <7.32 at admission or whose pH did not correct within the initial 24 h had a higher mortality and a higher incidence of MOSF. However, only a few studies on critically ill or trauma patients have investigated the prognostic value of the PCO₂ gradient, but most were using saline tonometry. Several studies were negative for PCO₂ gradient as a marker of mortality but some showed pH as a discriminating factor. On the other hand, other studies like ours have shown that the PCO₂ gradient, when measured by regional capnography with air tonometry has good prognostic value. Saline measurements are poorly reproducible and yield a lower gastric PCO₂ gradient.

Three studies have evaluated trauma resuscitation guided by a gastric tonometer but all used intramucosal pH [4][16][8]. Two small studies showed positive results [3][5] but a third larger study, comparing three outcome [13][30][31]. High risk surgical patients, we have shown that occult morbimortality, and early correction seems to improve the trauma patients, persistence of hypoperfusion is associated with increased mortality (58% vs. 11%).

Our patient population was rather small and we did not intend to propose a new critical value for any variable studied. Interestingly, all identified cutoff points were close to those found in previous studies. We found a cutoff point of 13.8 mmHg for a PCO₂ gradient (sensitivity 70%, specificity 83%) with 30% of included patients above that point after 24 hours, yielding a different mortality (58% vs. 11%).

High blood lactate in globally resuscitated patients also appears to be a predictor of morbimortality in traumatized and critically ill patients. In trauma patients, persistence of hypoperfusion is associated with increased morbimortality, and early correction seems to improve the outcome [3][38][33]. In high risk surgical patients, we have shown that occult hypoperfusion was a marker of organ dysfunction and death even after hemodynamically stable trans-operative and early postoperative periods [3]. This study showed that blood lactate levels were significantly higher for nonsurvivors, already after 6 hours and remained stable until 24 hours, while they decreased in survivors. The area under the curve was fair (0.582) and the RR was 2, both lower in comparison to a PCO₂ gradient.

The interpretation of tonometer parameters is not simple. The intramucosal pH value may underestimate tissue pH and in part reflects systemic acid load [37]. In our study, pH ability to predict outcomes was lower than BE or bicarbonate (p=NS). As in other studies, we found that PCO₂ gradient values were not significantly different between survivors and nonsurvivors at admission and 6 hours later while pH was lower in nonsurvivors since admission. As such, probably pH values were affected already at admission by inclusion of arterial pH in the calculation. Furthermore, the exact significance of the PCO₂ gradient remains unclear and additional factors other than changes in mucosal blood flow may affect gastric mucosal hypercarbia.

Limitations of our study include a relatively small population with a high severity, lack of data on type of and amount of fluid resuscitation in the emergency room and lack of blood lactate measurement in 10 patients (7 nonsurvivors) at 24 hours.

Effective management of shock depends on titration of therapies against reliable resuscitation end points. Conventional clinical and laboratory indices of shock are often insufficient to identify ongoing circulatory impairment. Hypoperfusion identified by blood lactate, acid-base derangement or gastric intramucosal acidosis may compound the initial and subsequent insult causing organ dysfunction and death [38][39]. Trauma patients with evidence of hypoperfusion have had poor outcomes. By detecting the presence of tissue acidosis as a proxy of ongoing hypoperfusion, gastric tonometry may facilitate a more timely and rational shock resuscitation.

In summary, we have demonstrated that gastric acidosis lasting longer than 24 hours is a risk factor for the development of organ dysfunction and death. However, it was not evidently a better predictor of survival than other markers of systemic acidosis. Further studies are still needed to demonstrate whether the identification and correction of gastric acidosis may be important to minimize both organ dysfunction and mortality in severe trauma patients.

Conflict of interest: none

Resumo

Desarranjo ácido-base e acidose gástrica intramucosal predizem desfecho de trauma grave

INTRODUÇÃO. O objetivo deste estudo prospectivo, não-intervencionista, foi avaliar o valor prognóstico da acidose gástrica intramucosal em pacientes com trauma grave admitidos numa UTI.

MÉTODOS. Cateteres tonométricos gástricos foram introduzidos para medir o nível de PCO₂ aéreo em 40 pacientes traumatizados. O pH gástrico intramucosal, o gradiente de PCO₂ aéreo, o lactato e os parâmetros ácido-base foram medidos na admissão e 6, 12 e 24 h após a admissão.

RESULTADOS. A idade mediana, o APACHE II e os escores SOFA médios foram maiores nos não-sobreviventes que nos sobreviventes (p<0.05). Não houve diferenças significativas para o gradiente de PCO₂ entre sobreviventes e não-sobreviventes após 12 e 24 horas (10±7 vs. 24±19 mmHg; 13±16 vs. 29±25 mmHg; P<0.05). Os valores de pH gástrico intramucosal foram menores nos não-sobreviventes que nos sobreviventes na admissão e após 12 ou 24 horas (P<0.05). O pH arterial e o bicarbonato foram menores, a concentração de lactato maior, o excesso de base mais negativo nos não-sobreviventes. Predição do desfecho (mortalidade e FMOS) nas 24 horas de UTI apresentou ROC foi similar (p=NS). Nas 24 horas, um
ACID-BASE DISARRANGEMENT AND GASTRIC INTRAMUCOSAL ACIDOSIS PREDICT OUTCOME FROM MAJOR TRAUMA

...bicarbonato, déficit de base, lactato, pH gástrico intramucosal e o gradiente de PCO2 discriminaram os sobreviventes dos não-sobreviventes de trauma. Um gradiente crítico de PCO2 aóreo >18 mmHg acarretou um risco relativo de 4.6 para óbito, um pouco maior que um HCO3 <20 mEq/L (RR=4.29) ou um excesso n° de base <-2 mmol/L (RR=3.65).

CONCLUSÃO. Bicarbonato, déficit de base, lactato, pH gástrico intramucosal e o gradiente de PCO2 discriminaram os sobreviventes dos não-sobreviventes de trauma. Um gradiente crítico de PCO2, aóreo acarretou o maior risco relativo para óbito após 24 horas de UTI. Fluxo sangüíneo regional inadequado detectado por um gradiente crítico de PCO2, parece contribuir para a morbidade e mortalidade de pacientes traumatizados graves. [Rev Assoc Med Bras 2008; 54(2): 116-21]


REFERÊNCIAS