Gastric intramural pH in mechanically ventilated patients

Zab Mohsenifar, Jack Collier, Spencer K Koerner

Abstract
Background – The hypothesis that gastric intramural pH (pHi) is predictive of outcome in haemodynamically stable, mechanically ventilated patients was tested in 25 patients on assisted mechanical ventilation for respiratory failure.

Methods – Simultaneous samples of arterial blood and gastric juice were obtained from patients on assist control, synchronised intermittent and pressure control ventilation during the first 48 hours of mechanical ventilation. Gastric pH was calculated from the equation: pHi = 6.1 + log HCO3/(gastric PCO2 × 0.03). The outcome was survival or death due to respiratory or circulatory failure within 45 days of admission.

Results – Gastric pH was proved to be a better predictor of outcome than all presently utilised parameters. Although all patients included in this study were haemodynamically stable and were similar for all laboratory indices, the only variable capable of accurately predicting outcome was gastric pH. Patients with a normal arterial pH, but a gastric intramural pH of less than 7.25 had an observed mortality of 66%. Standard severity of illness scores grossly underestimated mortality rates. The sensitivity and specificity of a gastric pH value of less than 7.25 in predicting death were 86% and 83%, respectively. A receiver operator curve for all variables exaggerates the superiority of gastric pH as a predictor of outcome.

Conclusion – Low gastric pH, a marker of gastrointestinal ischaemia, may occur in the presence of normal haemodynamics and may be used to predict severity of illness and mortality accurately.

Keywords: gastric intramural pH, mechanical ventilation, outcome, mortality.

Gastric intramural pH (pHi) has been used to assess the adequacy of tissue perfusion and oxygen delivery in the splanchnic mucosa. The association between a low pHi and decreased tissue perfusion in disease states was initially shown in animal models. Hussain et al found significant blood flow diversion to the respiratory muscles following the induction of endotoxaemia in spontaneously breathing dogs. This diversion of blood occurred at the expense of the “non-vital” organs such as the splanchnic bed where blood flow was significantly decreased.1 Gastrintestinal ischaemia thus ensues, resulting in tissue hypoxia and subsequent acidosis. It therefore follows that a patient with a reduced pH is in a compensated state of inadequate oxygen delivery relative to a patient with a normal pH who presumably has adequate blood flow to satisfy tissue demands. Gastric pH has recently been reported to predict sepsis, massive gastrointestinal bleeding, multiple organ failure, and outcome in critically unstable patients.2 The premise of all these reports is that a low pH is reflective of inadequate blood flow.

Most previous investigations have analysed a low pH in the face of haemodynamic instability. In an animal model, Magder et al demonstrated significant blood flow diversion with acute lung injury despite the maintenance of a normal cardiac output and blood pressure.7 We postulated that patients on mechanical ventilation who are haemodynamically stable yet have a low pH will have an increased mortality. This hypothesis was tested in haemodynamically stable patients admitted to the intensive care unit for respiratory failure.

Methods

STUDY POPULATION
Twenty five consecutive patients (10 men) of mean (SD) age 71 (21) years with acute respiratory failure on mechanical ventilation were prospectively included in the study. The reasons for mechanical ventilation were chronic obstructive pulmonary disease (n = 10), neuromuscular weakness (n = 2), pneumonia (n = 12), and pulmonary oedema (n = 1), and all were direct admissions to the intensive care unit. All patients were ventilated with Puritan-Bennett 7200a ventilators (Carlsbad, California, USA). The study was conducted 24–48 hours from the time of initial intubation. Study exclusion criteria included haemodynamic instability (hypotension), gastrointestinal bleeding, mechanical ventilation longer than 48 hours, absence of H2 blockers, and neurological deficits. All patients had a nasogastric tube in place and had received ranitidine for at least 24 hours before obtaining a gastric sample. The production of intraluminal carbon dioxide (CO2) can be enhanced by the titration of gastric bicarbonate (HCO3) by hydrogen ion thus underestimating the gastric pH. This potential source of error can be avoided by the use of H2 receptor blockers.6

STUDY PROTOCOL
The study was approved by the institutional review board. Patients enrolled in the study were identified within 24–48 hours of in-
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<table>
<thead>
<tr>
<th>Table 1 Mean (SD) characteristics of patients</th>
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<tbody>
<tr>
<td>pH ≤ 7-25 (n=9)</td>
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<td>-----------------</td>
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<tr>
<td>Age (years)</td>
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<td>Respiratory rate</td>
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<td>pHa</td>
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<tr>
<td>HCO3 (mEq/l)</td>
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<td>PaCO2 (kPa)</td>
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<td>PaO2 (kPa)</td>
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<td>Fio2 (%)</td>
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<tr>
<td>pHi</td>
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<tr>
<td>Heart rate</td>
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<tr>
<td>Mean BP (mmHg)</td>
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<tr>
<td>APACHE II</td>
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<tr>
<td>Mechanical ventilation (days)</td>
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<tr>
<td>Mortality (%)</td>
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</table>

*p < 0.05.

Mean intramusural pH was calculated on the basis of the Henderson-Hasselbalch equation whereby pH = e^(-1.0 + log arterial HCO3/gastric CO2 × 0.0307). This can also be expressed as pH = pHa − log (PaCO2/PaCO2). The reliability of determining the pH from this method has been validated by previous investigators.1

Two assumptions are made in calculating gastric intramusural pH via the Henderson-Hasselbalch equation: (1) PCO2 in the lumen of the stomach is the same as that in the gastric tissue wall, and (2) tissue HCO3 is equal to arterial HCO3. Fiddian-Green et al found that pH calculated from gastric CO2 and arterial HCO3 was linearly related to the pH measured directly with a pH probe.1 Under conditions of extreme ischaemia or no flow, Antonsen et al have shown that the pH may be underestimated, although the change is qualitatively reliable.1 Despite this potential source of error, many investigators have confirmed the original results of Fiddian-Green and have demonstrated the direct relationship between measured gastric pH and calculated pH;1,14-16

**DATA ANALYSIS**

Analysis of variance was used to compare the two groups. Means and standard deviations for all measurements combined and by outcome were calculated. In addition, sensitivity and specificity with 95% confidence intervals for outcome and likelihood ratios were determined. A stepwise discriminant analysis was run, using all variables, to determine which variables were useful in distinguishing between the groups. These variables included: blood pressure, heart rate, respiratory rate, tidal volume, APACHE II scores, Fio2, PaO2, PaCO2, pH, HCO3, age. A p value of less than 0.05 was considered significant.

**Results**

Nine patients had a gastric intramusural pH of less than 7-25 (group 1) on any of the three modes of ventilation. Three of these patients were successfully extubated and discharged from the hospital. The remaining six died of multiorgan failure on days 5, 8, 9, 10, 19, and 24 following admission. The diagnoses of these six on admission were COPD in three cases and pneumonia in the other three. Pulmonary infiltrates developed in two patients, existing infiltrates progressed in three, and Gram negative sepsis with hypotension and renal failure developed in one. Sixteen patients had a pH of greater than 7-25 on all three modes of ventilation (group 2) of whom 15 were successfully extubated and discharged while one had a stroke on day 20 and died of respiratory failure on day 35 following admission. The characteristics of the patients are listed in table 1.

As has been previously described, the gastric pH can be determined using the Henderson-Hasselbalch equation whereby pH = e^(-1.0 + log arterial HCO3/gastric CO2 × 0.0307). This can also be expressed as pH = pHa − log (PaCO2/PaCO2). The reliability of determining the pH from this method has been validated by previous investigators.1

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**CALCULATION OF GASTRIC pHi**

As has been previously described, the gastric pHi can be determined using the Henderson-Hasselbalch equation whereby pHi = e^(-1.0 + log arterial HCO3/gastric CO2 × 0.0307). This can also be expressed as pHi = pHa − log (PaCO2/PaCO2). The reliability of determining the pHi from this method has been validated by previous investigators.1

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or PSV. The gastric intramural pH value shown in Table 1 represents the lowest value obtained on any of the three modes of ventilation. Of the nine patients with a pH of less than 7.25, eight had a pH of less than 7.25 on A/C ventilation and the remaining patient had a pH of less than 7.25 on IMV mode. Seven patients had a pH of less than 7.25 in at least two of the three modes of ventilation. Mean random variation in pH in five patients in whom two consecutive measurements were taken was less than 3 (1)%.

Table 2

<table>
<thead>
<tr>
<th>pHi</th>
<th>Likelihood ratio</th>
<th>Expected mortality based on APACHE II score (%)</th>
<th>Expected mortality based on pH (%)</th>
<th>Observed mortality (%)</th>
</tr>
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<tbody>
<tr>
<td>&lt;7-20</td>
<td>11.8</td>
<td>75</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>&lt;7-25</td>
<td>5.1</td>
<td>56</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>7-30</td>
<td>3.0</td>
<td>43</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>

The only significant difference between the two groups was the observed mortality. Based upon the APACHE II scores, the expected mortality for both groups of patients was 15–20%. However, those patients with a pH of less than 7.25 had a significantly increased mortality rate of 67% while those with a pH of more than 7.25 had only a 6% mortality rate (p<0.05). Table 2 expresses the expected mortality using the likelihood ratios (a pretest expected mortality of 20% was assumed based upon the APACHE II score). The positive likelihood ratio expresses the post-test probability of death following a positive test. The expected mortality based upon the pH value is significantly greater than that expected from the APACHE II score alone. As can be seen in Table 2, the observed mortality was more accurately predicted by the pH values.

A receiver operator curve (ROC) is depicted in the figure. This is created by plotting the true positive rate against the false positive rate.

In this study the ROC represents the ability of a parameter to discriminate between death and survival. The greater the area under the curve, the greater the discriminating power of the parameter.17 In comparison to all other parameters, pH is distinctly superior in predicting death.

**Discussion**

Our study shows that gastric pH measured within 48 hours of admission in otherwise stable mechanically ventilated patients is a better predictor of outcome than the parameters presently used. Whereas severity of illness scores grossly underestimated mortality rates, a low pH value was found to be an accurate reflection of illness severity in these patients. We also found that parameters commonly followed in the intensive care unit such as blood pressure, heart rate, and bicarbonate levels were extremely poor predictors of patient outcome. This fact is exaggerated when these parameters are compared with gastric pH in the form of a receiver operator curve.

Maintenance of sufficient tissue oxygenation is an important principle in the management of mechanically ventilated patients. In general, as oxygen delivery decreases oxygen utilisation stays constant as long as oxygen delivery is above a certain threshold, although in certain conditions it has been shown that any decrease in oxygen delivery will be accompanied by a corresponding decrease in oxygen consumption.18 19 The issue is whether global measurements of oxygen consumption reflect events at various tissue levels. Gutierrez et al showed that tissue hypoxia may be present in septic patients while more conventional measures of systemic oxygenation such as lactate levels failed to detect inadequacy of oxygenation.20

Splanchnic blood flow has been shown to decrease early during states of global low flow or during periods of high demand for blood flow in other areas. Numerous studies have lent support to the concept that the gut is the “crystal ball” of oxygenation and can be used as an indicator of tissue oxygenation. This principle is exemplified by the work of Hussain et al who studied blood flow in respiratory muscle following the induction of endotoxaemia in spontaneously breathing dogs. Diversion of blood flow to the respiratory muscles was evident while blood flow to the splanchnic bed and other “non-vital” organ systems was significantly decreased.3 Blood flow to respiratory muscle increased from 51 (4) ml/min to 101 (22) ml/min at 60 minutes of shock while blood flow to the gut and spleen was correspondingly reduced by approximately 50%. Moreover, in a model of respiratory failure Magder et al found that increased respiratory effort, as defined by an increase in frequency and minute ventilation, was associated with decreased blood flow to the gut from 93 ml/min/100 g to 45 ml/min/100 g even in the presence of normal blood pressure and cardiac output1 – that is, blood flow to the splanchnic bed appears to decrease before global evidence of decreased oxygen transport.
A state of inadequate oxygen transport can thus exist at the tissue level before global compromise. The work by Magder in an animal model suggests that global measurements of oxygen consumption are not reflective of actual events at the various tissue levels.

All previous studies on human subjects have assessed the use of gastric pH in the face of haemodynamic instability. For example, Maynard et al investigated the importance of splanchic ischaemia in patients with circulatory collapse and found that gastric pH was the most reliable predictor of clinical outcome.\(^\text{21}\) In their study pH had a sensitivity of 88% and a specificity of 62% as a predictor of outcome, while systemic pH had a sensitivity and specificity of 73% and 52%, respectively.

Similarly, Gutierrez et al evaluated gastric pH as a therapeutic index of oxygenation in critically ill patients. Their results also support an inverse relationship between survival and gastric pH in patients who are haemodynamically unstable.\(^\text{22}\)

When a low flow state exists globally, various tissues including the splanchic bed will therefore exhibit evidence of hypoxaemia. Consequently, the patient will have a reduced pH which is a reflection of systemically reduced oxygen delivery. Mohsenifar et al showed that the gastric pH was a very sensitive and specific predictor of weaning success or failure from mechanical ventilation compared with conventional weaning predictors.\(^\text{23}\)

Most studies cited above have used luminal gastric tonometry. This method requires that a gastric tonometer be placed in a segment of the gut and subsequently infused with saline. After approximately 45–90 minutes, during which equilibration occurs between the gastric mucosal CO\(_2\) and fluid in the tonometer, the saline is withdrawn and analysed for CO\(_2\). As a result the CO\(_2\) value obtained from the tonometer is an averaged value rather than a fast acting measuring technique. Sun and colleagues\(^\text{24}\) directly sampled gastric intramural PCO\(_2\) in a model of anaphylactic shock and found an increase from 6-38 (0-79) kPa to 17-68 (0-66) kPa within minutes of inducing anaphylactic shock. In order to obtain “real time” CO\(_2\) we therefore sampled gastric juice directly instead of using a tonometer. Similarly, Fiddian-Green et al have shown that gastric pH measured from CO\(_2\) concentrations in gastric juice is linearly related to pH measured directly by a pH probe.\(^\text{3}\)

In addition, sampling gastric juice with a standard nasogastric tube is simpler and significantly less costly than with a gastric tonometer. The critical threshold of intramural pH is open for debate, with levels of 7-20–7–35 having been used as cutoff points.\(^\text{4,21,22}\)

It is apparent that lower pH values will be associated with a high specificity and a low sensitivity as shown in the ROC curve. We defined mortality as death within 45 days; although this may appear to be an arbitrary number, choosing 60 or 90 days as a cutoff point would not have made any difference. However, if 30 days had been chosen as the cutoff point the mortality in the group with a high pH would have been 0% since the one death in that group occurred on day 35.

In this study we have shown that gastric pH is predictive of outcome in haemodynamically stable patients. Those patients with low gastric pH are apparently in a compensated state of inadequate oxygen delivery which is not reflected in the usual laboratory and haemodynamic indices. Our study lends support to the hypothesis that selective blood flow diversion can and does occur prior to haemodynamic failure. The concept of blood flow diversion is based upon the principle that blood flow is diverted to “vital” organs at the expense of “non-vital” organs. Although all our patients were mechanically ventilated, it has been previously shown by Marini et al\(^\text{20}\) that patients with respiratory failure on mechanical support perform a significant amount of respiratory work. Similarly, diversion of blood to the respiratory muscles at the expense of the splanchic bed was experimentally proven by Magder in an animal model with respiratory failure.

In conclusion, based on our small cohort study, gastrointestinal ischaemia may occur in the presence of normal haemodynamics in patients who are mechanically ventilated and can be used to predict accurately the severity of the illness and mortality. If this preliminary study is substantiated by large prospective studies, monitoring of gastric intramural pH could prove to be the most important predictor of mortality in otherwise stable, mechanically ventilated patients. Perhaps such a sensitive marker will permit earlier intervention to change the poor prognosis.

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