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Gastric intramural pH in mechanically ventilated patients

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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 pHi was calculated from the equation: pHi = 6·1 + log HCO_3/(gastric $P_{CO_2} \times 0{\cdot}03$). The outcome was survival or death due to respiratory or circulatory failure within 45 days of admission.**

***Results* – Gastric pHi 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 pHi. 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 pHi 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 pHi as a predictor of outcome.**

***Conclusion* – Low gastric pHi, 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.**

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

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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] Gastrointestinal ischaemia thus ensues, resulting in tissue hypoxia and subsequent acidosis. It therefore follows that a patient with a reduced pHi is in a compensated state of inadequate oxygen delivery relative to a patient with a normal pHi who presumably has adequate blood flow to satisfy tissue demands. Gastric pHi has recently been reported to predict sepsis, massive gastrointestinal bleeding, multiple organ failure, and outcome in critically unstable patients.[2–6] The premise of all these reports is that a low pHi is reflective of inadequate blood flow.

Most previous investigations have analysed a low pHi 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 pHi 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 H_2 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 (CO_2) can be enhanced by the titration of gastric bicarbonate (HCO_3) by hydrogen ion thus underestimating the gastric pHi. This potential source of error can be avoided by the use of H_2 receptor blockers.[8]

STUDY PROTOCOL

The study was approved by the institutional review board. Patients enrolled in the study were identified within 24–48 hours of in-

Table 1 Mean (SD) characteristics of patients

	pHi <7·25 (n=9)	*pHi ≥7·25 (n=16)*	*Difference (95% CI)*
Age (years)	64 (28)	77 (13)	13 (−3 to 29)
Respiratory rate	14 (3)	14 (4)	0 (−3 to 3)
pHa	7·47 (0·03)	7·44 (0·05)	0·03 (−0·004 to 0·064)
HCO_3 (m/Eq/l)	24 (2)	25 (2)	1 (−1 to 3)
$Paco_2$ (kPa)	4·39 (1·06)	5·46 (1·33)	1·06 (0·05 to 1·99)*
Pao_2 (kPa)	13·96 (5·98)	13·16 (5·58)	0·79 (−3·99 to 5·58)
Fio_2 (%)	0·46 (0·1)	0·42 (0·1)	0·04 (−0·8 to 0·9)
pHi	7·09 (0·17)	7·44 (0·13)	0·35 (0·23 to 0·47)*
Heart rate	97 (22)	95 (15)	2 (−14 to 18)
Mean BP (mmHg)	89 (14)	78 (17)	11 (−4 to 26)
APACHE II	12 (5)	14 (5)	2 (−2 to 6)
Mechanical ventilation (days)	13 (12)	11 (10)	2 (−8 to 12)
Mortality (%)	67	6	61 (53 to 69)*

pHa = arterial pH; HCO_3 = arterial bicarbonate; $Paco_2$ = arterial carbon dioxide tension; Pao_2 = arterial oxygen tension; pHi = intramural pH.
* $p<0·05$.

tubation. All patients had nasogastric tubes in place and had not received anything through the tube for two hours before the study. The nasogastric tube was clamped for 30 minutes before obtaining the gastric juice with a 20 ml syringe. The first 4·5 ml of gastric juice were discarded to account for the dead space of the nasogastric tube. No filter was used before injection of the juice into the blood gas analyser. Gastric juices were analysed in the same blood gas electrolyte (BGE) analyser to determine the concentration of CO_2 in the gastric juice. At the time of aspirating the gastric juice, arterial blood gas samples were also obtained and analysed in a BGE analyser (Instrumentation Laboratory) to determine the $Paco_2$, Pao_2, and the pH. Subsequent gastric juice samples were also obtained on synchronised intermittent mechanical ventilation (SIMV) and high pressure support ventilation (PSV) modes after 30 minutes on each of these modes. The SIMV rate was set the same as the patient's rate on AC. The high pressure support value was selected as the minimal pressure support (that is, (peak pressure − static pressure) × spontaneous flow rate/ventilator flow rate) plus 50%. We selected these three different modes of ventilation because it has previously been shown that the work of breathing varies between mechanically initiated breaths, patient initiated breaths, and various modes of ventilation,[9 10] resulting in a variation in the level of blood flow diversion from the splanchnic region.[1] In five patients measurement of gastric CO_2 was repeated after being on the same setting for 20 minutes. No medical intervention was implemented based on intramural pH data.

Additional data obtained at the time of collecting gastric juice included respiratory rate, tidal volume, heart rate, and blood pressure. However, APACHE II scores were calculated based on the data at the time of admission to the intensive care unit.[11] The total number of days on mechanical ventilation (throughout the hospital stay) was recorded for each study patient. Mortality was defined as death due to respiratory or circulatory failure within 45 days from the time of admission to the intensive care unit.

CALCULATION OF GASTRIC pHi

As has been previously described, the gastric pHi can be determined using the Henderson-Hasselbach equation whereby $pHi = 6·1 + \log$ arterial HCO_3/gastric $CO_2 \times 0·0307$. This can also be expressed as $pHi = pHa - \log (Pgco_2/Paco_2)$. The reliability of determining the pHi from this method has been validated by previous investigators.[3 12–14]

Two assumptions are made in calculating gastric intramural pH via the Henderson-Hasselbach equation: (1) Pco_2 in the lumen of the stomach is the same as that in the gastric tissue wall, and (2) tissue HCO_3 is equal to arterial HCO_3. Fiddian-Green *et al* found that pHi calculated from gastric CO_2 and arterial HCO_3 was linearly related to the pHi measured directly with a pH probe.[3] Under conditions of extreme ischaemia or no flow, Antonsson *et al* have shown that the pHi may be underestimated, although the change is qualitatively reliable.[2] 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 pHi and calculated pHi.[2 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, Fio_2, Pao_2, $Paco_2$, pHa, pHi, HCO_3, age. A p value of less than 0·05 was considered significant.

Results

Nine patients had a gastric intramural 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 pHi 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 shown, there were no differences in Pao_2, HCO_3, pHa, age, APACHE II scores, heart rate, and mean blood pressure, but arterial Pco_2 was slightly lower in the group with low pHi implying an element of acute respiratory alkalosis. The gas exchange and haemodynamic data shown in table 1 were obtained during AC ventilation and did not differ during SIMV

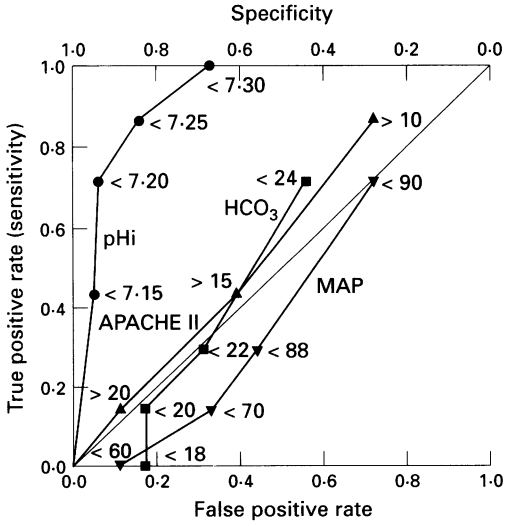
Table 2 Expected mortality based on pHi and APACHE II score

pHi	Likelihood ratio	Expected mortality based on APACHE II score (%)	Expected mortality based on pHi (%)	Observed mortality (%)
<7·20	11·8	20	75	83
<7·25	5·1	20	56	66
<7·30	3·0	20	43	53

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 pHi of less than 7·25, eight had a pHi of less than 7·25 on A/C ventilation and the remaining patient had a pHi of less than 7·25 on IMV mode. Seven patients had a pHi of less than 7·25 in at least two of the three modes of ventilation. Mean random variation in pHi in five patients in whom two consecutive measurements were taken was less than 3 (1)%. The mean difference between the first and second gastric P_{CO_2} in these patients was 0·26 (0·26) kPa (range 0·13–0·53 kPa).

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 pHi of less than 7·25 had a significantly increased mortality rate of 67% while those with a pHi 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.[17] The expected mortality based upon the pHi 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 pHi 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.



Receiver operator curve of true positive rate (sensitivity) plotted against false positive rate. pHi = intramural pH; HCO_3 = sodium bicarbonate; MAP = mean arterial pressure.

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, pHi was distinctly superior in predicting death.

Discussion

Our study shows that gastric pHi 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 pHi 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 pHi 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.[1] 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 output[7] – 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 pHi in the face of haemodynamic instability. For example, Maynard *et al* investigated the importance of splanchnic ischaemia in patients with circulatory collapse and found that gastric pHi was the most reliable predictor of clinical outcome.[21] In their study pHi 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 pHi as a therapeutic index of oxygenation in critically ill patients. Their results also support an inverse relationship between survival and gastric pHi in patients who are haemodynamically *unstable.*[22] When a low flow state exists globally, various tissues including the splanchnic bed will therefore exhibit evidence of hypoxaemia. Consequently, the patient will have a reduced pHi which is a reflection of systemically reduced oxygen delivery. Mohsenifar *et al* showed that the gastric pHi was a very sensitive and specific predictor of weaning success or failure from mechanical ventilation compared with conventional weaning predictors.[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[24] directly sampled gastric intramural P_{CO_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 pHi calculated from CO_2 concentrations in gastric juice is linearly related to pH measured directly by a pH probe.[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.[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 pHi would have been 0% since the one death in that group occurred on day 35.

In this study we have shown that gastric pHi is predictive of outcome in haemodynamically *stable* patients. Those patients with a low gastric pHi 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*[10] 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 splanchnic 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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