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Gastric tonometry and prediction of outcome in the critically ill

Arterial to intramucosal pH gradient and carbon dioxide gradient

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Summary

Splanchnic ischaemia is thought to be of central importance in the development of multi-organ failure and hence death in critically ill patients. It has been suggested that the arterial to gastric intramucosal pH gradient and the difference in partial pressure of carbon dioxide between gastric mucosa and arterial blood are more sensitive markers of splanchnic ischaemia than gastric intramucosal pH itself and thus should be predictors of mortality in the critically ill. We studied 62 critically ill patients within 6 h of admission to the intensive care unit and found no significant difference at 0, 12 or 24 h after admission to the study in either the arterial to gastric intramucosal pH gradient or the difference in partial pressure of carbon dioxide between gastric mucosa and arterial blood between survivors and nonsurvivors. We conclude that in contrast to gastric intramucosal pH neither the arterial to gastric intramucosal pH gradient nor the difference in partial pressure of carbon dioxide between gastric mucosa and arterial blood distinguish survivors from nonsurvivors.

Keywords *Measurement techniques*; gastric tonometry. *Complications*; mortality.

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Splanchnic ischaemia is postulated to be of major importance in the development of multi-organ failure, and hence death, in critically ill patients [1]. Low gastric intramucosal pH (pH_i) is associated with poor outcome [2–4]. However, it is possible that low pH_i may simply be a reflection of systemic acidosis rather than splanchnic ischaemia [5]. High arterial to gastric intramucosal pH gradient ($pH_a - pH_i$) or a large difference in the partial pressure of carbon dioxide between gastric mucosa and arterial blood ($P_iCO_2 - P_aCO_2$) have been postulated to be more specific indicators of splanchnic ischaemia and predictors of outcome [6, 7]. Our study was designed to test this hypothesis. Although it is $pH_a - pH_i$ that has been proposed to be a measure of splanchnic ischaemia, this parameter is mathematically invalid because of the log scale and so we also examined the value of arterial to gastric mucosal hydrogen ion gradient (H^+ gradient) as a prognostic marker.

Method

Following approval by our Ethics Committee, 62 consecutive emergency adult admissions to our medical/surgical intensive care unit (ICU) were recruited. Informed consent was obtained from the patient or a close relative. Patients were not studied if the primary reason for admission was cerebrovascular accident or cerebral trauma as these patients do not commonly die from multi-organ failure. Other exclusion criteria were a contra-indication to the insertion of a nasogastric tube, active gastrointestinal bleeding and previous total gastrectomy. Recruitment continued until at least 22 patients had survived to ICU discharge and 22 had died in ICU to ensure at least 90% power to detect a one standard deviation difference in our measurements between survivors and nonsurvivors.

Arterial blood gases and P_iCO_2 were measured on admission to the study and then 12 and 24 h later. Intramucosal PCO_2 was measured using a gastric tonometer (Trip NGS, Tonometrics Inc., Hopkinton, MA, USA) according to the manufacturer's instructions. Prior to insertion, all air was removed from the tonometer. The balloon of the tonometer was then inserted into the stomach by the nasogastric route and its position was confirmed radiographically. Two and a half millilitres of saline was injected into the balloon taking care not to

Table 1 Admission diagnoses.

Admission diagnosis	No. of patients
Severe sepsis or septic shock	22
Congestive cardiac failure	10
Asthma	7
Diabetic ketoacidosis or hyperosmolar nonketotic coma	3
Chronic obstructive pulmonary disease	3
Pneumonia	3
Massive transfusion	2
Trauma	2
Complicated myocardial infarction*	2
Miscellaneous	8

* Excluding pulmonary oedema.

inject any air and were left to equilibrate for 60–90 min. At the end of the equilibration period the saline was aspirated anaerobically, the first 1 ml was discarded and the remaining 1.5 ml was analysed. Immediately after aspiration, the tonometer was reprimed with a further 2.5 ml of saline. At the same time a sample of arterial blood was taken. Both samples were immediately analysed in a blood gas analyser (Ciba-Corning 288, Ciba-Corning Diagnostics Corp., Medfield, MA, USA) and the saline P_{CO_2}, P_aCO_2 and arterial actual bicarbonate values were recorded. The P_iCO_2 was subsequently calculated by multiplying the saline P_{CO_2} by a correction factor which is dependent on the equilibration period and is provided by Tonometrics Inc. Intramucosal pH was calculated using a modification of the Henderson–Hasselbach equation:

$$pH_i = 6.1 + \log_{10}(\text{arterial bicarbonate concentration}/P_iCO_2).$$

Gastric intramucosal hydrogen ion concentration was calculated from the formula:

$$[H^+] = K'(P_iCO_2/\text{arterial bicarbonate}),$$

where $K' = 180$.

Patients were entered into the study within 6 h of ICU admission. All received ranitidine 50 mg intravenously every 8 h and were fasted during the study period. Acute Physiology and Chronic Health Evaluation (APACHE II) scores were calculated.

The end points were ICU mortality and 30-day mortality. Statistical analysis was performed using Student's *t*-test for continuous data and the Chi-squared test for categorical data. A probability value of less than 0.05 was considered significant. Receiver operating characteristic curves were plotted from the sensitivity and specificity of pH_i, pH_a, $pH_a - pH_i$, H^+ gradient and $P_iCO_2 - P_aCO_2$ at each value obtained in our patients (i.e. without binning of data).

Results

Intensive Care Unit and 30-day mortality figures were 39% and 44%, respectively. Predicted mortality based on admission diagnoses and APACHE II scores was 48%. Mean APACHE II score was 25, mean age was 57 years and 60% of patients were male. Admission diagnoses are shown in Table 1. Mean (SD) values of pH_i, pH_a, $pH_a - pH_i$, H^+ gradient and $P_iCO_2 - P_aCO_2$ in survivors and nonsurvivors are given in Table 2. The areas under the receiver operating characteristic curves for the ability of pH_i, pH_a, $pH_a - pH_i$, H^+ gradient and $P_iCO_2 - P_aCO_2$ at 0 h to predict ICU mortality were 0.66, 0.68, 0.52, 0.58 and

Table 2 Mean (SD) values in survivors and nonsurvivors.

	Time; h	ICU survivors	ICU nonsurvivors	30-day survivors	30-day nonsurvivors
pH_i	0	7.25 (0.20)	7.12 (0.27)*	7.27 (0.22)	7.12 (0.24)*
	12	7.27 (0.16)	7.27 (0.26)	7.29 (0.18)	7.25 (0.23)
	24	7.24 (0.18)	7.20 (0.14)	7.22 (0.19)	7.23 (0.14)
pH_a	0	7.31 (0.13)	7.20 (0.19)*	7.31 (0.14)	7.20 (0.17)†
	12	7.36 (0.07)	7.30 (0.16)	7.36 (0.08)	7.30 (0.14)*
	24	7.36 (0.06)	7.3 (0.13)	7.35 (0.06)	7.32 (0.12)
$pH_a - pH_i$	0	0.06 (0.14)	0.08 (0.16)	0.05 (0.15)	0.08 (0.15)
	12	0.08 (0.14)	0.03 (0.16)	0.07 (0.14)	0.05 (0.16)
	24	0.12 (0.17)	0.10 (0.12)	0.13 (0.18)	0.09 (0.11)
H^+ gradient; $nmol.l^{-1}$	0	−11 (22)	−25 (67)	−12 (23)	−23 (62)
	12	−14 (30)	−10 (12)	−13 (31)	−11 (13)
	24	−21 (32)	−13 (15)	−23 (34)	−11 (14)
$P_iCO_2 - P_aCO_2$; kPa	0	1.2 (2.1)	1.9 (4.2)	1.1 (2.2)	1.9 (4.0)
	12	1.7 (3.9)	1.2 (2.6)	1.7 (4.0)	1.2 (2.5)
	24	2.6 (4.6)	2.0 (2.2)	2.9 (4.8)	1.8 (2.0)

pH_i, gastric intramucosal pH; pH_a, arterial pH; P_iCO_2, gastric intramucosal P_{CO_2}. * $p < 0.05$ survivors vs. nonsurvivors; † $p < 0.01$ survivors vs. nonsurvivors.

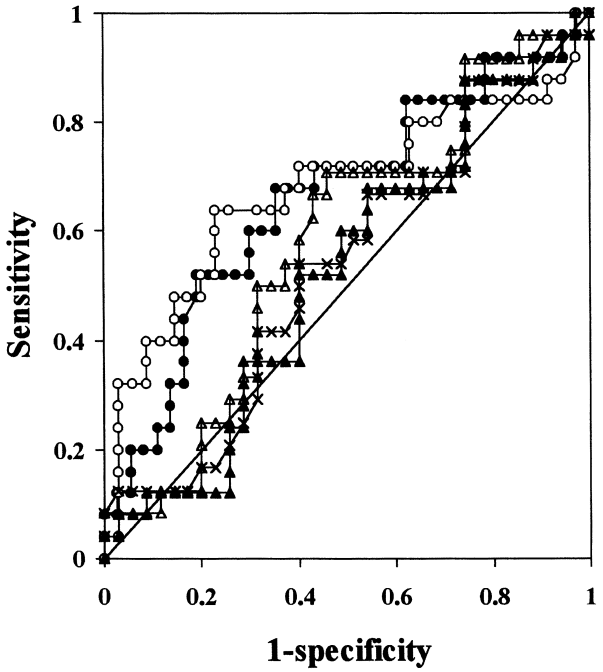

Figure 1 Receiver operating characteristic curves for ability of pH_a (open circles), pH_i (closed circles), $pH_a - pH_i$ (closed triangles), H^+ gradient (open triangles) and $P_iCO_2 - P_aCO_2$ (crosses) on admission to predict ICU mortality. The diagonal line indicates the curve that would be expected of a test of no predictive ability.

0.54, respectively. The curves are shown in Fig. 1. The corresponding values for 30-day mortality were 0.68, 0.69, 0.57, 0.57 and 0.57. Receiver operating characteristic curves for the 12- and 24-h values were not plotted as only pH_a at 12 h was significantly different between survivors and nonsurvivors at these times.

Discussion

Multi-organ failure is the major cause of death in patients admitted to ICU [8] and splanchnic ischaemia is believed to be of major importance in its pathogenesis [1]. The $pH_a - pH_i$ gradient and $P_iCO_2 - P_aCO_2$ are claimed to be better indicators of splanchnic ischaemia than pH_i because the effect of systemic acid-base balance on gastric intramucosal acid-base balance is eliminated [6, 7]. Our results confirm previous findings showing that pH_i can distinguish survivors from nonsurvivors. It was expected that $pH_a - pH_i$, H^+ gradient and $P_iCO_2 - P_aCO_2$ would distinguish survivors from nonsurvivors. The lack of a significant difference in $pH_a - pH_i$, H^+ gradient and $P_iCO_2 - P_aCO_2$ between survivors and nonsurvivors indicates that this is not the case. The similarity of the results for $pH_a - pH_i$ and H^+ gradient indicate that the failure of the former to predict outcome is not a result of problems related to the use of a log scale.

The accuracy and therefore usefulness of a test depends on its ability to discriminate between two subclasses of subjects, i.e. its sensitivity and specificity. However, for any test there is a series of pairs of sensitivities and specificities depending on the cut-off value chosen. The receiver operating characteristic curve is a graphical display of all the sensitivity/specificity pairs resulting from continuously varying the cut-off value over the entire range of values observed [9]. Thus, not only does the receiver operating characteristic curve give a more complete picture of the accuracy of a test but it also allows assessment of a test for which there is no reason to choose a single specific cut-off value. The area under the receiver operating characteristic curve is a convenient global measure of the accuracy of a diagnostic test. Values range from 1.0 (a perfect test) to 0.5 (a test of no diagnostic value). The areas under of the receiver operating characteristic curves for $pH_a - pH_i$, H^+ gradient and P_iCO_2-P_aCO_2 were all close to 0.5, indicating that these parameters are of very limited use in predicting outcome in critically ill patients. From visual inspection of the curves it is apparent that there is no value of any of these parameters at which there is a combination of even moderate sensitivity and specificity.

To our knowledge, data on the relationship between $pH_a - pH_i$, $P_iCO_2 - P_aCO_2$ or H^+ gradient and mortality has only been published once before. Gårdebäck *et al.* studied the effect of dopexamine on low pH_i in 19 patients undergoing heart valve replacement [10]. *Post hoc* analysis of their data revealed that the five patients with postoperative complications (classified *post hoc* as infection, myocardial infarction, single or multiple organ failure and death) had a greater number of observations of $pH_a - pH_i$ greater than 0.12. However, the number of measurements made in any given patient was determined by the duration of ICU stay. As those patients with postoperative complications probably had a longer ICU stay, they would have a greater absolute number of observations of $pH_a - pH_i$ greater than 0.12 by chance alone.

Other investigators have measured $pH_a - pH_i$ but have either not given the data related to this parameter or have not attempted to examine the relationship between it and mortality. Fiddian-Green & Baker examined the relationship between a number of variables (including $pH_a - pH_i$) and outcome in 85 patients undergoing elective cardiac surgery [11]. However, despite claims that this study shows that $pH_a - pH_i$ is a predictor of outcome [6, 10, 12], no data were provided to indicate whether or not this was the case. Diebel *et al.* demonstrated an increased $pH_a - pH_i$ in 11 patients undergoing chronic haemodialysis. In the subsequent 12 months, three of these patients but none of the seven normal controls developed gastrointestinal

bleeding [12]. Unfortunately, there was a considerable delay in analysing the saline P_{CO_2} which may invalidate the results and the authors made no attempt to examine the relationship between the magnitude of $pH_a - pH_i$ gradient and gastrointestinal haemorrhage. As a result of this and because of the use of an inappropriate control group, it is not possible to draw any conclusions from these data regarding the clinical significance of an increased $pH_a - pH_i$.

There are three possible explanations for our finding: $pH_a - pH_i$, H^+ gradient and $P_iCO_2 - P_aCO_2$ are not markers of splanchnic ischaemia, splanchnic ischaemia is not important in determining mortality in the critically ill or splanchnic ischaemia was near absent in our patients. The first explanation seems to be the most plausible in view of the paucity of evidence linking $pH_a - pH_i$ or $P_iCO_2 - P_aCO_2$ with splanchnic ischaemia, as well as evidence that an increased H^+ gradient may be associated with supranormal ileal mucosal oxygen tension. In a canine study published in abstract form only, an increased $pH_a - pH_i$ gradient was shown to indicate intestinal ischaemia produced by total vascular occlusion. Although it is not explicitly stated, it seems that the tonometers were placed in the part of the bowel rendered totally ischaemic [13]. Given the extremely rare occurrence of isolated total occlusion of the blood supply to the stomach, the relevance of this finding to gastric tonometry in humans is questionable. It has been claimed, based on this study, that $pH_a - pH_i$ gradient is a better diagnostic test than pH_i [6] but the claim is not borne out by the statistical analysis of the data [13]. The evidence linking an increased $P_iCO_2 - P_aCO_2$ with splanchnic ischaemia is similarly sparse. In a pig study, also only published in abstract form so far, Chagnon demonstrated that administration of a hypoxic mixture resulted in an increase in intestinal $P_iCO_2 - P_aCO_2$ but that this did not occur until the pigs were breathing a mixture with an inspired oxygen fraction of 0.08 [14], suggesting that $P_iCO_2 - P_aCO_2$ is at best an insensitive measure of splanchnic ischaemia. Data from Van der Meer *et al.* suggest that H^+ gradient is not a specific indicator of splanchnic ischaemia either. These investigators demonstrated in a pig model of resuscitated septic shock that the ileal H^+ gradient was raised in the presence of a supranormal ileal mucosal oxygen tension [15].

It may be argued that $pH_a - pH_i$ is a measure of splanchnic ischaemia but that splanchnic ischaemia only occurred in a few patients in our study, on the basis that the $pH_a - pH_i$ values obtained in our patients were similar or lower than those seen in subjects with normal splanchnic perfusion. This seems unlikely in view of the low pH_i, high APACHE II score and high mortality in our patients. Three studies provide data on which to base a normal range for $pH_a - pH_i$. Superficially, two of these provide evidence that most of our patients had 'normal' $pH_a - pH_i$ values [11, 16]. Parvianen *et al.* studied 12 healthy volunteers and found a mean $pH_a - pH_i$ of 0.09 with a standard deviation of 0.06 [16]. Taking the upper limit of normal to be the mean plus two standard deviations this would give a value of 0.21. Using the same method to determine the upper limit of normal, Fiddian-Green & Baker arrived at the value of 0.13 after studying 45 stable anaesthetised patients about to undergo cardiac surgery [11]. In contrast, data from Diebel *et al.*'s control group would suggest that the figure should be 0.04 [12]. However, none of these results is directly applicable to our patients. The use of different blood gas analysers may modify $pH_a - pH_i$ by 0.1–0.15 pH units [16]. Compared with the ABL 500 analyser (Radiometer, Copenhagen, Denmark) used by Parvianen *et al.* [16], the Ciba-Corning blood gas analyser tends to overestimate the pH_i [17] and therefore to underestimate the $pH_a - pH_i$ and thus the upper limit of normal will be lower. Fiddian-Green *et al.* [11] unfortunately do not specify which blood gas analyser was used and in Diebel *et al.*'s study [12] there were delays of up to 30 min in analysing the samples. As even small delays can lead to inaccuracies in saline P_{CO_2} values the results from the latter study may be unreliable [18].

In contrast, based on recent data from 37 patients undergoing cardiac surgery [19], many of our patients had an abnormally high $P_iCO_2 - P_aCO_2$. Before cardiopulmonary bypass the tonometer–arterial P_{CO_2} gradient, measured with an ABL analyser, ranged from −1.4 to 1.87 with a median of 0.28. Multiplying the tonometer P_{CO_2} by the appropriate correction factor to obtain P_iCO_2 would have resulted in slightly higher values for $P_iCO_2 - P_aCO_2$ but against this must be balanced the tendency of the Ciba-Corning analyser to underestimate saline P_{CO_2} and thus underestimate $P_iCO_2 - P_aCO_2$ in our patients.

Finally, it should be borne in mind that the use of any parameter derived from gastric tonometry to detect splanchnic ischaemia as opposed to gastric ischaemia requires the assumption that the splanchnic circulation behaves in a homogeneous manner. This may not be the case. In a study of a pig model of hyperdynamic sepsis, blood flow to the ileum and caecum was decreased while blood flow to the rest of the intestine, stomach, pancreas, spleen and liver was normal [20].

We conclude that neither pHa – pHi, H^+ gradient nor $P_iCO_2 - P_aCO_2$ predict mortality in a heterogeneous group of critically ill patients. We feel the most likely explanation for this finding is that none of these parameters is a measure of splanchnic ischaemia. In view of the absence of good evidence supporting the use of $pH_a - pH_i$, H^+ gradient or $P_iCO_2 - P_aCO_2$ and our data showing the lack of a relationship between these parameters and death we

believe that there is likely to be little clinical value in monitoring any of these parameters.

References

1 Meakins JL, Marshall JC. The gastrointestinal tract: the 'motor' of MOF. *Archives of Surgery* 1986; **121:** 197–201.
2 Doglio GR, Pusajo JF, Egurrola MA, *et al*. Gastric mucosal pH as a prognostic index of mortality in critically ill patients. *Critical Care Medicine* 1991; **19:** 1037–40.
3 Maynard N, Bihari D, Beale R, *et al*. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *Journal of the American Medical Association* 1993; **270:** 1203–10.
4 Friedman G, Berlot G, Kahn RJ, Vincent JL. Combined measurements of blood lactate concentrations and gastric intramucosal pH in patients with severe sepsis. *Critical Care Medicine* 1995; **23:** 1184–93.
5 Boyd O, Mackay CJ, Lamb G, Bland JM, Grounds RM, Bennett ED. Comparison of clinical information gained from routine blood-gas analysis and from gastric tonometry for intramural pH. *The Lancet* 1993; **341:** 142–6.
6 Fiddian-Green RG. Gastric intramucosal pH, tissue oxygenation and acid-base balance. *British Journal of Anaesthesia* 1995; **74:** 591–606.
7 Gutierrez G, Clark C, Brown SD, Price K, Ortiz L, Nelson C. Effect of dobutamine on oxygen consumption and gastric intramucosal pH in septic patients. *American Journal of Respiratory and Critical Care Medicine* 1994; **150:** 324–9.
8 Deitch EA. Multiple organ failure: pathophysiology and potential future therapy. *Annals of Surgery* 1992; **216:** 117–34.
9 Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clinical Chemistry* 1993; **39:** 561–77.
10 Gårdeback M, Settergren G, Öhquist G, Tirén C. Effect of dopexamine on calculated low gastric intramucosal pH following valve replacement. *Acta Anaesthesiologica Scandinavica* 1995; **39:** 599–604.
11 Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. *Critical Care Medicine* 1987; **15:** 153–6.
12 Diebel L, Kozol R, Wilson RF, Mahajan S, Abu-Hamdan D, Thomas D. Gastric intramucosal acidosis in patients with chronic kidney failure. *Surgery* 1993; **113:** 520–6.
13 Fiddian-Green RG. The pH-gap: a measurement for establishing the presence or absence of intestinal mucosal ischaemia independently of disturbances in systemic acid base balance (Abstract). *European Surgical Research* 1993; **25** (Suppl.): 25–6.
14 Chagnon J. Effects of hypoxemic hypoxia on veno and gut mucosal arterial PCO2 gradient in pigs (Abstract). *Intensive Care Medicine* 1996; **22** (Suppl. 3): S436.
15 VanderMeer TJ, Wang H, Fink MP. Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. *Critical Care Medicine* 1995; **23:** 1217–26.
16 Parviainen I, Vaisänen O, Ruokonen E, Takala J. Effect of nasogastric suction and ranitidine on the calculated gastric intramucosal pH. *Intensive Care Medicine* 1996; **22:** 319–23.
17 Takala J, Parviainen I, Siloaho M, Ruokonen E, Hämäläinen E. Saline PCO2 is an important source of error in the assessment of gastric intramucosal pH. *Critical Care Medicine* 1994; **22:** 1877–9.
18 Wood PR, Cudworth P, Davies GE, Lawler PG. Potential hazards in estimation of gastric intramucosal pH. *The Lancet* 1992; **340:** 913.
19 Riddington DW, Venkatesh B, Boivin CM, *et al*. Intestinal permeability, gastric intramucosal pH, and systemic endotoxemia in patients undergoing cardiopulmonary bypass. *Journal of the American Medical Association* 1996; **275:** 1007–12.
20 Xu D, Qi L, Guillory D, Cruz N, Berg R, Deitch EA. Mechanisms of endotoxin- induced intestinal injury in a hyperdynamic model of sepsis. *Journal of Trauma* 1993; **34:** 676–83.

