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Measuring Intramucosal pH in Very Low Birth Weight Infants

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ABSTRACT

Maintenance of adequate perfusion is essential for health of the intestinal mucosa. Methods available to assess intestinal perfusion provide information on mesenteric blood flow, which may differ from mucosal flow. Intramucosal pH (pH_i) is influenced by tissue oxygenation and perfusion. Gastric pH_i can be measured using the technique of tonometry. A prospective observational clinical study was performed to examine relationships between measured gastric pH_i and mucosal CO_2 (mCO_2), and acid-base balance, gastrointestinal complications (necrotizing enterocolitis and perforation), and death in infants <1500 g birth weight. A nasogastric tonometry catheter (size 5F) was inserted into the stomach of infants, and pH_i was calculated from mCO_2 levels measured using saline tonometry. Measurements were performed at 3, 12, 24, and 48 h, then daily until arterial access was unavailable. Two hundred eleven sets of measurements were performed on 38 infants [birth weight (mean ±SD), 863 ± 241 g; gestation, 26.5 ± 1.8 wk; and median Clinical Risk Index for Babies score, 8.0 (interquartile range, 5.0–10.75)]. Mean pH_i was 7.27 (95% confidence interval, 7.26–7.28) and mean mCO_2 was 47.0 mm Hg (95% confidence interval, 45.7–48.3 mm Hg). pH_i and mCO_2 correlated significantly with arterial pH (pH_a), arterial P_{CO_2} ($Paco_2$), and arterial base excess. There were no significant relationships between pH_a and pH gap ($pH_a - pH_i$) or CO_2 gap ($mCO_2 - Paco_2$). Recurrent low pH_i (<7.2 on more than one occasion) and an $mCO_2/Paco_2$ ratio of ≥1.29 were significantly associated with an increase in gastrointestinal complications. There were no statistically significant associations with death. In conclusion, changes in pH gap and CO_2 gap can occur without alteration in pH_a. Abnormalities in pH_i might predict gastrointestinal complications in infants <1500 g. **(*Pediatr Res* 50: 398–404, 2001)**

Abbreviations

pH_i, intramucosal pH
pH_a, arterial pH
mCO_2, mucosal CO_2
GI, gastrointestinal
NEC, necrotizing enterocolitis
VLBW, very low birth weight
CI, confidence interval
CV, coefficient of variability
SMA, superior mesenteric artery
CRIB, clinical risk index for babies
$Paco_2$, arterial P_{CO_2}

Mesenteric ischemia has been implicated in the pathogenesis of NEC (1, 2), which remains a significant cause of morbidity and mortality in VLBW infants (3). Hypoxia, either ante- or postnatally, may lead to redistribution of the cardiac output away from nonessential organs, including the intestine, to preserve oxygenation of essential organs. This may result in an imbalance of oxygen supply and demand in the gut, which may be further exacerbated by the introduction of enteral nutrition.

The ability to study intestinal perfusion at the mucosal level might benefit both the researcher attempting further to understand NEC and the clinician determining the optimal time to introduce milk feeds (4, 5). Previously the only method available for the study of intestinal perfusion in the human newborn infant has been the study of blood flow velocity in the SMA and celiac artery using Doppler ultrasound. Although this may give insight into the resistance in the intestinal vascular bed, it cannot give information about the health of the intestinal mucosa.

Gastric pH_i, which will be influenced by oxygenation and perfusion, has been measured in animals and humans using the minimally invasive technique of gastric tonometry (6). The presence of large quantities of carbonic anhydrase in gastric mucosal cells enables rapid equilibration of CO_2 from the submucosa to the gastric lumen. This technique is dependent on being able to measure CO_2 at the mucosal surface (mCO_2) by equilibration with sterile saline in an intragastric gas-permeable Silastic balloon and substituting the result together with a concurrent estimate of arterial bicarbonate into the Henderson-Hasselbach equation.

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In animals this measurement of pH_i has been shown to fall in response to gut ischemia induced by mechanical (7), physiologic (8, 9), and pharmacologic (10) methods. In newborn piglets a relationship has been shown between pH_i and SMA blood flow (10). These studies have shown that pH_i may change in response to ischemia or regional hypoxia in the absence of changes in systemic acid-base balance or hemodynamics.

In adult critical care, sustained low gastric pH_i has been associated with an increased risk of mortality and multiple organ dysfunction (11). Changes in mucosal blood flow both in the small intestine and the stomach measured using scanning laser Doppler have been correlated with pH_i (12, 13) measurements.

In limited data from the pediatric population, low values of pH_i have been demonstrated to be predictive of mortality in septic shock (14) and independently to predict mortality in intensive care patients (15). In a population of children undergoing extracorporeal life support, the CO_2 gap ($Paco_2 - mCO_2$) had greater predictive power for mortality than pH_i, the predictive value for death with a CO_2 gap of >10 mm Hg being 92% (16).

The objectives of the present study were to assess whether tonometry could be successfully performed in a population of VLBW infants; to establish ranges of values for pH_i and mCO_2 in this population in the early neonatal period, and to explore relationships between measured variables and systemic acid-base to quantify imbalances in O_2 supply and demand at the mucosal level. In addition, pilot data were collected to examine for associations between the measured and calculated variables and the development of major GI complications and death.

METHODS

This was a prospective observational clinical study of pH_i in infants <1500 g birth weight in the early neonatal period.

Inclusion criteria were a birth weight <1500 g and the presence of an indwelling arterial catheter. All catheters were placed for clinical purposes at the discretion of the responsible clinician. Infants with life-threatening congenital malformations or chromosomal anomalies were excluded. Recruitment only occurred when M.E.C. was available to perform measurements.

The study protocol was approved by the East London and City Health Authority Research Ethics Committee, and informed parental consent was obtained before study entry. Infants were recruited into the study as early as possible after delivery up to 24 h of age from the population admitted to the Neonatal Intensive Care Unit at the Homerton Hospital, London, during the period September 1998 to December 1999 inclusive. All intensive care management was conducted according to standard unit protocol. Decisions on the timing of commencement of enteral feed were made by the attending clinicians, who were not informed of pH_i and mCO_2 values.

After recruitment, measurements were taken at 3, 12, 24, and 48 h after study entry and thereafter on a daily basis until death or removal of the indwelling arterial line. Tonometry measurements were performed using a standard protocol. A single-use size 5F dual-lumen nasogastric tonometry catheter (Tonometrics Inc., Worchester, MA, U.S.A.) was passed into the infant's stomach, and correct placement was confirmed at the time of routine abdominal radiography for arterial line position. At each sampling time the catheter balloon was instilled with 1.0 mL of sterile 0.9% saline and left to equilibrate for 45 min. After equilibration, 0.3 mL of saline was withdrawn and discarded. The remaining 0.7-mL sample was withdrawn anaerobically and immediately analyzed for CO_2 content using a standard blood gas analyser (ABL Radiometer 520, Radiometer Medical A/S, DK-2700, Brønshøj, Denmark). The tonometry catheter used contained a gas-permeable Silastic balloon for which the correction factors for equilibration time for CO_2 had been predetermined by the manufacturers. mCO_2 levels were calculated using the correction factor for a 45-min dwell time, mCO_2 = saline $CO_2 \times 1.13$. Concurrent arterial blood samples of 0.2-mL volume were drawn for measurement of blood gases and serum lactate (YSI 2300 Glucose/Lactate Analyzer, YSI, Inc., Yellow Springs, OH, U.S.A.). A single observer (M.E.C.) performed all measurements.

The nasogastric lumen of the catheters was left on free drainage and aspirated every 4–6 h. The gastric contents were aspirated before performing all measurements. Infants were not routinely given H_2 receptor antagonists.

Intramucosal pH (pH_i) was calculated using the Henderson-Hasselbalch equation: $pH_I = 6.1 + \log [HCO_3]/(mCO_2 \times 0.031)$. Where 6.1 is the negative logarithm of the dissociation coefficient of carbonic acid and 0.031 is the solubility of CO_2 in plasma, mCO_2 is the mucosal CO_2 measured tonometrically and HCO_3 is the bicarbonate concentration of a concurrent arterial blood gas. The following variables were calculated: pH gap = $pH_a - pH_i$, CO_2 ratio = $mCO_2/Paco_2$, and CO_2 gap = $mCO_2 - Paco_2$.

Repeatability of saline CO_2 measurements was assessed by aspirating two samples simultaneously after removal of the catheter dead space. Samples were sealed and then immediately analyzed for CO_2 content.

The following clinical data were collected:

Gestational age, birth weight, length, and cord gases as available.

Arterial blood gas and serum lactate were estimated concurrently with the tonometry saline CO_2 measurements.

CRIB (severity of illness) scores, which has been shown to predict mortality in this birth weight group (17), were calculated for all subjects at 12 h of age. The total possible score of 22 is contributed to by birth weight (>1350 g, 0; 851–1350 g, 1; 701–850 g, 4; ≤ 700 g, 7), gestational age (>24 wk, 0; ≤ 24 wk, 1), congenital malformations (none, 0; not acutely life-threatening, 1; acutely life-threatening, 3), maximum base excess (>-7.0 mM, 0 -7.0 to -9.9 mM, 1; -10.0 to -14.9 mM, 2; ≤ -15.0 mM, 3), minimum appropriate inspired O_2 ($\leq 40\%$, 0; 41–60%, 2; 91–100%, 3), and maximum appropriate inspired O_2 ($\leq 40\%$, 0; 41–80%, 1; 81–90%, 3; 91–100%, 5).

Neonatal complications including overt signs of NEC.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS; Chicago, IL, U.S.A.). Statistical significance was set at the 95% level. Data are

presented as mean ±SD except when populations were not normally distributed, in which case data are presented as median (interquartile ranges).

Differences among groups were analyzed using ANOVA, *t* test, and Mann-Whitney when normality tests failed. Differences in proportions between two groups were analyzed using Fisher's exact test and for more than two groups using χ^2 for trend analysis. The CV was calculated using the following formula: CV (%) = SD/mean × 100.

Correlation of mean values from individual subjects was used to assess the strength of the relationship between variables. Correlations were performed using Pearson's parametric correlation.

The clinical outcomes of death and major GI complications (NEC proven by the presence of intramural gas or perforation) were assessed in relation to the following tonometry-derived variables:

1. pH_i, with the subjects divided into three groups according to the lowest recorded pH_i value (group A lowest $pH_I \geq 7.25$, group B lowest $pH_I < 7.25$, and group C lowest $pH_I < 7.2$ more than one occasions). These three groups were mutually exclusive.
2. A CO_2 gap >10 mm Hg.
3. A CO_2 ratio ≥ 1.29; this ratio represents the upper limit of a CO_2 gap of >10 mm Hg within the normal $Paco_2$ range of 35–45 mm Hg.

RESULTS

During the study period, 38 infants were recruited (Table 1). Thirty-seven infants had umbilical arterial lines, and one infant had a radial arterial line inserted.

Gastric tonometry was successfully performed in all 38 infants; in one infant the tonometry catheter was found on radiography to be in the right main bronchus and was replaced. There were no complications encountered with tube dislodgement or balloon leakage. A total of 211 paired measurements of pH_a and pH_i were performed in the 38 subjects.

Repeatability of saline CO_2 measurements under stable ventilatory and acid-base conditions were assessed on 26 occasions, the CV of CO_2 was 5.6% (95% CI, 4.3–7.1%).

Mean values for pH_a, pH_i, $Paco_2$, mCO_2, pH gap, CO_2 gap, and arterial base excess from all measurements ($n = 211$) are summarized in Table 2. The mean difference between pH_a and pH_i was 0.064 ± 0.046 (95%CI, 0.058–0.07; $p < 0.001$) and between $Paco_2$ and mCO_2 was 5.41 ± 4.6 mm Hg (95% CI, 4.79–6.03 mm Hg; $p < 0.001$). Mean pH_a and pH_i at each time point measured during the first 5 d of life are illustrated in Figure 1.

Table 1. *Characteristics of study infants*

Characteristic	Study infants ($n = 38$)
Birth weight (g)	862.7 ± 241
Birth weight SD score	−0.35 (−0.16 to 0.1)
Gestation age (wk)	26.5 ± 1.8
Sex	24 male:14 female
CRIB score (severity of illness)	8 (5–10.75)
Cord pH ($n = 28$)	7.29 ± 0.1
Antenatal steroids	35 (92%)
Positive-pressure ventilation	37 (97%)
Exogenous surfactant	37 (97%)
Survival to discharge (%)	26 (68.4%)

Data presented as mean ± SD except for birth weight SD score and CRIB score, which are presented as median (interquartile range).

Table 2. *Mean values of measured and calculated variables*

Variable	$n = 211$
Arterial pH	7.33 (7.325–7.345)
Intramucosal pH	7.27 (7.26–7.28)
Arterial CO_2 (mm Hg)	41.61 (40.35–42.9)
Mucosal CO_2 (mm Hg)	47.02 (45.73–48.31)
pH gap ($pH_a - pH_i$)	0.064 (0.058–0.070)
CO_2 gap ($mCO_2 - Paco_2$) (mm Hg)	5.41 (4.79–6.03)
Arterial base excess	−3.86 (−4.21 to −3.51)

Data are presented as mean (95% CI).

Relationships between variables were examined using correlation analysis by calculating the mean values of each variable for each subject ($n = 38$) (Table 3).

mCO_2 values correlated significantly with $Paco_2$ ($r = 0.9$; $p < 0.001$; (Fig. 2) and pH_a ($r = -0.83$; $p < 0.01$). Similarly the calculated pH_i values correlated significantly with $Paco_2$ ($r = -0.635$; $p < 0.001$) and pH_a ($r = 0.88$; $p < 0.001$; Fig. 3). There were no significant relationships between pH_a and pH gap or CO_2 gap. Arterial base excess correlated significantly with mCO_2 ($r = -0.35$; $p = 0.03$), pH_i ($r = 0.79$; $p < 0.0001$; Figs. 4 and 5), and pH gap ($r = -0.21$; $p < 0.001$). There was no significant relationship between base excess and CO_2 gap or CO_2 ratio.

Lactate levels were high at birth; the mean value at 3 h was 1.44 mM (95% CI, 1.16–1.72 mM), then decreased significantly ($p < 0.0001$). There was no significant relationship demonstrated between lactate and pH_i or mCO_2.

Birth weight and gestation were not significantly different among groups A, B, and C, although there was a nonsignificant trend toward lower gestation and birth weight in group C (Table 4). There was a significant trend toward an increased

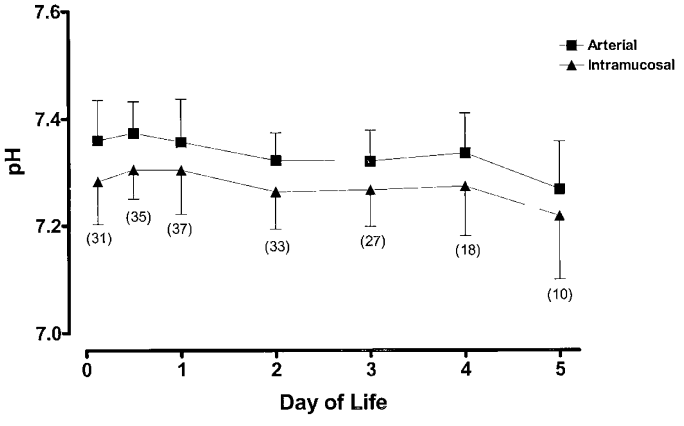

Figure 1. Changes in arterial and intramucosal pH. Mean values (±SD) for arterial and intramucosal pH at each time point during the first 5 d of life are presented; the number of subjects from which measurements were taken at each time point are presented in parentheses. pH_i values are significantly lower than pH_a values at each time point.

Table 3. *Mean values for measured and calculated variables in each individual subject*

Subject	CRIB	No. of measurements	pH_a	pH_i	Mucosal CO_2	Arterial CO_2	pH gap	CO_2 gap	CO_2 gap > 10 mm Hg	pH_i < 7.2 on more than one occasion	CO_2 ratio ≥ 1.29	Survival to discharge	GI complications
1	6	4	7.41	7.36	5.63	5.08	0.044	0.54	No	No	No	Yes	No
2	8	7	7.37	7.31	5.81	5.15	0.064	0.67	Yes	No	Yes	Yes	No
3	14	5	7.24	7.16	7.33	6.17	0.084	1.16	Yes	Yes	No	No	No
4	7	5	7.33	7.29	5.74	5.40	0.037	0.34	No	No	Yes	Yes	No
5	11	12	7.35	7.29	6.04	5.42	0.058	0.62	Yes	No	No	No	No
6	7	3	7.34	7.23	6.12	4.84	0.114	1.28	No	No	Yes	No	Yes
7	5	5	7.42	7.33	4.57	3.81	0.087	0.76	Yes	No	Yes	Yes	No
8	5	6	7.30	7.26	5.85	5.54	0.036	0.31	No	No	No	Yes	No
9	1	5	7.34	7.32	5.37	5.33	0.021	0.04	No	No	No	Yes	No
10	1	10	7.35	7.34	5.78	5.74	0.017	0.04	No	No	No	Yes	No
11	5	10	7.35	7.26	6.6	5.93	0.060	0.67	No	No	No	Yes	No
12	5	4	7.33	7.27	6.23	5.59	0.055	0.64	Yes	Yes	No	Yes	No
13	11	6	7.37	7.36	5.63	5.59	0.009	0.04	No	No	No	Yes	No
14	6	5	7.31	7.25	6.58	5.75	0.059	0.82	Yes	No	Yes	Yes	No
15	15	4	7.29	7.22	7.43	6.53	0.069	0.89	No	Yes	No	Yes	Yes
16	3	7	7.31	7.24	6.55	5.71	0.068	0.84	Yes	Yes	Yes	Yes	No
17	11	6	7.35	7.28	6.71	5.89	0.066	0.82	Yes	No	Yes	Yes	No
18	17	2	7.52	7.44	4.51	3.77	0.078	0.73	No	No	No	No	No
19	4	5	7.35	7.31	5.97	5.51	0.044	0.45	No	No	No	Yes	No
20	8	5	7.35	7.25	5.76	4.85	0.093	0.91	Yes	No	No	Yes	No
21	8	5	7.32	7.27	6.67	6.06	0.053	0.61	No	No	No	Yes	No
22	9	7	7.28	7.22	7.35	6.64	0.060	0.72	No	Yes	No	No	No
23	6	5	7.36	7.26	5.84	4.76	0.099	1.08	Yes	No	Yes	Yes	No
24	11	6	7.31	7.23	6.82	5.95	0.079	0.88	Yes	Yes	Yes	Yes	No
25	10	5	7.34	7.28	5.41	4.94	0.056	0.46	No	No	No	No	No
26	2	4	7.42	7.33	5.12	4.21	0.090	0.91	Yes	No	Yes	Yes	No
27	16	3	7.37	7.30	5.64	5.00	0.068	0.63	No	No	No	No	No
28	8	4	7.30	7.22	6.76	6.08	0.083	0.69	No	No	Yes	No	No
29	7	2	7.36	7.31	6.11	5.60	0.045	0.51	No	No	No	Yes	No
30	10	5	7.32	7.27	6.42	5.46	0.045	0.96	No	No	No	No	No
31	8	9	7.34	7.24	6.79	5.38	0.106	1.42	Yes	Yes	Yes	No	Yes
32	9	7	7.37	7.28	5.88	4.97	0.084	0.90	Yes	No	Yes	Yes	Yes
33	13	5	7.30	7.24	6.18	5.52	0.062	0.66	No	Yes	No	No	No
34	10	6	7.31	7.24	6.76	6.10	0.061	0.66	Yes	Yes	Yes	Yes	Yes
35	5	5	7.29	7.19	7.64	6.42	0.102	1.22	Yes	Yes	Yes	Yes	Yes
36	12	8	7.29	7.20	7.42	6.15	0.094	1.27	Yes	Yes	Yes	No	Yes
37	1	5	7.39	7.28	5.48	4.35	0.110	1.12	No	No	Yes	Yes	No
38	2	4	7.31	7.22	6.74	5.67	0.093	1.07	Yes	Yes	Yes	Yes	No

incidence of major GI complications in group C ($p = 0.038$, $df = 1, \chi^2 = 4.5$). There were no differences among groups in survival to discharge.

Eighteen infants had a CO_2 gap of >10mm Hg. There was a trend toward an increased incidence of GI complications in these infants (5 of 18) in comparison to those with a gap of <10mm Hg (1 of 20), but this did not achieve statistical significance ($p = 0.08$).

A CO_2 ratio of ≥1.29 was present in 18 infants, six of whom developed major GI complications; there were no GI complications in the 20 infants with a ratio of <1.29 ($p = 0.007$).

There were no statistically significant associations between low pH_i, a raised CO_2 gap, or CO_2 ratio and death.

DISCUSSION

There are few previous published data on gastric tonometry in the pediatric population, and there are none in preterm infants.

We have performed a total of 211 tonometry measurements in a population of 38 VLBW infants without complication. Measurement errors were minimized by having all measurements performed by a single operator. Saline CO_2 levels were highly reproducible with a CV of 5.6%. Problems relating to the instability of CO_2 in saline were minimized by immediate analysis of saline samples. The underestimation of saline CO_2 levels by standard blood gas analyzers (18) has been shown to be improved by the use of a phosphate-buffered solution (19). We elected to use a normal saline solution in the tonometry balloon as the blood gas analyzer used in this study (ABL 520) has been demonstrated to have the smallest bias in saline CO_2 measurement (18). That no measurement of pH_i was higher than concurrent pH_a suggests that there was little CO_2 diffusion before measurement in the blood gas analyzer. Errors may occur as a result of CO_2 being generated in the stomach by the neutralization of gastric acid by duodenal bicarbonate. This effect may be minimized by administration of H_2 receptor antagonists (20, 21) or by aspiration of gastric contents before performing tonometry measurements (22). In a population of critically ill patients, pH_i values were not affected by the use of ranitidine (23). In this study H_2 receptor antagonists were not

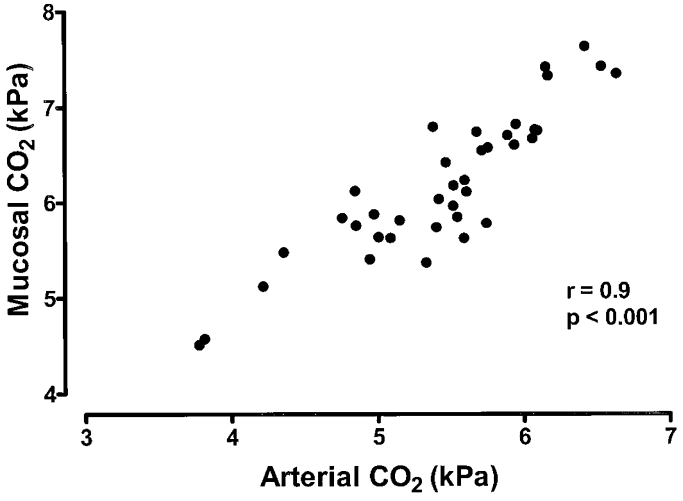

Figure 2. Correlation of arterial and mucosal CO_2. Mean values for arterial and mucosal CO_2 from all 38 subjects are plotted, demonstrating a highly significant correlation.

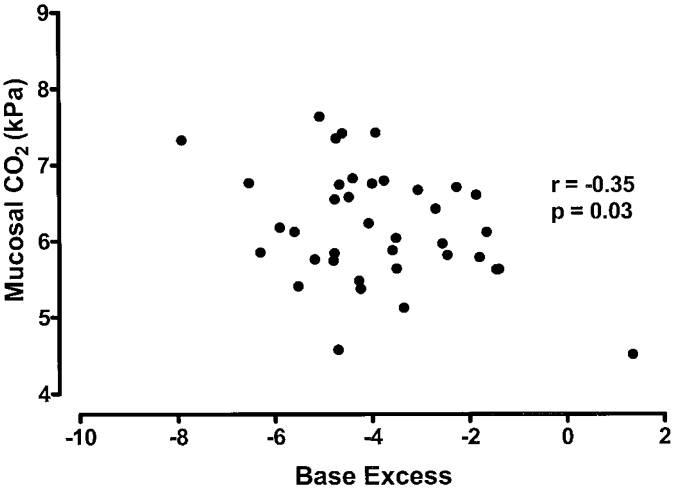

Figure 4. Correlation of arterial base excess and mucosal CO_2. Mean values for both variables from all 38 subjects are plotted against each other. A significant negative correlation is demonstrated.

routinely administered; however, nasogastric tubes were kept on free drainage and aspirated before the tonometry measurements. The removal of the arterial line coincided with the commencement of enteral nutrition in all but one infant, who received 0.5 mL/6 h expressed maternal milk for a 24-h period while being studied. None of these infants were receiving H_2 antagonists; premature infants demonstrate little unstimulated acid secretion, and acid-neutralization is unlikely to be a source of significant error. Theoretically tonometry measurements can be performed in infants being fed provided there is a sufficient time interval between feeds to allow for saline equilibration and all gastric contents are aspirated before study, but there are no published data in this population.

The time taken for CO_2 equilibration using saline tonometry may mask acute changes occurring in mCO_2 generation. This problem may be overcome using the technique of recirculating gas tonometry (24, 25), but currently suitable size 5F catheters are not available.

Using the total set of 211 measurements, we have established ranges for pH_i, pH gap, mCO_2, and CO_2 gap in this population of infants (Table 2). pH_i values have previously been reported in healthy children undergoing general anesthesia [mean $pH_i = 7.35 \pm 0.06$; (26)] and in a population of children with sepsis receiving intensive care [$pH_i = 7.32 \pm 0.18$ in nonsurvivors and 7.48 ± 0.07 in survivors; (27)]. The mean value reported in the present study ($pH_i = 7.27 \pm 0.078$) is lower than in these pediatric populations.

This difference is likely to be contributed to by the tight control of ventilation achieved by clinical protocols in older children, by increased buffering capacity in comparison with this preterm population, and by the severity of illness in the study population as indicated by high CRIB scores (Table 1).

In previous studies relationships have been found between pH_i and serum lactate (28, 29). In this study the high early lactate levels reflect the obstetric complications leading to preterm delivery. These elevated levels may not be attributable only to anaerobic glycolysis but also to direct effects of epinephrine on lactate metabolism in a stressed population (30,

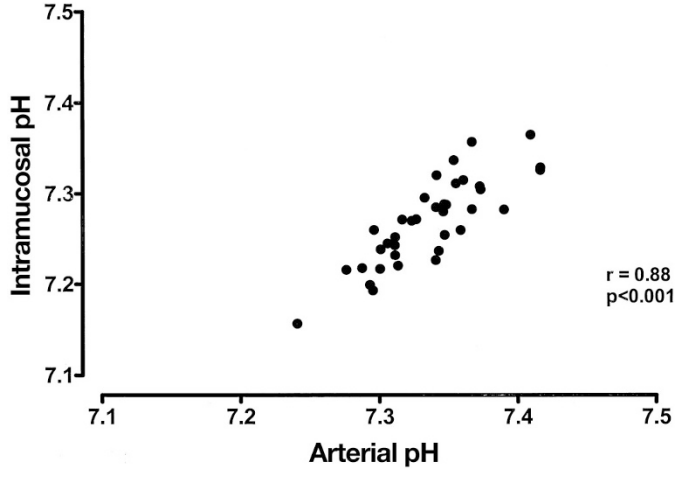

Figure 3. Correlation of arterial and intramucosal pH. Mean values for arterial and intramucosal pH from all 38 subjects are plotted, demonstrating a high degree of correlation.

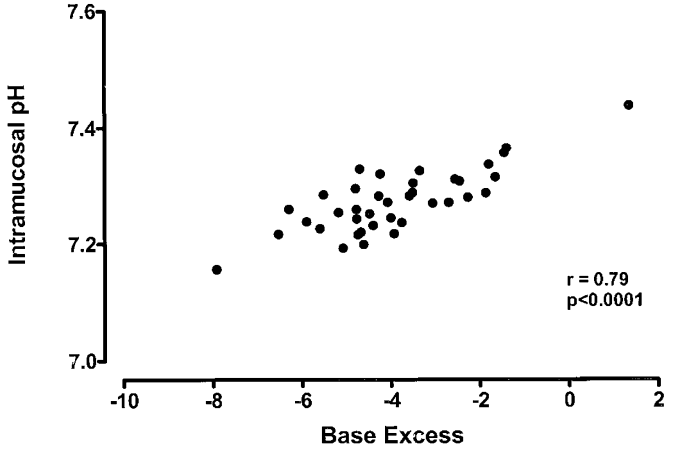

Figure 5. Correlation of arterial base excess and intramucosal pH. Mean values for both variables from all 38 subjects are plotted against each other. A highly significant correlation is demonstrated.

Table 4. *Classification of study infants according to lowest recorded pH_i measurement**

Variable	Group A ($n = 9$)	Group B ($n = 17$)	Group C ($n = 12$)	p Value
Birth weight median (range)	890 (460–1365)	892 (507–1337)	764 (507–1212)	NS
Gestation median (range)	26.29 (23.43–30.0)	26.86 (24.14–30.0)	25.71 (24.0–29.14)	NS
GI complications	0	2	4	0.038
Death	3	4	5	NS

* Group A, lowest $pH_i \geq 7.35$; group B, lowest $pH_i < 7.2$; group C, lowest $pH_i < 7.2$ on more than one occasion; groups A, B, and C are mutually exclusive.

31). The high lactate levels in the first 48 h may be masking an underlying relationship with pH_i. Unfortunately there are insufficient data beyond this time to explore associations satisfactorily.

The pH gap, CO_2 gap, and CO_2 ratio were all independent of pH_a. Calculated pH gap and CO_2 gap provide an indication of the adequacy of oxygenation at the mucosal level, widening gaps reflecting progressive imbalance in oxygen delivery and mucosal cell metabolism. The absence of significant relationships between these variables and systemic acid-base status demonstrate the ability of the technique of gastric tonometry to detect problems at the mucosal level that might not be suspected from routine measurements of arterial blood gases.

The potential clinical usefulness of tonometry in VLBW infants has been confirmed by recurrent low values of pH_i and a CO_2 ratio of ≥ 1.29 both being associated with major GI complications. The association between low pH_i and major GI complications has been previously reported in two term infants with hypoplastic left heart syndrome, who developed low levels of pH_i before the onset of NEC (32).

Changes in arterial CO_2 levels affect the small-caliber resistance vessels producing constriction and dilation in response to systemic hypocapnia or hypercapnia (33). In experimental animals, Guzman *et al.* (34) have shown that systemic hypocapnia results in ileal mucosal and serosal hypoperfusion. $Paco_2$ levels in the study population varied in response to episodes of acute respiratory deterioration. To adjust for these effects, we calculated CO_2 ratio ($mCO_2/Paco_2$), in a neonatal model. CO_2 ratio has been shown to increase with decreasing intestinal blood flow (10). A ratio of ≥ 1.29 was significantly associated with increased incidence of major GI complications ($p = 0.007$), with a sensitivity of 1.0 (95% CI, 0.54–1.0) and specificity of 0.625 (95% CI, 0.44–0.79) for identifying infants who had GI complications.

In contrast to reported adult (11, 29) and pediatric data (14–16, 27) from critically ill patients, we have not found statistically significant associations between death and recurrent low pH_i, CO_2 ratio of ≥ 1.29, and CO_2 gap of >10 mm Hg in this heterogeneous group of VLBW infants. A larger study would be required to confirm associations between these measurements and death in the newborn. If size 5F catheters for recirculating gas tonometry become available, the sensitivity and specificity of tonometry to predict adverse neonatal outcomes may increase.

Tonometry provides a simple, reproducible way of assessing mucosal metabolic status. This study provides data that suggest that pH_i is independently predictive of major GI complications in the neonatal intensive care unit setting. The extent of its usefulness in the research and clinical fields on its own or in combination with other techniques such as Doppler ultrasound needs further evaluation.

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