

Tonometry to estimate intestinal perfusion in newborn piglets

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Abstract

Aim—To determine the correlation between gastric intramucosal pH and superior mesenteric artery (SMA) flow in newborn piglets.

Methods—Fourteen newborn piglets were randomly assigned to either a control or to an epinephrine group which received 0, 1, 2, 4, 0 µg/kg/min of epinephrine for 60 minutes, each dose. Gastric tonometry was performed, SMA flow was measured, and intramucosal pH and the ratio of tonometer pCO₂ over arterial pCO₂ (rCO₂) were calculated.

Results—Intramucosal pH decreased over time in both groups, but tended to be lower in the epinephrine group. With increasing dose of epinephrine, SMA flow decreased; this in turn increased rCO₂ (p = 0.04) with a tendency to decrease intramucosal pH (p = 0.06).

Conclusions—Gastric tonometry may be useful in human neonates to evaluate gut ischaemia.

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Keywords: tonometry; ischemia; inotropes; bowel

Tonometry is a minimally invasive method of calculating intracellular pH in a hollow viscus.^{1–3} Intramucosal pH in the gastric mucosa can be estimated indirectly by measuring partial pressure of carbon dioxide (PCO₂) in the lining of the stomach with a silicone balloon catheter, and the arterial bicarbonate concentration. These two values are then substituted in the Henderson–Hasselbach equation:

$$pH_{im} = 6.1 + \log[HCO_3]/(PCO_2 \times 0.031).$$

For gastric tonometry, a modified gastric tube is inserted into the stomach with a silastic gas permeable balloon at the end into which 0.9% saline or phosphate buffered saline is instilled.^{4–7} After the buffer has equilibrated with the PCO₂ in the superficial mucosa it is analysed in a blood gas analyser.

Animal studies have shown that intramucosal pH falls in response to haemorrhagic shock^{8–11} and in mechanically induced gut ischaemia.^{12–14} In clinical practice, the presence of an abnormally low gastric intramucosal pH has been correlated with increased mortality in both critically ill adults^{15–17} and in children with septic shock.¹⁸ A low gastric intramucosal pH is a relatively frequent postoperative finding in patients who have undergone heart surgery.¹⁹

Mesenteric ischaemia is one of the factors implicated in the pathogenesis of necrotising

enterocolitis. This has an incidence of 1.3 to 2.4 per 1000 live births with a reported prevalence of up to 10% in very low birthweight infants.²⁰ Epinephrine is frequently used to treat hypotension in neonates; high doses reduce superior mesenteric artery (SMA) blood flow in newborn piglets.^{21–22} It is not known whether gastric tonometry correlates with mesenteric perfusion in newborn infants receiving epinephrine.

The objectives of this pilot study were to investigate whether increasing amounts of epinephrine reduce SMA flow, inducing a fall in gastric intramucosal pH and a rise in rCO₂, and whether tonometry is a useful tool for estimating intestinal perfusion changes in the newborn piglet.

Methods

Fourteen 1–3 day old piglets (Camborough/Canabreed) who had been fasted for a minimum of 4 hours were randomly assigned to one of two groups. After 45 minutes of stabilisation the control group was studied for 4 hours while kept anaesthetised. The study group similarly stabilised and received a stepwise increasing infusion of 1, 2, and 4 mcg/kg/min of epinephrine for 60 minutes for each dose, followed by 60 minutes of regular maintenance fluid without epinephrine. Both groups received 20 ml/kg/hour of 0.9% saline/5% dextrose as maintenance solution.

Under general anaesthesia with halothane, a double lumen catheter was placed in the external jugular vein through a midline neck incision, while a single lumen catheter was inserted into the carotid artery. After tracheotomy and placement of an endotracheal tube, assisted ventilation was started. Animals were ventilated (Health Dyne 105 Ventilator) with room air at pressures and rates to maintain normal arterial PCO₂ between 35 and 45 mm Hg and arterial pH between 7.30 and 7.45.

Halothane was then discontinued, boluses of ace promazine (0.2 mg/kg) and fentanyl (10 µg/kg) were administered followed by a continuous fentanyl infusion (10 µg/kg/hour). Paralysis was maintained using pancuronium bromide (0.2 mg/kg initially followed by 0.1 mg/kg every 60 minutes). To inhibit gastric acid production, a loading dose of ranitidine (1 mg/kg) was administered, followed by a continuous infusion (0.125 mg/kg/hour).

The aorta was exposed retroperitoneally by a left flank incision and the SMA was identified. A 3 mm extraluminal flow probe (Transonic Systems Inc., Ithaca, NY, USA) was gently placed around the SMA. After inserting the probe the incision was closed and good signals

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of flow measurement were ensured. SMA flow, mean arterial blood pressure, heart rate and pulse oximetry oxygen saturation were continuously monitored, and the analog outputs were digitised and stored on hard disc. Fifteen minute segments of the digitised data recordings at the end of each 60 minute period were analysed and averaged.

The animals were then left to stabilise for 45 minutes before baseline recordings were made. Stability was defined as variability of 10% or less for blood pressure and heart rate, oxygen saturations > 90%, pH between 7.30 and 7.45, and PaCO₂ between 35 and 45 mm Hg. A tonometer catheter (TRIP 7F Sigmoid, Tonometrics Inc, Worchester, MA) was inserted into the stomach. The balloon was instilled with 2.5 ml of a phosphate buffered saline solution and left to equilibrate for 60 minutes. Sampling was performed according to the manufacturer's recommendations and PaCO₂ was measured in a standard blood gas analyser. Samples were removed before each change of epinephrine dose; each new sample had been allowed to equilibrate for 60 minutes. Epinephrine was administered using high precision intravenous pumps at 1 µg/kg/min between 0 and 60 minutes, 2 µg/kg/min between 60 and 120 minutes, 4 µg/kg/min between 120 and 180 minutes and was discontinued between 180 and 240 minutes. Blood and tonometry samples were collected at baseline and at the end of every 60 minutes. Blood samples were analysed for arterial blood gases, electrolytes, glucose and lactate. For lactate analysis, blood was collected on ice, plasma was separated, and stored immediately at -80°C. Lactate was measured using an enzymatic-spectrophotometric method (Sigma Diagnostic, St Louis, MO, USA), as described before (Sigma Diagnostics) and our laboratory achieved a linearity of $r = 0.99$ at 0 to 13.3 mM/l of lactate in calibration and a test-retest stability of 0.99.²¹

Animals were killed at the end of the study with sodium pentobarbital (30 mg/kg). No animals died during the 4 hour recording.

Approval of the Health Sciences Animal Welfare Committee of the University of Alberta was obtained for all procedures, according to the guidelines of the Canadian Council of Animal Care.

All values are expressed as mean and standard deviation. Using ANOVA, assuming a 50% difference in SMA flow between groups receiving 4 µg/kg/min of epinephrine,²² and assuming a standard deviation of 15, a minimum sample size of seven for each group would be needed to reach a power of 80% with an α value of 0.05 (Sigmastat 1.0 for Windows, Jandel Scientific, San Rafael, CA, USA). Differences within each group were analysed using one way repeated measures analysis of variance, between groups using two way analysis of variance, and for multiple comparisons the Student Newman-Keuls test was used. When the normality or equal variance test failed, a Kruskal-Wallis one way ANOVA on ranks was used: $p < 0.05$ was considered significant.

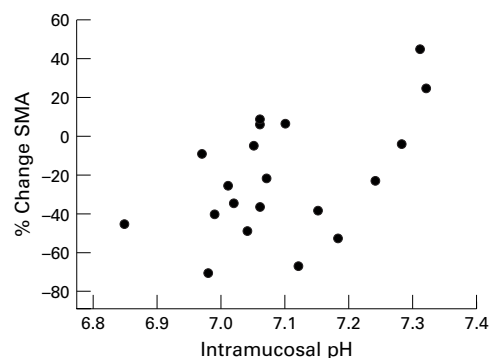


Figure 1 In the epinephrine group gastric intramucosal pH decreased with decreasing SMA flow ($p=0.065$). SMA flow is expressed as % change from baseline. For the epinephrine group: 0, 60, 120, 180 and 240 minutes represent 0, 1, 2, 4, and 0 µg/kg/min epinephrine, respectively.

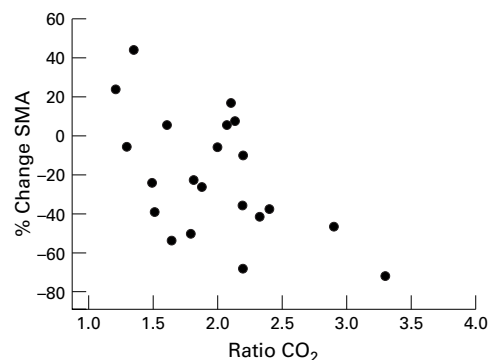


Figure 2 In the epinephrine group, rCO₂ increased with decreasing SMA flow ($p=0.04$). SMA flow is expressed as % change from baseline. For the epinephrine group: 0, 60, 120, 180 and 240 minutes represent 0, 1, 2, 4, and 0 µg/kg/min epinephrine, respectively.

Intramucosal pH and the ratios of pCO₂ in tonometer over arterial blood (rCO₂) were calculated as follows:

$$\text{pHim} = 6.1 + \log \frac{[\text{HCO}_3]}{\text{P}_t\text{CO}_2 \times 0.031}$$

$$\text{rCO}_2 = \text{P}_t\text{CO}_2 / \text{PaCO}_2$$

where [HCO₃] is arterial bicarbonate concentration, P_tCO₂ is tonometer partial pressure of carbon dioxide, PaCO₂ is arterial partial pressure of carbon dioxide and 0.031 solubility of carbon dioxide in plasma.

Repeated measures regression analysis was used to investigate the association between the continuous variable SMA% (percentage change from baseline for superior mesenteric artery flow during epinephrine infusion) with each of the continuous variables rCO₂ and intramucosal pH. Repeated measures regression was implemented by using the generalised linear mixed model (GLMM), as outlined in *SAS System for Mixed Models 1996* (SAS Institute Inc., Cary, NC, USA). This approach allows for a regression model to be specified while adjusting for the correlated model error terms induced by repeated measurements. To ensure valid inference on model parameters it is important to choose a covariance structure that adequately reflects the

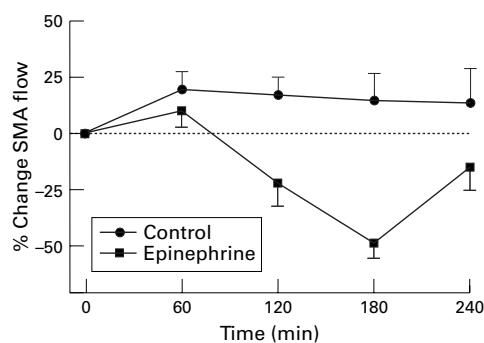


Figure 3 SMA flow did not change over time in the control group. SMA flow decreased significantly at 2 and 4 $\mu\text{g}/\text{kg}/\text{min}$ of epinephrine (120 and 180 minutes) and tended to return to baseline 60 minutes after discontinuing the epinephrine infusion (240 minutes) (mean \pm standard error bars are shown).

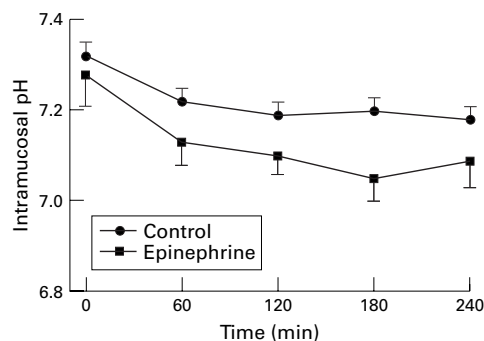


Figure 4 Gastric intramucosal pH decreased between 0 and 60 minutes, after which there was no further drop in intramucosal pH. Although the study group has a lower intramucosal pH than control animals at all times, significance at the respective time intervals was not reached (mean \pm standard error bars are shown). For epinephrine group: 0, 60, 120, 180 and 240 minutes represent 0, 1, 2, 4 and 0 $\mu\text{g}/\text{kg}/\text{min}$ epinephrine, respectively.

structure of the data and the conditions under which the repeated measures were obtained. In our data the levels of the fixed within subjects factor epinephrine were not equally spaced (1, 2, and 4 $\mu\text{g}/\text{kg}/\text{min}$). Furthermore, the amounts of epinephrine were not randomly assigned on the occasions when the observations were made. Together this information suggested that a spatial exponential covariance structure of the model errors would be appropriate. Other suitable covariance structures were also used, but the spatial exponential covariance structure resulted in the best fit regression model. Figures 1 and 2 were used to determine the functional form of the regression equations. It was felt that linear regression would adequately describe the data and hence two linear regression models were fitted to the data. The first model specified both SMA% and an

epinephrine factor (representing the doses) as the dependent variables and intramucosal pH as the independent variable. The second model was the same, except that $r\text{CO}_2$ replaced intramucosal pH as the independent variable. Note that the between subjects effect (piglet effect) is a random effect the variability of which is accounted for by the covariance structure. For both regression models no significant interaction existed between SMA% and the epinephrine factor (assuming a level of significance of 0.05). This implies that the effect of SMA% on either dependent variable remained constant whatever the epinephrine dose.

Results

Body weights were similar in the control ($n = 7$; mean (SD) 1646 (122) g) and in the epinephrine group ($n = 7$; mean (SD) 1569 (253) g). Blood pressure, heart rate, blood gases, serum electrolytes and glucose remained within normal values and did not differ between the two groups at any time. Baseline SMA flows were similar in both groups. In the control group, SMA flow did not change significantly from baseline throughout the experiment. In the epinephrine group SMA flow decreased progressively with increasing doses of epinephrine in a dose dependent manner, resulting in a 21 and 48% decrease from baseline at 2 and 4 $\mu\text{g}/\text{kg}/\text{min}$, respectively (table 1) (fig 3). Compared with the control group, the epinephrine group had significantly lower SMA flows at 2 and 4 $\mu\text{g}/\text{kg}/\text{min}$ of epinephrine (table 1) (fig 3). Sixty minutes after epinephrine had been discontinued, SMA flow in the epinephrine group was no longer significantly different from that of the control group or from baseline (table 1) (fig 3). Both arterial pH and base excess remained stable in both control and study groups, but intramucosal pH decreased from baseline in both groups. Although there was a trend towards lower intramucosal pH for each dose in the epinephrine group compared with that in the control group, this was not significant (table 1) (fig 4). The ratio of tonometer over arterial PCO_2 ($r\text{CO}_2$) did not change during the study in the control group, but increased above baseline values in the epinephrine group. At the highest dose of epinephrine, 4 $\mu\text{g}/\text{kg}/\text{min}$, $r\text{CO}_2$ and serum lactate were significantly higher than in the control group and than baseline (table 1). In the control group lactate concentrations were lower at 120 and 240 minutes than at baseline (table 1). A positive association was found between percentage change in SMA flow from baseline and intramucosal pH

Table 1 Mean (SD) SMA flow, gastric intramucosal pH, $r\text{CO}_2$, serum lactate

Time (min)	% change in SMA flow		Gastric intramucosal pH		$r\text{CO}_2$		Lactate (mM/l)	
	Controls	Epinephrine	Controls	Epinephrine	Controls	Epinephrine	Controls	Epinephrine
0	0	0 ^a	7.32 (0.06) ^a	7.28 (0.17) ^a	1.36 (0.35)	1.26 (0.24) ^a	3.71 (1.5) ^a	3.46 (1.1) ^a
60	20.3 (18.7)	10.5 (17.6) ^a	7.22 (0.07) ^b	7.13 (0.12) ^b	1.64 (0.53)	1.82 (0.39) ^b	3.36 (2.0) ^a	4.39 (1.2) ^b
120	17.9 (19.1)*	-21.5 (25.2) ^{bc}	7.19 (0.08) ^b	7.10 (0.11) ^b	1.71 (0.27)	1.88 (0.38) ^b	2.83 (1.4) ^b	4.97 (1.4) ^b
180	15.8 (27.9)*	-47.7 (16.7) ^c	7.20 (0.06) ^b	7.05 (0.13) ^b	1.66 (0.16)*	2.22 (0.49) ^b	2.13 (1.2) ^b	5.49 (1.6) ^{bc}
240	14.7 (38.8)	-14.8 (24.2) ^{ab}	7.18 (0.07) ^b	7.09 (0.16) ^b	1.71 (0.32)	2.15 (0.72) ^b	2.17 (1.6) ^b	5.09 (1.6) ^{bc}

SMA: superior mesenteric artery; $r\text{CO}_2$: ratio of PCO_2 in tonometer over PCO_2 in arterial blood; * $p < 0.05$ v controls

^{a,b,c}: numbers with different superscript are significantly different within the same column

($p = 0.06$; SMA% coefficient 0.019; SE 0.009) (fig 1). Although this was not significant at the 5% level, it suggests an association. There was a significant negative association between percentage change in SMA flow from baseline and $r\text{CO}_2$ ($p = 0.04$; SMA coefficient -0.01 ; SE 0.0044) (fig 2). Both regression models fit the data adequately as indicated by Akaike's Information Criterion, Schwarz's Bayesian Criterion, and Residual Log Likelihood values.

Discussion

Tonometry can show a fall in intramucosal pH during haemorrhagic shock,⁸⁻¹¹ in bowel ischaemia,¹²⁻¹⁴ and the presence of low intramucosal pH correlated with increased mortality.¹⁵⁻¹⁸ In neonates undergoing corrective cardiovascular surgery for left heart obstructive anomalies, a decrease in gastric intramucosal pH was shown, supporting an association between intestinal blood flow and gastric intramucosal pH.²³

In this pilot study we investigated the value of gastric tonometry in a newborn animal model. This model is known to develop splanchnic vasoconstriction at high epinephrine doses²² which might allow us to determine whether changes in SMA blood flow can be used to predict gastric intramucosal pH, and vice versa. Our preliminary data confirm that SMA flow decreases with increasing epinephrine dose,^{21, 22} returning to baseline values once epinephrine has been discontinued. However, inaccuracies in estimating intramucosal pH from gastric pH can arise through back diffusion of acid and/or production of CO_2 from neutralising gastric acid by duodenal bicarbonate. By administering ranitidine, an H_2 -receptor blocker, we should have minimised this effect.^{24, 25}

After an initial drop within 60 minutes, gastric intramucosal pH was not significantly altered in either the control or epinephrine group. The fact that intramucosal pH dropped from baseline in both groups may have been the consequence of the surgical manipulation for line insertion and tracheostomy, or, more likely, it may have been the result of manipulating the SMA flow itself during flow probe placement. The fact that there was no significant change in SMA flow from baseline in the control group supports the fact that the haemodynamics of these animals remained stable during the 4 hour study. Moreover, arterial pH, base excess, blood pressure, and oxygen saturations did not alter in either group for the duration of the entire study. Although there was a modest dose dependent decrease in intramucosal pH with epinephrine infusion, we could not show a difference between the groups for the respective epinephrine doses. It has been shown that intramucosal pH only falls significantly when SMA flow is reduced to less than 60% of baseline flow,¹⁵ which is about the level of SMA flow reduction the animals receiving 4 $\mu\text{g}/\text{kg}/\text{min}$ of epinephrine experienced. The three animals whose SMA flows dropped by more than 50% had the largest drop in intramucosal pH—0.3 or more. $r\text{CO}_2$ increased with decreasing SMA blood flow (p

$= 0.04$), and intramucosal pH tended to decrease with decreasing SMA flow ($p = 0.06$). However, the large scatter and small sample size would preclude us from accurately predicting intramucosal pH and/or $r\text{CO}_2$ from SMA flow measurements. Furthermore, we used very high doses of epinephrine at 2 and 4 $\mu\text{g}/\text{kg}/\text{min}$ to obtain circulatory and pH effects in the gastrointestinal system. Therefore, the usefulness of this technology remains to be established in preterm infants who probably experience much smaller changes in blood flow redistribution.

In adults intramucosal pH monitoring has been used to influence the timing of weaning from artificial ventilation and the introduction of enteral feeding.^{26, 27} A significant fall in gastric intramucosal pH in association with maximal ventilatory weaning, presumably due to diversion of blood away from the intestine to the respiratory muscle system, has been reported.²⁶ Similarly, introduction of enteral feeding has been associated with a drop in intramucosal pH, probably as a result of the regional intestinal perfusion not being able to maintain enough blood flow to satisfy the metabolic demands of the bowel in response to feeds.²⁷ Whereas the studies in adults investigated treatment effects on groups, individual predictability was of limited value. In preterm infants changes in mesenteric blood flow have been associated with the development of necrotising enterocolitis.²⁸ While the role of tonometry in the critically ill neonate remains to be proved, the application may provide information supplementing the clinical management of necrotising enterocolitis or bowel ischaemia, even in the presence of normal haemodynamic and biochemical data.

Serum lactate concentrations decreased over time in the control group. Starting values are within the range of previously reported values for piglets,²² and the fact that values further decreased with time supports that our animals were not hypoxic or hypotensive. The fact that lactate increased with increasing epinephrine doses does not necessarily indicate increased lactate production due to peripheral tissue hypoxia and anaerobic respiration, but may merely reflect β -adrenoceptor stimulation at low doses of epinephrine infusion.²⁶ Furthermore, high doses of epinephrine infusion may result in impaired hepatic use of lactate due to decreased hepatic perfusion, and/or enzymatic inhibition due to α -stimulation.^{29, 30}

In conclusion, our pilot study shows that in newborn piglets, using epinephrine as a pharmacological means of decreasing the SMA flow, intramucosal pH decreases and $r\text{CO}_2$ increases with decreasing SMA flow. Although gastric tonometry may be useful to sequentially monitor intramucosal pH, $r\text{CO}_2$, and splanchnic perfusion within the individual patient, normal reference group values need to be generated in larger groups of infants, and preferably of different gestational and postnatal ages.

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