Effect of ranitidine on basal and bicarbonate enhanced intragastric PCO_2 : a tonometric study

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Abstract

A high intragastric PCO_2 (iPCO_2), determined tonometrically, is the main factor participating in a low gastric intramucosal pH (pHi) and may point to gastric mucosal ischaemia. iPCO_2 might also increase, however, after buffering of gastric acid by bicarbonate; the magnitude of this effect and the efficacy of H_2 blockers to prevent it are unclear. Ten healthy volunteers (20-24 years) were studied at baseline and after oral ingestion of 500 mg sodium bicarbonate. The same test was carried out one hour after intravenous injection of 100 mg ranitidine. A glass pH electrode for continuous gastric juice pH measurements and a Tonomitor catheter were placed 10 cm distally from the gastro-oesophageal junction. iPCO_2 was measured in saline boluses, infused at 30 minute intervals in the balloon at the tip of the Tonomitor. Before ranitidine was given, basal iPCO_2 (mean (SD)) was 8.40 (2.53) kPa, and increased to 19.20 (5.87) kPa after sodium bicarbonate ($p < 0.001$). After ranitidine, the gastric juice pH increased from 1.8 (0.9) to 5.6 (1.3) ($p < 0.05$), while basal iPCO_2 was 5.60 (0.67) kPa ($p < 0.01$) and did not change after sodium bicarbonate (6.27 (2.27 kPa)). iPCO_2 values after acid secretion suppression were similar to those in capillary blood (5.60 (0.40 kPa)). The difference between intragastric and blood PCO_2 during normal acid secretion probably results from buffering of gastric acid by gastric bicarbonate, rather than by duodenogastric reflux or saliva entering the stomach. During acid secretion suppression, intragastric equals blood PCO_2 , even after oral ingestion of sodium bicarbonate. Hence, acid secretion inhibition is mandatory for proper assessment of iPCO_2 and pHi as specific measures of the adequacy of gastric mucosal blood flow.

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A high intraluminal PCO_2 (iPCO_2) in the gastrointestinal tract, as determined tonometrically, is the main factor participating in a lowered gut intramucosal pH (pHi) and may point to gastrointestinal mucosal ischaemia, as shown in animals studies.¹⁻⁴ Tonometric measurement of iPCO_2 and calculation of pHi in the stomach proved useful in predicting bleeding from gastric stress ulcers,⁵ development of multiple organ failure,⁶ and mortality^{7,8} in critically ill patients. In this last

group of patients, treatment aimed at a rise in pHi may even improve outcome.⁹

The relation, however, between a high iPCO_2 and mucosal ischaemia in the stomach might be invalidated if carbon dioxide is produced intraluminally after buffering of gastric acid by salivary, duodenal or gastric bicarbonate.¹⁰ Hence, suppression of acid secretion by H_2 receptor blockers has been advocated for proper measurement of iPCO_2 and pHi .¹⁰ The magnitude, however, of the buffering effect on iPCO_2 and the efficacy of H_2 blockers to prevent it are unclear. This uncertainty and the fear that H_2 blockade in critically ill patients increases the risk for nosocomial infection^{11,12} probably explains why in some studies gastric tonometry was performed in the absence of acid secretion inhibition.^{5,7,13} An unpaired study in healthy volunteers suggested that iPCO_2 is lower after administration of the H_2 blocker ranitidine compared with that in untreated subjects.¹⁴ The mechanisms causing this difference remained unclear, because measurement of gastric juice pH, necessary to detect alkaline duodenogastric reflux or salivary bicarbonate entering the stomach, was not performed.

We therefore studied 10 healthy volunteers and measured gastric juice pH and iPCO_2 before and after ranitidine, and before and after oral ingestion of a physiological dose of sodium bicarbonate, to simulate buffering of alkali entering the stomach from duodenum or saliva.

Patients and methods

We studied 10 healthy volunteers, 20-24 years of age, who were not receiving any treatment. The pH of the gastric fluid was measured continuously, using a combined glass electrode with integral Ag/AgCl reference electrode near the tip (Ingold 440, Ingold Messtechnik, Urdorf, Switzerland). Before introduction, the electrode was calibrated at pH 4.0 and 7.0, and this was repeated after withdrawal. The electrode was connected to a receiver, storing the mean pH for every six second period. These data were stored in a hospital developed microcomputer system for pH analysis.¹⁵ The electrode was introduced through the nose and advanced under direct pH measurement until the tip was 10 cm below the gastro-oesophageal junction, identified by an abrupt pH decrease as the probe entered the stomach.

A Tonomitor (Tonometrics Inc, Bethesda, Maryland, USA), sigmoid model, consisting of a silastic, CO_2 impermeable nasogastric tube with a silicone CO_2 permeable balloon at the tip, was placed nasogastrically at the same

distance from the nose as the pH electrode. Measurement of $i\text{PCO}_2$ was performed by aspirating 2.5 ml saline, installed in the balloon for exactly 30 minutes, using a standard blood gas analyser (Corning 178, Ciba-Corning, Houten, The Netherlands). The samples were analysed within fifteen minutes after aspiration. Because complete equilibration of CO_2 in the Tonomitor and surrounding fluid takes about one hour, a correction factor has to be applied. Using different fluids and PCO_2 values the correction factor for 30 minutes equilibration was shown to be 1.29.¹⁶ In the midgut of dogs this correction factor proved valid.¹⁶ Thus, $i\text{PCO}_2 = 1.29 \times \text{measured } \text{PCO}_2$. A capillary blood sample from a finger was used to determine the actual bicarbonate content and PCO_2 , using the blood gas analyser. Gastric intramucosal pH was calculated according to the Henderson-Hasselbalch equation, using $i\text{PCO}_2$ (in mm Hg) and the bicarbonate content of the capillary blood: $\text{pH} = 6.1 + \log (\text{bicarbonate} / (0.04 \times i\text{PCO}_2))$. The validity of this calculation was established in animal models using submucosally tunnelled pH electrodes.^{4 10} The coefficient of variation for three successive measurements of intragastric PCO_2 is 1.12 (0.8)%, according to published works.¹⁷

Sodium bicarbonate 500 mg was dissolved in 50 ml water. The volunteers drank the solution in 10 minutes while in the left supine position to prevent immediate passage through the pylorus.

PROTOCOL

The protocol was approved by the hospital committee on ethics. After introduction of the pH probe and the Tonomitor ($t=0$ minutes) we measured $i\text{PCO}_2$ from 0 to 30 minutes (period I), and took a capillary blood sample at $t=20$ minutes. In some pilot experiments

introduction of the pH probe and Tonomitor led to abdominal discomfort and, thus, possibly duodenogastric reflux. Therefore, we chose to measure basal $i\text{PCO}_2$ from 60 to 90 minutes (period II); a capillary blood sample was obtained at $t=80$ minutes. From 90 to 100 minutes the sodium bicarbonate solution was slowly swallowed. To determine the immediate effects of this buffer we measured $i\text{PCO}_2$ from 90 to 120 minutes (period III), for late effects we measured from 120 to 150 minutes (period IV). Then, at $t=150$ minutes, 100 mg of ranitidine was given intravenously. This dose sufficiently suppresses acid secretion within one hour, and this lasts for at least four hours.¹⁸ From 210 to 240 minutes (period V) we measured basal $i\text{PCO}_2$ during acid secretion suppression and took a capillary blood sample at $t=230$ minutes. From 240 to 250 minutes sodium bicarbonate was ingested with measurement of $i\text{PCO}_2$ from 240 to 270 minutes and from 270 to 300 minutes (periods VI and VII).

For calculation of pHi the bicarbonate content in blood taken at $t=20$ for period I, at $t=80$ for periods II, III, and IV, and $t=230$ for periods V, VI, and VII was used. We chose not to draw blood samples for all study periods because it can be calculated that the maximal rise in blood bicarbonate after oral ingestion of 500 mg of sodium bicarbonate, approximately 0.2 mmol/l, would not exceed the error of its measurement.

We calculated mean, maximum, and minimum pH for every 30 minute period, time matched with measurement of $i\text{PCO}_2$. We calculated duration and magnitude of alkaline shifts, defined as a gastric juice pH profile >4.0 , during period I and II.^{19 20} For graphic presentation, we calculated the mean (SD) pH for 90 second periods.

STATISTICAL ANALYSIS

The analysis of variance was used to test for period differences. Thereafter, differences between periods were examined with the paired Student's t test. To examine relations, linear regression analysis was used. A $p<0.05$ was considered statistically significant. Data were expressed as mean (SD).

Results

GASTRIC JUICE pH

The gastric juice pH (Fig 1) differed between periods ($p<0.001$). Between period I and II, however, no difference in mean gastric juice pH (1.8 (0.7), and 1.8 (0.9), respectively, $p>0.05$), in maximum pH (2.97 (1.0) and 2.79 (1.5), $p>0.05$), or in time of $\text{pH}>4.0$ (0.3 (0.9) and 1.2 (2.7) minutes, respectively) was found. Ingestion of sodium bicarbonate increased gastric juice pH to 3.5 (2.4) in period III ($p<0.05$ v II) with a maximum pH of 5.2 (1.6); the mean duration of gastric juice $\text{pH}>4$ was 12 (10) minutes.

After ranitidine was given, gastric juice pH in period V was 5.6 (1.3) ($p<0.001$ v period

Figure 1: Mean (SD) of the mean of 90 second gastric juice pH values of individual volunteers ($n=10$). Period I, II, and V: basal (fasting) period, period III and VI: during oral ingestion of 500 mg sodium bicarbonate, period IV and VII: after ingestion of sodium bicarbonate. The gap between period I and II was used to obtain an optimal steady state situation after introduction of the pH electrode and Tonomitor. Immediately after period IV, ranitidine was given, and 60 minutes was taken for effective acid secretion suppression. $\uparrow$ B: sodium bicarbonate, $\uparrow$ R: 100 mg ranitidine given intravenously.

Figure 2: Values of tonometrically determined iPCO₂ during the study in individual volunteers (n=10). Period I, II, and V: basal (fasting) period, period III and VI: during oral ingestion of 500 mg sodium bicarbonate, period IV and VII: after ingestion of sodium bicarbonate. ↑B: oral ingestion of 500 mg sodium bicarbonate, ↑R: 100 mg ranitidine given intravenously.

II); the minimum pH was <4.0 in 4 of 10 volunteers. After ingestion of sodium bicarbonate, the gastric juice pH in period VI increased to 7.1 (0.7) (p<0.005 v period V); in all volunteers the minimum pH was >4.0. In period VII the gastric juice pH was 6.7 (0.7) (p<0.05 compared with period VI, p<0.01 compared with period V); in 2 of 10 volunteers the minimum pH decreased below 4.0.

iPCO₂
iPCO₂ differed (p<0.001) between periods (Fig 2). Before ranitidine, during period II, basal iPCO₂ was 8.40 (2.53) and rose to 19.20 (5.87) kPa in period III after oral sodium bicarbonate (p<0.001). This increase in iPCO₂ was shortlived, with a iPCO₂ of 10.00 (1.71) kPa in period IV (p<0.001 compared with period III, p<0.05 compared with period II). After inhibition of acid secretion, basal iPCO₂ in period V was 5.60 (0.67) kPa (p<0.005 compared with II), and 6.00 (2.27) kPa in period VI during ingestion of sodium bicarbonate (p.0.05 v V). In this period, the two volunteers with the lowest gastric juice pH immediately before sodium bicarbonate was given, 3.6 and 4.6, showed the highest iPCO₂ of 3.87 and 4.53 kPa, respectively. After the sodium bicarbonate, in period VII, iPCO₂ was 6.55 (0.85) kPa (p>0.05 compared with period V).

BLOOD
Blood pH, PCO₂, and bicarbonate content did not change during the study period (Table). Before ranitidine was given, a significant

difference between intragastric and blood PCO₂ was found (Fig 3), under basal circumstances (period II) of 2.81 (2.28) kPa (p<0.01), rising to 13.49 (5.75) kPa after sodium bicarbonate ingestion in period III (p<0.001). After ranitidine, the basal iPCO₂ in period V and the iPCO₂ during sodium bicarbonate ingestion in period VI were similar to blood PCO₂ (differing by 0.07 (0.81) and 0.45 (2.77) kPa, respectively, p>0.05). In period VII, during which gastric acid secretion recurred in some subjects, a small, but significant difference between intragastric and blood PCO₂ (0.83 (0.95) kPa, p<0.05) was again noticed, however.

pHi
Before ranitidine, basal pHi was 7.24 (0.13) decreasing to 6.89 (0.15) during sodium bicarbonate ingestion in period III (p<0.001). After ranitidine was given in period V, basal pHi was 7.41 (0.06), higher than pHi before acid secretion suppression in period II (p<0.005), and 7.39 (0.21) during sodium bicarbonate ingestion in period VI (p.0.05 compared with period V). As blood bicarbonate content was constant during the study, calculated pHi inversely followed changes in iPCO₂ (Fig 4).

iPCO₂ IN RELATION TO GASTRIC JUICE pH
To further delineate the mechanisms underlying the difference in basal iPCO₂ before and after ranitidine we calculated the correlation coefficient between iPCO₂ and mean gastric juice pH, duration, and area under the curve of alkaline shifts, and peak pH in periods I and II. No correlation between iPCO₂ and any of these parameters was found, suggesting that basal iPCO₂ is not affected by bicarbonate from duodenum or oesophagus periodically entering the stomach.

Discussion
Our study in healthy volunteers shows that proper tonometric assessment of iPCO₂, as an index of the adequacy of gastric mucosal blood flow, warrants suppression of acid secretion. After ranitidine, iPCO₂ was similar to blood PCO₂, even during ingestion of 500 mg sodium bicarbonate, mimicking reflux of the bicarbonate produced by the duodenum per hour. Because healthy volunteers have adequate gastric mucosal blood flow, even after acid secretion suppression,²¹ the PCO₂ in the gastric mucosa roughly equals blood PCO₂. Thus, for gastric tonometry, an increased iPCO₂, or decreased pHi, would be a valid indicator of mucosal ischaemia, for instance after haemorrhage, sepsis, and arterial occlusion,^{1-4 22} only if acid secretion is suppressed. The source of intraluminal hypercapnia during hypoperfusion is an increased organ CO₂ content because blood flow is insufficient to remove all produced CO₂.²³⁻²⁵ In addition, in ischaemic cells an excess of hydrogen ions is produced because ATP hydrolysis exceeds ATP synthesis²⁶; buffering

Capillary blood gas analysis in 10 healthy volunteers (mean (SD))

	t=20 (period I)	t=80 (period II)	t=230 (period V)
pH	7.40 (0.002)	7.40 (0.01)	7.40 (0.02)
PCO ₂ (kPa)	41.9 (2.4)	42.9 (2.6)	42.9 (3.7)
PO ₂ (kPa)	69.0 (8.0)	65.4 (5.3)	67.7 (8.8)
HCO ₃ (mmol/l)	26.0 (1.7)	25.9 (1.0)	25.6 (1.0)

Figure 3: Difference between $iPCO_2$ and capillary blood PCO_2 (kPa); values expressed as mean (SD) ($n=10$). Period I, II, and V: basal values, period III and VI during oral ingestion of 500 mg sodium bicarbonate, and period IV and VII immediately after ingestion of oral sodium bicarbonate. Periods I–IV before 100 mg ranitidine given intravenously, period V–VII after ranitidine was given $\uparrow B$: oral ingestion of 500 mg sodium bicarbonate, $\uparrow R$: 100 mg ranitidine given intravenously.

of these hydrogen ions results in increased production of CO_2 . As CO_2 readily diffuses across the gastrointestinal mucosa,^{10 27 28} the intraluminal PCO_2 will rise during ischaemia.

Our study confirms and extends the findings by Heard *et al.*,¹⁴ suggesting that suppression of acid secretion decreases basal $iPCO_2$, but in that study there were no within subject comparisons. As suppression of acid secretion does not affect basal gastric blood flow, the fall in $iPCO_2$ with H_2 blockade might be explained by less buffering of acid by duodenal or salivary bicarbonate entering the stomach. This is unlikely, however, as analysis of the gastric juice pH data showed no correlation between alkaline shifts and $iPCO_2$. Therefore, the most probable cause of a higher $iPCO_2$ during normal *v* suppressed acid secretion is either buffering of gastric acid by gastric

Figure 4: Values of the pHi , calculated from $iPCO_2$ and blood bicarbonate content in individual volunteers ($n=10$). Period I, II, and V: basal (fasting) period, period III and VI: during oral ingestion of 500 mg sodium bicarbonate, period IV and VII: after ingestion of sodium bicarbonate. $\uparrow B$: oral ingestion of 500 mg sodium bicarbonate, $\uparrow R$: 100 mg ranitidine given intravenously.

bicarbonate²⁹ or buffering of gastric acid by bicarbonate in the first part of the duodenum, followed by reflux of CO_2 through the pylorus, as the $iPCO_2$ in the duodenal bulb may reach values of 500 mm Hg (or 67 kPa).³⁰

Authors using tonometry to assess the adequacy of gastrointestinal blood flow consider the gastric mucosa highly permeable for CO_2 . On the other hand, most authors who use luminal PCO_2 to calculate mucosal bicarbonate production^{31–34} discard diffusion of PCO_2 from mucosa to lumen, or consider the gastric mucosa hardly permeable for CO_2 . Although contradictory at first glance, these views are not incompatible. Under normal circumstances, there is net production of CO_2 in the stomach and duodenum as a consequence of buffering of gastric acid by duodenal bicarbonate.^{30 35} This CO_2 diffuses slowly to the surrounding mucosa, with complete equilibration in 240 minutes.^{10 29 36} When the luminal PCO_2 is lower than mucosal PCO_2 , however, as in gastric tonometry with introduction of saline in the intragastric balloon, diffusion of CO_2 from mucosa to lumen is completed within 60 minutes.^{10 27–29 37} The cause of this directional difference in diffusion velocity is not clear, but might relate to the high concentration of carbonic anhydrase in the gastric epithelium,³⁸ facilitating transport of CO_2 from mucosa to lumen.³⁹ Thus, when performing gastric tonometry, CO_2 diffuses comparatively rapidly from the surrounding mucosa to the saline in the gastric balloon. Conversely, the high intragastric PCO_2 after exogenous sodium bicarbonate, presumably did not lead to severe gastric intramucosal acidosis because the period of increased PCO_2 is too short for complete diffusion of produced CO_2 into the mucosa. Hence, the calculated pHi of 6.89 (0.15) overestimates true gastric mucosal acidity. The calculated pHi of 7.24 (0.13), however, during steady state CO_2 generation in the presence of acid secretion (period II), compared with the pHi after ranitidine (7.41 (0.06) in period V), may signify intramucosal acidosis during acid secretion.

The dosage regimen of ranitidine, needed to ensure adequate suppression of acid secretion for proper tonometric determination of $iPCO_2$ for long periods, is unclear. In this study, basal $iPCO_2$, measured one hour after 100 mg ranitidine was given intravenously, roughly equalled blood PCO_2 in all volunteers, even though the gastric juice pH was still <4.0 in 4 of 10. Even during ingestion of 500 mg sodium bicarbonate, the $iPCO_2$ hardly changed in 8 of 10 volunteers; only in the two volunteers with the lowest gastric juice pH immediately before sodium bicarbonate was given, was an increase in $iPCO_2$ above blood concentrations seen. Two and a half hours after ranitidine was given intravenously, however, a small, but significant difference between blood and intragastric PCO_2 was noted. Therefore, the usual ranitidine dosage regimen in intensive care patients, 50 mg intravenously at eight hourly intervals, might be insufficient to ensure adequate tonometric measurements

throughout the day. Future studies are needed to establish the adequate acid secretion suppression regimen for proper tonometric measurements of iPCO₂ in critically ill patients.

In conclusion, our results in healthy volunteers show that the proper determination of iPCO₂ as a measure of gastric mucosal PCO₂ and thus the adequacy of gastric mucosal blood flow, necessitates suppression of acid secretion. After ranitidine, iPCO₂ equals the PCO₂ in capillary blood. The gradient between iPCO₂ and blood PCO₂ during acid secretion is probably caused by buffering of gastric acid by gastric mucosal or duodenal bicarbonate.

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