Increased gastric P\textsubscript{CO\(_2\)} during exercise is indicative of gastric ischaemia: a tonometric study

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Abstract

**Background**—Diagnosis of gastric ischaemia is difficult and angiography is an invasive procedure. Angiographic findings may not correlate with clinical importance.

**Aims**—To investigate whether tonometric measurement of intragastric P\textsubscript{CO\(_2\)} during exercise can be used to detect clinically important gastric ischaemia.

**Methods**—Fourteen patients with unexplained abdominal pain or weight loss were studied. Splanchnic angiography served as the gold standard. Three patients were studied again after a revascularisation procedure. Gastric P\textsubscript{CO\(_2\)} was measured from a nasogastric tonometer, with 10 minute dwell times, and after acid suppression. Gastric and capillary P\textsubscript{CO\(_2\)} were measured before, during, and after submaximal exercise of 10 minutes duration.

**Results**—Seven patients had normal angiograms; seven had more than 50% stenosis in the coeliac (n=7) or superior mesenteric artery (n=4). Normal subjects showed no changes in tonometry. In patients with stenoses, the median intragastric P\textsubscript{CO\(_2\)} (P\textsubscript{ICO\(_2\)}) at rest was 5.2 kPa (range 4.8–11.2) and rose to 6.4 kPa (range 5.7–15.7) at peak exercise; the median intragastric blood P\textsubscript{CO\(_2\)} gradient increased from 0.0 kPa (range −0.8 to 5.9) to 1.7 kPa (range 0.9 to 10.3; p<0.01). Only two subjects had abnormal tonometry at rest; all had supernormal values at peak exercise. The P\textsubscript{ICO\(_2\)} gradient correlated with clinical and gastroscopic severity; in patients reexamined after revascularisation (n=3), exercise tonometry returned to normal.

**Conclusion**—Gastric tonometry during exercise is a promising non-invasive tool for diagnosing and grading gastrointestinal ischaemia and evaluating the results of revascularisation surgery for symptomatic gastric ischaemia.

Gut 1999;44:163–167

Keywords: gastric ischaemia; tonometry; carbon dioxide; exercise test

Symptomatic chronic gastrointestinal ischaemia is rarely diagnosed despite a relatively high prevalence of significant splanchnic atherosclerosis in angiographic and autopsy studies. This discrepancy is explained by the abundant collateral circulation of the gastrointestinal tract, preventing ischaemia if a single vessel has been occluded. It is therefore widely accepted that surgery is indicated only in patients with multiple vessel occlusions. In contrast, symptomatic single vessel occlusion, with complete resolution of symptoms after surgery, has been repeatedly reported, and a large retrospective angiographic study found unexplained abdominal complaints to be sevenfold more common in patients with single vessel stenosis than in those with normal angiograms. The main problem in determining the true incidence of symptomatic splanchnic ischaemia is the lack of a functional test that can identify and grade the severity of gastrointestinal ischaemia. Measurement of intragastric P\textsubscript{CO\(_2\)} (P\textsubscript{ICO\(_2\)}) may be an accurate test for gastrointestinal ischaemia, as ischaemia was invariably associated with an elevated P\textsubscript{ICO\(_2\)}. As most patients with gastrointestinal ischaemia are without symptoms at rest and often have pain postprandially, tonometry during a test meal has been used to provoke ischaemia and to establish the diagnosis. However, a test meal seems unsuitable during tonometry as it may affect the P\textsubscript{ICO\(_2\)} independently of mucosal P\textsubscript{CO\(_2\)}. We therefore looked for an alternative measure to provoke ischaemia. An exercise test might serve that goal, as it stresses the abdominal vasodilator reserve by diverting blood flow from the splanchnic circulation to the exercising muscles, with a reduction in superior mesenteric artery blood flow of 43%, as shown in healthy subjects.

In this study we evaluated the potential value of gastric tonometry during exercise for diagnosing gastrointestinal ischaemia, as compared with angiographic findings, in patients with otherwise unexplained abdominal symptoms.

**Methods**

The study was conducted according to the guidelines produced by the ethics committee of our institution concerning pilot studies. Fourteen patients (nine women, five men) with a mean age of 56 (range 30–75) years were studied, after informed consent. The medical history was taken and a physical examination performed in all subjects. One patient was enrolled for persisting pain, 18 months after reconstruction for a coeliac artery (CA) compression syndrome; another patient for recurrence of pain 18 months after an abdominal revascularisation procedure for CA and...
superior mesenteric artery (SMA) occlusions. The other 12 patients had abdominal pain related to food intake or exercise (n=5), pain combined with weight loss (n=5), or diarrhoea (n=2). The severity of complaints was scored by a symptom score before the tonometry test and angiography on a four point scale: 1, no complaints; 2, minor complaints, no interference with daily activities; 3, moderate complaints, some restrictions of normal daily activities; 4, severe complaints, normal daily activities impossible. In these 12 patients, extensive investigations including gastroscopy, abdominal ultrasonography, barium enema, and abdominal computed tomography had revealed no clues for a diagnosis. In all patients, gastroscopy and angiography were performed within a time frame of two weeks from exercise tonometry. Three patients were reevaluated by angiography and exercise tonometry, one (n=1) or eight weeks (n=2) following reconstructive vascular surgery.

GASTRODUODENOSCOPY
Gastroduodenoscopy was performed within two weeks of tonometry, and the severity of gastroscopic abnormalities was scored on a five point scale: 1, normal findings; 2, oedema; 3, the presence of erosions; 4, localised ulceration; 5, extensive ulceration.

ABDOMINAL ANGIOGRAPHY
Abdominal angiography was performed within two weeks of tonometry, using a Siemens Polytron (Siemens, Erlangen, Germany) after Ultravist 300 (Schering, Berlin, Germany) as contrast medium. A non-selective bidirectional abdominal aortic angiogram was obtained in all patients, followed by selective angiography of the CA, SMA, and inferior mesenteric artery (IMA), unless the non-selective images showed complete obstruction. The angiograms were judged by two radiologists, blinded to the clinical information, and stenosis was expressed as the percentage change in calibre. When these reports showed conflicting results, a final score was performed to reach consensus. The angiographic findings were scored on a five point scale: 1, normal; 2, more than 50% stenosis of branches; 3, more than 50% stenosis in single main splanchic vessel; 4, stenosis in two main splanchic vessels; 5, stenosis in all three splanchic vessels.

EXERCISE TONOMETRY
For the tonometry study, patients were not allowed to eat or drink from 2200 the night before the day of the study. In the morning, 100 mg of ranitidine was given intravenously to suppress gastric acid secretion. A tonometer (Sigmoid model, Tonometrics, Bethesda, USA), a CO2 impermeable nasogastric tube with a CO2 permeable silicone balloon at its tip, was placed intragastrically at 60 cm from the tip of the nose. The Pco2 was measured as follows. At the start of measurement 2.5 ml saline was infused into the tonometer. After a given dwell time in the tonometer balloon, in this study 10 minutes, the saline was aspirated from the tonometer. The first 1 ml was expelled as it represents dead space volume, and the Pco2 was measured from the rest of the saline using a Corning 278 blood gas analyser (Ciba-Corning, Houten, The Netherlands). To calculate steady state Pico2 during the measurement interval, the measured Pco2 was multiplied by 1.86, to correct for incomplete equilibration at 10 minutes and the bias of the blood gas analyser. An arteriolised capillary blood sample from a warmed finger was drawn, for determination of pH, Pco2 (Pco2), and bicarbonate (bic) content using the blood gas analyser. The intragastric-blood gradient for Pco2 was calculated. The Pico2 was measured twice at rest, during 10 minutes exercise (from 0 to 10 minutes), and three times after exercise: from t=10 to 20, from t=20 to 30, and from t=40 to 50 minutes. The exercise test (from t=0 to 10 minutes) was aimed at a submaximal exercise level of 70–80% of the predicted maximal heart rate by stepping up and down stairs. The level of exercise was assessed from the percentage of the maximal heart rate at peak exercise and the decrease in blood bicarbonate content, an indicator of exercise induced anaerobiosis and lactate production.

STATISTICAL ANALYSIS
Data are expressed as median and range. The interobserver variability for assessment of angiographic abnormalities was evaluated with the kappa test. Based on the angiographic findings, patients were divided into two groups: those with normal arteries (normal group, n=7), and those with at least one vascular stenosis (stenotic group, n=7). The difference in tonometric parameters between periods was evaluated with the Kruskal-Wallis analysis of variance for repeated measurements followed by a Wilcoxon signed rank test for matched pairs; the differences between groups were evaluated with a Mann-Whitney test. For calculation of sensitivity and specificity of tonometric parameters for the detection of gastric ischaemia, the angiographic findings were used as the gold standard. The normal threshold values were obtained from a human volunteer study: Pico2 ≤ 6.1 kPa, Pco2 gradient ≤ 0.8 kPa. The relations between the clinical severity (symptom and gastroscopic score), tonometric parameters, and angiographic severity score, were evaluated using Spearman’s rank correlation coefficients. A value of p<0.05 was considered statistically significant.

Results
PATIENT CHARACTERISTICS
Table 1 presents the patients’ features. Among patients with stenotic lesions, abdominal pain or discomfort was reported more often compared with those with a normal abdominal angiogram. The triad of abdominal angina (meal related pain, epigastric bruit, and weight loss) was observed in two patients with stenotic lesions.

GASTROSCOOPY
In the group with normal angiograms, all subjects had normal gastroscopic findings. In the
group with stenotic lesions, two patients had normal findings, one subject showed focal, sharp, delineated white areas with adjacent cyanotic areas, two showed gastritis with erosions, one had gastritis with two ulcers, and one had extensive ulceration in the stomach, with congested mucosa and gastroparesis.

### ANGIOGRAPHY

The interobserver agreement between both radiologists was good, with a kappa value of 0.69 for assessment of the roots of the CA, SMA, and IMA and a kappa of 0.88 for the main vessel branches to the stomach. Identification of the left gastric artery and gastroduodenal artery could be achieved in all patients. The right gastric and right and left gastric epiploic arteries could not be identified in four, two, and 12 patients, respectively. In the stenotic group, three patients had occlusion of all three splanchnic vessels, two patients had occlusion of the CA and IMA, one had occlusion of the left gastric artery only, and one had several areas of 50–80% stenosis in branches of the CA and SMA and was later diagnosed as having polyarteritis nodosum.

### EXERCISE

The aimed exercise level (70% of maximal predicted heart rate) could not be achieved in two patients with stenotic lesions, because of near exhaustion and abdominal pain, and in one with a normal angiogram, who had low back pain. These two patients in the stenotic group stopped exercise after five minutes; all patients with normal angiograms could exercise for 10 minutes. In the group with stenoses, four subjects could not climb stairs (all due to abdominal complaints) and the other three climbed 19, 95, and 190 stair steps, respectively. In the group with normal angiograms, two subjects could not climb stairs, due to low back pain. The other five subjects climbed 95 to 190 stair steps. No group differences in percentage of maximal heart rate (median 71% (range 61–87%) in the stenotic versus 77% (range 62–91%) in the normal group; p>0.05), or the fall in cBic (median 2.6 mmol/l (range 0.0–4.6) versus median 2.1 mmol/l (range 0.7–5.4), respectively; p>0.05) were seen, indicating a similar level of exercise among the groups.

### TONOMETRY

Figure 1 shows the time dependent changes in Pco2 gradient before, during, and after exercise. No difference in both basal Pco2 values was found (median difference −0.1 kPa (range −0.6 to 0.7), coefficient of variation 8%); the mean of these values was taken as resting Pico2.

In patients with normal angiograms the median Pco2 at 4.5 kPa (range 4.4 to 5.5) at rest and 5.1 kPa (range 4.3 to 6.0) during exercise (NS). In this group, the median Pco2 gradient at rest was −0.5 kPa (range −0.9 to 0.5) and rose slightly to 0.3 kPa (range −0.7 to 0.8) during exercise (p<0.05). In the group with splanchnic stenoses, the median Pico2 at rest was 5.2 kPa (range 4.8 to 11.2) and rose to 6.4 kPa (range 5.7 to 15.7) during exercise (p<0.01). In the group with stenoses, the median Pco2 gradient at rest was 0.0 kPa (−0.8 to 5.9) and rose to 1.7 kPa (range 0.9 to 10.3) during exercise (p<0.05). The resting Pico2, but not the Pco2 gradient, differed between normal and stenotic patients (p<0.05 and p=0.07, respectively). The Pico2 and Pco2 gradient during exercise was higher in the stenotic compared with the normal group (p<0.001 and p<0.01, respectively). No correlation between any tonometer parameter and indicators of exercise level (heart rate, bicarbonate level) was found.
POSTOPERATIVE FOLLOW UP
Three patients, who underwent a vascular reconstruction of the splanchnic vessels, were reevaluated postoperatively. Patient A was evaluated one week after surgery. The PCO₂ gradient at rest of 3.9 kPa before the operation decreased to 0.3 kPa after surgery. In patients B and D, the exercise test was repeated eight weeks postoperatively. Both patients were without symptoms, had gained weight, and had a notably increased exercise tolerance. The PCO₂ gradient at peak exercise decreased from 3.7 kPa preoperatively to 0.7 kPa and from 1.7 kPa preoperatively to 0.8 kPa after surgery, for patients B and D, respectively. In the latter patients, initial gastroscopy showed ulceration and gastritis; repeated gastroscopy eight and 10 weeks after surgery showed normal gastric mucosa.

CORRELATIONS
In the patients with stenotic lesions, the maximal PCO₂ gradient during exercise correlated with the severity of ischaemia, as indicated by the symptom score and the gastroscopy score (fig 2; r=0.97, p<0.0001 and r=0.87, p<0.01, respectively). The angiographic score correlated poorly with the symptom score and not with the gastroscopy score (r=0.68, p<0.05 and r=0.44, p>0.05, respectively).

Discussion
This study indicates that measurement of an increased gastric PCO₂ during exercise may identify subjects with symptomatic chronic gastrointestinal ischaemia. The technique could potentially be useful as a screening test in patients with unexplained abdominal complications and weight loss, for the decision to perform angiography or even reconstructive surgery, or for the assessment of surgical results.

The provocation of gastric ischaemia during peak exercise in patients with stenotic lesions most probably resulted from diversion of blood flow away from the splanchnic area to the exercising muscles.19 A potential pitfall with exercise as a provocation test is that gastrointestinal ischaemia has been reported after heavy, extended exercise in healthy, well-trained individuals. However, with the level of exercise applied in this study, gastrointestinal ischaemia was not observed in subjects with normal angiograms, in contrast to the patients with abnormal angiograms. Although some patients could not endure the entire 10 minute exercise or walk stairs, no false negative tests were seen. With more precise prediction of the required exercise level, and a more flexible exercise protocol the drawbacks of the current exercise protocol may be overcome in future studies. The undertaking of such studies may be worthwhile as the major advantage of using exercise as provocation is that problems associated with a test meal during tonometry are avoided.20 The main problem with a test meal is an erroneous increase in PCO₂, from buffering of meal stimulated acid secretion even in the presence of H₂ antagonist treatment, and an initial decrease in PCO₂ due to the dilution effect of the ingested test meal with an atmospheric PCO₂ of 0 kPa.17 The latter phenomenon probably caused the negative results of tonometry during a test meal to detect ischaemia in a recent prospective study.21 As exercise tonometry is performed in the fasting state, these problems are avoided.

The correlation between peak PCO₂ gradient and the clinical and gastroscopic severity of ischaemia may indicate that exercise tonometry could be used to grade severity of ischaemia. That tonometric variables are related to the degree of ischaemic damage has been shown in several animal studies, where the increase in mucosal and regional venous PCO₂ correlated with the severity of ischaemia.12 25–27 It has even been suggested that the stages of hypoperfusion and ischaemia could be derived from tonometry. In experiments with progressive hypoperfusion, the small bowel PCO₂ gradient in dogs was between 1.5 and 2.3 kPa, just below the threshold of anaerobic metabolism, and 5.0 to 10.0 kPa during severe ischaemia with anaerobic metabolism and lactic acidosis.25 27 Indeed, in our study, patients with gradients above 2.0 kPa showed more pronounced mucosal damage at gastroscopy, indicating more severe ischaemia. Future studies are needed to confirm the association between severity of ischaemia and tonometry, and whether a critical PCO₂ gradient during exercise tonometry can be identified that separates patients with severe ischaemia, who would likely benefit from surgery, and those with moderate ischaemia who could be managed conservatively.

The poor relation between angiographically proved stenoses and their clinical relevance is in accordance with previous studies.5 7 Furthermore, the blood flow parameters obtained with
duplex ultrasonography of the splanchnic vessels may have no relation to the presence or severity of ischaemia, and may have considerable overlap with normal subjects.\textsuperscript{28} Moreover, with duplex ultrasonography, the visualisation of the CA proved impossible in about 20\% of cases.\textsuperscript{28} Tonometry does not provide data on gastric blood flow or vascular anatomy, but merely on the adequacy of gastrointestinal blood flow.\textsuperscript{28} In the current study, we measured in the stomach only, and the results might be biased since all patients had CA stenoses. Although the CA is involved in the majority of cases, splanchnic atherosclerosis, gastric tonometry might very well be insensitive in patients with small bowel ischaemia from SMA stenosis with normal CA anatomy, a combination which may occur in 12\% of patients.\textsuperscript{5} Theoretically, this may be overcome by placement of a tonometer in the small bowel.\textsuperscript{18} Future studies would need to determine whether combined gastric and small bowel PiCO\textsubscript{2} measurements might enhance the diagnostic accuracy of exercise tonometry.

In conclusion, gastric tonometry of PiCO\textsubscript{2} during exercise may a promising tool for detection of chronic gastric ischaemia, and possibly of grading of ischaemic severity. Further studies are needed to confirm these preliminary conclusions.

This work was made possible by support of GlaxoWellcome, the Netherlands.

17 Groeneveld ABJ, Vervloet M, Kolkman JJ. Gastric tonometry in the fed or fasting state? Crit Care Med (in press).