EXERCISE TONOMETRY FOR THE DIAGNOSIS OF CHRONIC GASTROINTESTINAL ISCHEMIA

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Exercise Tonometry for the Diagnosis of Chronic Gastrointestinal Ischemia

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Contents

Chapter 1

Introduction, Aims and Outline

Chronic gastrointestinal ischemia is considered to be a rare disease. It is referred to as chronic mesenteric ischemia, abdominal angina, or chronic splanchnic syndrome. Its diagnosis is notoriously difficult and mainly relies on clinical presentation, exclusion of other diagnoses, and angiography as final diagnostic modality [2,8]. Typical symptoms, including postprandial pain, fear of eating, and weight loss, combine in a condition referred to as chronic splanchnic syndrome or chronic mesenteric ischemia.

Angiography as well as most if not all other currently available diagnostic tools (such as duplex sonography, CT- and MR-angiography) have in common that they provide information about vessel anatomy, vessel patency or blood flow, but not about end-organ ischemia. However, in the gastrointestinal tract it is crucially important to be informed not only about the presence of vascular stenoses but about presence or absence of ischemia as well, because many patients with splanchnic stenoses remain asymptomatic and thus have no indication for treatment. In other words: detection of a stenosis alone does not prove ischemia [6,7,15].

Because of the extensive collateral circulation between its three main arterial branches (celiac artery (CA), and superior (SMA) and inferior (IMA) mesenteric artery), it is widely recognized that the gastrointestinal tract is resistant to ischemia [12,13]. Many authors have stated that at least two of the three major splanchnic arteries have to be stenotic or occluded to give ischemic symptoms. But studies that reported the rarity of an isolated stenosis of CA as cause of complaints [5,14] are in contrast with series showing disappearance of symptoms after treatment of isolated CA stenoses [10,11].

As some but not all patients with splanchnic stenoses benefit from treatment the main question is therefore how to chose who to treat and who not to treat. It was already acknowledged over a decade ago that "a functional and physiological test distinguishing symptomatic ischemia, the chronic splanchnic syndrome from non-ischemic stenoses, the chronic splanchnic disease, was urgently warranted" [1].

Measurement of gastrointestinal intraluminal PCO_2 by means of tonometry has been shown to provide exactly that information: the presence or absence of ischemia. Gastrointestinal tonometry is until now the only clinically feasible, i.e. minimally invasive and bedside, technique for monitoring of the adequacy of gastrointestinal (mucosal) perfusion.

Uncertainties about the physiological background, methodology, and clinical use hampered tonometry from gaining the status of a routine diagnostic technique. However, most of its initial methodological problems have been addressed and solved, for instance by the introduction of automated air tonometry. In **chapter two** an update on the current thoughts on tonometry is given.

Gastric tonometry after food provocation has been used as diagnostic test for chronic gastrointestinal ischemia. This has resulted in varying and disappointing accuracies [1,3,4,9]. Using physical exercise as an alternative provocative manoeuvre, gastric tonometry showed to be a promising test for the detection of symptomatic chronic gastrointestinal ischemia [9]. Uncertainties arising from this pilot study were the intensity of exercise

needed for provocation of gastrointestinal ischemia, the best way to monitor this exercise intensity and the best location in the GI tract for tonometric measurements.
In **chapter three** the influence of exercise intensity on gastric mucosal perfusion adequacy as measured by tonometry is investigated in a volunteer study with two different (submaximal and maximal) exercise levels.
In **chapter four** different monitoring regimes (heart rate monitoring, respiratory gas exchange ratio -RQ-, and rapid serial arterial lactate measurements) for determining exercise intensity are compared.
In **chapter five** the first results of small bowel tonometry are presented. Our concern has been that measurement in the stomach alone (perfused by the celiac artery) might cause false-negative tonometry results in patients with stenoses in the superior mesenteric artery, supplying the small bowel. Therefore, we performed exercise tonometry tests with an additional tonometer positioned beyond Treitz's ligament. The results of small bowel tonometry were compared with measurements in the stomach.
In **chapter six** gastric exercise tonometry testing is validated as a diagnostic tool in a cohort of patients suspected for chronic gastrointestinal ischemia.
In **chapter seven** we retrospectively evaluate three potential diagnostic regimens for suspected chronic gastrointestinal ischemia, yielding a novel approach for the workup of these patients.

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Chapter 2

Gastrointestinal Luminal PCO_2 Tonometry: An Update on Physiology, Methodology and Clinical Applications

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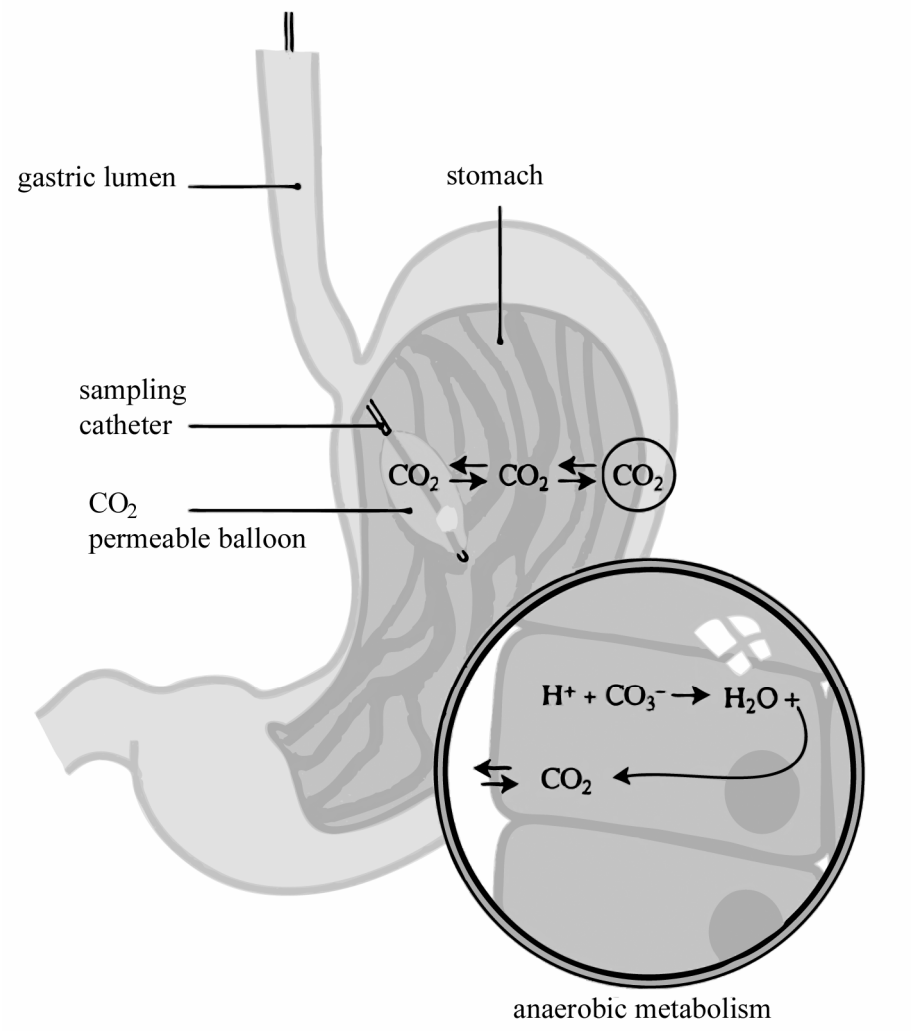
ABSTRACT

Gastrointestinal luminal PCO_2 tonometry has been introduced in critically ill patients, to derive the mucosal pH (pHi) as a measure of mucosal perfusion adequacy, from the regional, luminal PCO_2 determined with help of a balloon-tipped and saline or air-filled tonometer, and the blood bicarbonate content. Some physiological, methodological and clinical aspects of gastrointestinal PCO_2 tonometry remain unclear. Recent literature suggests that, as expected from normal physiology, the blood-tonometer balloon PCO_2 gradient is a more specific and sensitive indicator of mucosal hypoperfusion than the pHi, even though the threshold of the PCO_2 gradient that indicates the onset of tissue anaerobic metabolism is unclear. Otherwise, gastric buffering of acid by bicarbonate, derived from feeding or entering the stomach from the duodenum, can elevate luminal PCO_2 independently from mucosal PCO_2, and experiments indeed suggest that acid secretion suppression may increase the validity and utility of the technique. Some sources of error inherent to the manual saline tonometry technique are circumvented by the recently developed semi-continuous automated air tonometry technique in the stomach, that has been proven to give reliable results clinically. The value of tonometry in small and large bowel is being explored. The evidence that tonometric derived variables are prognostically important, in terms of predictive value for morbidity and mortality in a variety of conditions, even more so than global haemodynamic variables, is accumulating, but controversy remains whether the PCO_2 gradient is superior to the pHi in this prediction. Taken together, wider knowledge of the physiological background and sources of error of tonometry may widen the clinical applicability of the technique by which regional perfusion adequacy can be assessed non-invasively and which can be used on a routine basis to guide treatment of critically ill patients with hypoperfusion.

Figure 1. Principle of gastric tonometry (reproduced with permission from the editor: J.A. Otte et al. PCO_2 tonometrie van de maag. *Ned Tijdschr Geneesk* 2000;144(49):2341-5)



Gastrointestinal mucosal pH (pHi), calculated from the tonometrically measured P_{CO_2} in the gastrointestinal lumen and the blood bicarbonate content using the Henderson-Hasselbalch equation, has been suggested to constitute an index of the adequacy of splanchnic mucosal perfusion. This may relate to the prognosis of critically ill patients, as bowel wall hypoperfusion may result in tissue injury, increased permeability, endotoxin-bacterial translocation and a harmful inflammatory (cytokine) response [11,12,26,30,37,54,62,68,71,73,99,107,115,123,131,132]. The theory is that hypoperfusion below a critical level causes tissue (mucosal) carbon dioxide accumulation and acidosis. As carbon dioxide diffuses easily across membranes, the P_{CO_2} in the gut lumen also increases, leading to widening of the blood-tonometer P_{CO_2} gradient. In fact, the pHi has been used successfully to guide treatment and to improve the outcome of critically ill patients [36,46,49,62,68]. Nevertheless, tonometry has not yet become a routine intensive care monitoring technique. This may relate to uncertainties regarding the physiological background, the methodology, and the clinical usefulness [46]. This review will therefore update current thoughts on these aspects [36,46].

PHYSIOLOGICAL BACKGROUND

Gastrointestinal hypoperfusion

Several conditions may lead to altered gut perfusion (Table 1). Haemorrhagic hypotension, cardiac tamponade, cardiac bypass or vasopressin infusion for example, may lead to mucosal hypoperfusion along the entire gastrointestinal tract, and this may be assessed with the help of simultaneous tonometric measurements in various gastrointestinal segments [1,83,85,102,118,119,135]. In fact, the bowel P_{CO_2} gradient may increase and pHi decrease during hypoperfusion states, similar to changes in gastrically determined tonometric variables. This may also apply to sepsis and shock, even if the oxygen demands by the bowel wall increase [102], and to cardiopulmonary bypass surgery, during which bowel wall oxygen demands may decrease following hypothermia and increase during rewarming [3,11,29,53,107,111,112,130]. Moreover, shock may result in early selective splanchnic vasoconstriction so that gastric tonometry may yield an early indicator of general hypoperfusion [33,36,46,55,102,135]. The gastric tonometric P_{CO_2} gradient proved an early, sensitive indicator of hypovolaemia during haemorrhage in healthy volunteers [55]. An increase in the gastric P_{CO_2} gradient and decrease in pHi during general hypoperfusion in humans may relate to angiotensin II-induced selective splanchnic vasoconstriction [67,110].

Experimental studies utilizing vascular occlusion and reperfusion, induction of shock or pharmacological splanchnic vasoconstriction have revealed that changes in blood flow to the gut wall, as measured by microspheres, laser Doppler, electromagnetic or ultrasonic flow probes, or reflectance spectrophotometry, were paralleled by concordant changes in tonometric variables [2,57,70,73,83,85,102,109,116,118,119,120,126,132,135]. A decrease in blood flow to less than 50 % of baseline during incremental hypoperfusion leads to an increased tonometric P_{CO_2} relative to supplying (and draining) blood values. This

results in a decrease in pHi, in parallel with the decreasing blood flow and the fall in tissue P_{O_2} and oxygen consumption [1,2,13,36,46,50,55,57,73,83,85,102,104,109,116,118,119,120,126,135]. This may result in tissue damage and increased mucosal permeability [1,11,12,26,71,73,107,123,132]. In critically ill, septic, and mechanically ventilated patients, laser-Doppler (and reflectance spectroscopy) measurement of gastric mucosal blood flow, hepatosplanchnic blood flow measured by indocyanine green, or hepatic breakdown of injected lidocaine to monoethylglycinexylidide, were lower in patients with an increased P_{CO_2} gradient and subnormal pHi than in those without these tonometric abnormalities, or in healthy controls [35,94,103,128]. In fact, drug-induced changes in blood flow assessed by these techniques can be paralleled by concordant changes in the P_{CO_2} gradient and pHi [34,94,102,103,128].

Table 1. Conditions in which tonometry is of potential clinical value.

Perioperative monitoring in major surgery, including cardiopulmonary bypass, major (emergency) vascular surgery and liver transplantation
Myocardial infarction and shock
Heart failure
Pulmonary embolism and shock
Traumatic/hypovolaemic shock
Sepsis and shock
Pericardial tamponade
Fluid and drug therapy for shock
Infusion of vasopressin or other vasoconstrictors
Acute pancreatitis
Mesenteric thrombosis
Necrotizing enterocolitis
Ischaemic colitis
Bowel obstruction
Chronic celiac and mesenteric vascular disease
Assessment of bowel viability
Intolerance to tube feeding
Weaning from mechanical ventilation
Haemodialysis

However, tonometric variables are indicators of the blood flow to demand ratio. Changes in splanchnic blood flow, as assessed by the indocyanine green clearance or laser Doppler techniques, are not necessarily accompanied by changes in tonometric variables and vice versa, particularly when demand changes, for example with the variation in body temperature associated with cardiopulmonary bypass surgery and sepsis. During hypothermic cardiopulmonary bypass surgery, gastric mucosal (Doppler) blood flow may decrease, but neither the gastric luminal to blood P_{CO_2} gradient nor the pHi may change [3,107,115]. The generally observed fall in pHi during rewarming and in the

postoperative phase may not concord with splanchnic blood flow changes and oxygen consumption, which may even increase, and this discrepancy suggests either an increased oxygen demand, or insufficient ability of pHi to reflect the balance between oxygen supply and demand [53,107,110,111,115,130]. Even during normothermic cardiopulmonary bypass surgery, bowel demands may increase and may be insufficiently met by an increase in blood flow, thereby lowering the pHi [53]. Discordant changes in cardiac output and gut blood flow on the one hand and tonometric variables on the other during treatment with catecholamines, with an increase in the former but no improvement in the latter, may relate in part to redistribution of blood flow within the stomach or gut wall, away from the mucosa [11,111,112,128,130]. During endotoxaemic-septic shock, gut blood flow may not decrease and gut P_{O_2} and oxygen consumption may increase, but this may not prevent a subnormal gastrointestinal pHi developing, suggesting redistribution of blood flow, impaired oxygen use, or both [132]. Finally, it remains to be seen if deterioration in tissue oxygenation and increased anaerobic metabolism through severe hypoxemia or anaemia also result in tonometry changes [70] as it is conceivable that a high blood flow but insufficient oxygen delivery may limit the increase in P_{CO_2} and decrease in pHi [3].

Sublingual, oesophageal, gastric, and bowel P_{CO_2} tonometry

Luminal production of carbon dioxide during buffering of gastric acid by bicarbonate or bacterial fermentation may limit the specificity of the luminal P_{CO_2} and thus the pHi as indicators of the adequacy of mucosal perfusion in the stomach and large bowel, respectively. This may not occur with tonometry in the oesophagus or sublingually as these areas are not supplied by splanchnic blood vessels. Thus the sensitivity of tonometry for early detection of general hypoperfusion may be inferior to that for detecting hypoperfusion in the stomach or small bowel, where selective vasoconstriction may occur [33]. During severe haemorrhage or sepsis in animals, sublingual, oesophageal and gastric P_{CO_2} nevertheless increased in parallel and simultaneously with the decrease in blood flow and increase in blood lactate concentration [52,64,101,119,124]. With regard to the value of small bowel tonometry *vs.* gastric tonometry, widening of the tonometer-blood P_{CO_2} gradient in pigs may be earlier in the small bowel than in the stomach during haemorrhagic shock, but not during cardiac tamponade [1]. The increase in jejunal P_{CO_2} during endotoxaemia in horses was less and occurred later than that of the gastric P_{CO_2} [125]. Walley and colleagues [135], showed that during haemorrhagic hypotension, widening of the tonometer-blood P_{CO_2} gradient was less variable in the jejunum than in the stomach, largely because of greater measurement error in the latter.

P_{CO_2} gradient *vs.* pHi as an indicator of mucosal hypoperfusion

It has been argued repeatedly that pHi is a composite variable, consisting of a systemic and locally derived variable, and should be replaced by the blood-tonometer P_{CO_2} (or perhaps pH) gradient. This is especially so if tonometry is being done to yield a sensitive and specific measure of the adequacy of gastrointestinal mucosal perfusion, inde-

pendent of systemic metabolic and respiratory alterations [26,42,46,51,55,62,63,64,73,88,121,135]. Indeed, the major pitfall in the calculation of the pHi from gastric PCO_2 and the arterial bicarbonate content is the assumption that the latter equals mucosal content. In humans, the mucous layer of the acid-secreting stomach also contains bicarbonate, which is secreted by non-parietal cells and helps to protect the underlying mucosa from the gastric acid secreted by parietal cells [69]. Mild hypovolaemia in human volunteers decreases gastric bicarbonate secretion more than acid secretion, and this may be associated with alterations in the tissue bicarbonate concentration [69]. Hence, the bicarbonate content of the mucosa may be normally higher than in blood, while hypoperfusion may result in a dissimilar decrease in blood and mucosal bicarbonate content, depending on the balance between general and regional hypoperfusion, diminished bicarbonate secretion, and the degree of buffering of lactic acid in the hypoperfused stomach wall [73,116,120,126]. Conversely, changes in arterial blood bicarbonate content may lead to alterations in calculated pHi, independent of changes in the degree of mucosal hypoperfusion and the increase of the PCO_2 gradient [121]. Intravenous bicarbonate administration to a patient with mesenteric thrombosis resulted in an increase of gastric tonometer pHi to normal values, despite a necrotic bowel later found at laparotomy, but the stomach may not have represented the small bowel [10]. Conversely, in cardiac surgery patients, a rapid decrease in arterial bicarbonate content by volume loading during surgery may contribute to a lowered gastric pHi, independently of luminal PCO_2 [5].

Moreover, gastric PCO_2 closely parallels local arterial (and draining venous) blood PCO_2 values during changes in alveolar ventilation, as demonstrated in animals and human volunteers with (presumably) normal perfusion, so that changes in pHi may result from changes in alveolar ventilation, independent of mucosal hypoperfusion [13,27,31,80,118]. Conversely, changes in alveolar ventilation in patients undergoing mechanical ventilation resulted in changes in tonometric variables similar to blood PCO_2, if gastric mucosal blood flow remained adequate [13,31]. The dependency of pHi on arterial blood bicarbonate content and PCO_2 may underlie the observed concurrent changes or correlations between calculated pHi on the one hand and acid-base variables, including lactate concentration, on the other [19,31,41,49,62,84,136].

It is still unclear as to the threshold for anaerobic metabolism, but the upper limit of a normal gradient would be approximately 1.2 kPa [80,88,116,127]. The increased luminal PCO_2 during hypoperfusion is assumed to stem from two sources. With a moderately gradual reduction in perfusion, mucosal PCO_2 accumulates after a reduced washout and an increase in tissue and venous PCO_2. A further decrease in blood flow results in a steep increase in tissue (luminal) and to a lesser extend venous PCO_2 and this may be caused by buffering of anaerobically produced lactate and protons by mucosal bicarbonate [57,73,116,120,135]. Hence, a gradient between tissue and draining venous PCO_2, in spite of allegedly high diffusibility of carbon dioxide, may be a marker of anaerobic tissue metabolism. It seems that a fall in tissue oxygen consumption and tension and development of anaerobic metabolism and production of lactic acid occurs at a PCO_2 gradient

of 3.3 kPa or greater, a value that can be regarded as the critical gradient [2,36,116,120,135]. A lower gradient, however, does not exclude a focal oxygen deficit in the mucosa [80]. The baseline PCO_2 tonometer-blood gradient in patients with gastric erosions or ulcerations and stenotic or occluded celiac and mesenteric vessels at angiography was about 0.4 kPa and rose to about 2.5 kPa during submaximal exercise, whereas no such increase was observed in patients with a normal angiography [78]. Thus, some patients had lesions in the stomach attributable to hypoperfusion in spite of a resting PCO_2 gradient presumably below the critical value of approximately 3.3 kPa [78]. The lesion may relate to intermittent or patchy hypoperfusion rendering the mucosa susceptible to damage by other factors.

METHODOLOGICAL CONSIDERATIONS

Comparison of tonometric with directly measured variables

In the control state, tonometric pHi may agree with directly measured tissue pH in the stomach and bowel [40]. Some authors have shown that the directly measured PCO_2 is higher than the tonometrically derived PCO_2, and that the response time of the latter is slower [36,104]. This may result in tonometric pHi overestimating directly measured tissue pH during sudden hypoperfusion [2,36]. The latter may also relate to the erroneous bicarbonate assumption discussed above.

Normal values

Normal values for gastric tonometry have been defined, taking *in vivo* determined correction factors and blood-gas analyzer bias (see below) into account [80]. The upper limit of normal values for PCO_2 was 6.5 kPa and for the tonometer to blood PCO_2 gradient 1.2 kPa, so that, tonometric PCO_2 is a few kPa higher than in the blood supply. The lower limit of normal for pHi is 7.33 and for the pH gradient -0.06 [80]. This may partly agree with other reports, wherein the upper limit of normal pH varied between 7.32 and 7.35 [12,19,30,35,49,59,60,65,68,80,84,90,99,100,109,127]. Data on normal PCO_2 or the PCO_2 gradient in the human gut are lacking. Bass et al. noted that the control intestinal (jejunal or ileal) mass spectrometer PCO_2 was 11.9 kPa in dogs, but arterial values were not given [9]. The normal fiberoptic/tonometric ileal to blood PCO_2 gradient may, as in the stomach, amount to 1.3-2.7 kPa in pigs and dogs [73,83,103,116,120]. The normal oesophagus to blood PCO_2 gradient is also in that range [52,83]. There is no information on the normal tonometer balloon equilibration characteristics from the oesophagus to large bowel, where changes in luminal contents and diffusion conditions may have an effect.

Gastric PCO_2 as a measure of gastrointestinal mucosal PCO_2

It is generally assumed that rapid diffusion results in luminal PCO_2 being identical to mucosal PCO_2. Nevertheless, the increase in tonometric PCO_2 may underestimate that of directly measured PCO_2 [39,104]. Carbon dioxide diffuses rapidly from mucosa into the

lumen with complete equilibration in 60 minutes, while diffusion in the opposite direction is about four times slower [38]. Even though carbonic anhydrase, present in the gastric mucosa, may contribute to the difference in diffusion rate, inhibition of carbonic anhydrase activity did not decrease the rate of PCO_2 build-up in the tonometer balloon [75]. This suggests that the balloon PCO_2 arises from gastric contents as opposed to the gastric mucosa. Indeed, gastric carbon dioxide content may decrease by 6 % and PCO_2 may decrease by 0.3 kPa during equilibration of 1.5 ml of tonometer balloon saline, in the absence of transmucosal diffusion [75]. Gastric balloon rather than transmucosal carbon dioxide diffusion may be the rate limiting step during gastric PCO_2 tonometry [75].

Gastric secretion of acid

The close approximation of luminal and mucosal PCO_2 may be lost in the stomach when carbon dioxide is produced by buffering of gastric acid, contributing to a relatively poor reproducibility of gastric pHi [135]. Indeed, in the normally perfused upper gastrointestinal tract, luminal PCO_2 may directly relate to the amount of acid secreted and buffered in the stomach, and has even been used as measure of acid secretion [106,117]. This luminally produced carbon dioxide stems from the buffering of gastric acid by bicarbonate secreted by the gastric mucosa or by bicarbonate entering the stomach through duodenal reflux or from saliva via the oesophagus [106]. The increase in PCO_2 resulting from buffering can be prevented by inhibition of acid secretion [38,106]. Hence it has been recommended to perform tonometry H_2 block of gastric acid secretion [36,46]. In fact, gastric PCO_2 in human volunteers is 1.3-2.7 kPa above blood levels and decreases towards arterial levels with less interindividual variation after inhibition of acid secretion by the H_2 blocker ranitidine, so that calculated pHi is higher in the presence of prior H_2 block [77,113,127]. When duodenogastric reflux is simulated by oral administration of bicarbonate in an amount approximating the hourly pancreaticoduodenal production, gastric PCO_2 increases to approximately 10.7 kPa above blood levels but only in the absence and not in the presence of prior H_2 block [77]. Removal of gastric acid by suction may not decrease gastric PCO_2 towards blood values [113]. This can be explained by the fact that gastric acid, which is produced in the deep pits of the gastric mucosa, is buffered by gastric bicarbonate in the mucus layer covering these pits [77]. Buffering of gastric acid by administration of non-CO_2 releasing antacids like aluminium oxide-magnesium hydroxide also releases large amounts of carbon dioxide *in vitro* and is therefore not useful [133].

It can be questioned whether data in healthy subjects would apply to critically ill patients as H_2 blockers, which could be expected to lower PCO_2, had no effect on gastric PCO_2 in the seriously ill [22]. Together with the concept that inhibition of acid secretion may predispose to gastric bacterial colonization and nosocomial infections, this may be the reason that many authors do not use H_2 block before tonometry in critically ill patients [17,31,34,110,111,112,122,130]. Similarly, administration of sucralfate, which has acid-buffering capacities and increases gastric bicarbonate secretion, and could

therefore be expected to increase PCO_2 in the presence of acid, had no effect on the PCO_2 in critically ill patients [21]. This may be explained by a reduction in gastric acid secretion, as shown by a relatively high gastric juice pH that fails to decrease after pentagastrin infusion in many critically ill patients after operation [5,44,60].

During the first 24 h after cardiopulmonary bypass surgery, gastric fluid may be acidic (pH<4.0) in a minority of patients [5]. Simulation of duodenogastric reflux by gastric bicarbonate administration had no effect on gastric PCO_2 immediately after surgery, indicating lack of gastric acid secretion but increased gastric PCO_2, on the first postoperative day by 2.7 kPa in six of 10 subjects [5]. The observations suggest postoperative recovery occurs after reduced gastric acid secretion caused by transient hypoperfusion.

Indeed, gastric acid secretion is an active, energy-demanding process [69]. During haemorrhagic hypotension, gastric mucosal blood flow and gastric acid (and bicarbonate) secretion diminish, but less so in pentagastrin- or histamine-stimulated conditions than in animals pre-treated with H_2 blockers [69]. This suggests that gastric acid secretion in shock is blood flow dependent and that administration of H_2 blockers (or proton pump inhibitors) may further diminish energy-demanding gastric acid secretion and blood flow and may protect against development of stress ulcers related to hypoperfusion [66,69,93]. In fact, a low pHi may be associated with failure to acidify the gastric lumen in response to pentagastrin [65]. The combination of a reduced demand and an increased perfusion reserve during inhibition of acid secretion probably results in a lowered sensitivity of tonometry as an indicator of early perfusion failure or gastric mucosal hypoperfusion. A patient who develops an increased PCO_2 gradient might either have mucosal hypoperfusion or recurrence of gastric acid secretion after amelioration of hypoperfusion. Inhibition of acid secretion reduces the incidence of this dilemma, and simple measurement of gastric juice pH, preferably by continuous monitoring, could solve the problem. An aspirated juice pH above 4.0-5.0, checked with the help of litmus paper, would suggest minimum or no buffering effects [5,67,86,127], so that changes in gastric PCO_2 would probably the result from changes in mucosal perfusion only.

However, H_2 blockers such as ranitidine may fail to control gastric juice pH, even in critically ill patient [98]. The efficacy of the first dose after i.v. administration is reduced within 24 h [96], and after 48 h, the gastric juice pH is again less than 4.0 for 60% of the time [44]. The proton pump inhibitor omeprazole increases gastric juice pH more efficiently and continuously than H_2 antagonists, even 24 hours after administration [96]. While abolishing acid and inhibiting bicarbonate secretion, the drug may maintain mucosal perfusion, in contrast to H_2 blockers that may decrease both acid secretion and mucosal blood flow [93]. Preserved blood flow after proton pump inhibitors may contribute to prevent stress ulcer bleeding during haemorrhagic hypotension [66].

Tonometry in fed or fasting state?

Eating a meal might serve as a stress test for mucosal vasodilator reserve as the meal stimulates gastric acid secretion, and small bowel secretions, and active resorption of

nutrients. The increased energy expenditure of the gut causes an increase in blood flow to the stomach and small gut mucosa [85]. Indeed, luminal PCO_2 may increase to 53.5 kPa in the normal stomach and duodenum after gastric feeding, as a result of buffering of the increased acid by the increased bicarbonate output [117]. As the increased post-prandial PCO_2 is caused by acid buffering, it might be expected that acid suppression could circumvent this increase. However, although H_2 antagonists can effectively block basal or fasting acid secretion, the suppression of meal-stimulated gastric acid secretion may be incomplete, even in critically ill patients [98]. Even in the presence of H_2 blockers, gastric feeding of critically ill patients may increase the gastric PCO_2 relative to blood values, presumably as a consequence of the production of carbon dioxide [77,91]. This may also occur in some individuals where acid secretion has been inhibited completely by a combination of ranitidine and the muscarinic receptor antagonist pirenzepine [76,98]. The cause of this increase proved to be the buffering of the amino acid-containing food by gastroduodenal bicarbonate [76,91]. PCO_2 may also decrease shortly after gastric feeding because of dilution. Hence the volume of food given and the gastric emptying rate determine this dilution effect [76]. Finally, when the reserve in cardiac output is limited, a meal may increase blood flow in the proximal gastrointestinal tract while diminishing blood flow and pHi in the distal gastrointestinal tract [85]. Hence, normal tonometry variables after a meal do not exclude gastrointestinal hypoperfusion. Taken together, it is recommended to perform gastric tonometry in the fasting state as this may increase specificity, even though it may decrease the sensitivity of the method [36,46,47,76,77,91]. Alternatively, duodenal feeding may affect gastric tonometry less than gastric feeding.

Confounding factors

In the colon, carbon dioxide production by bacteria may lead to a lower normal pHi than in the stomach [12,37]. Indeed, normal colonic PCO_2 may amount to 40 kPa, depending on the diet [20]. In horses, who have a large bacterial flora and eat almost exclusively carbohydrates, the normal colonic PCO_2 was >26.7 kPa [125]. These observations should prompt collection of data for normal values of colonic PCO_2 or the effects of bowel preparation, laxatives or antibiotics, as sigmoid tonometry has been reported to be of value in aortic surgery patients. Entry of environmental air into the stomach may transiently lower gastric PCO_2 [20]. Hence a negative gradient may indicate a measurement artefact. This occurs particularly in non-intubated, spontaneously breathing patients.

Sources of error during manual fluid tonometry

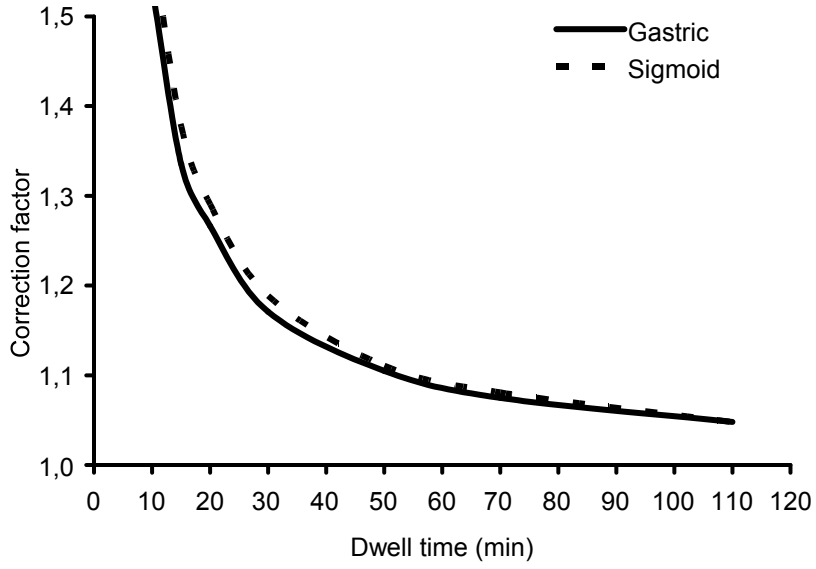
Manual fluid (usually saline) PCO_2 tonometry is laborious and involves seven steps, each carrying a risk of error so that reproducibility may be relatively poor (Table 2) [28,135]. The steps are: (1) infusion of exactly 2.5 ml in the catheter, (2) waiting a fixed dwell time to allow for (partial) equilibration with surrounding luminal PCO_2 (in most studies 30 min), (3) withdrawing and discarding the first 1.0 ml representing catheter dead space, (4) aspiration of the final 1.5 ml in a syringe, capping and storage on ice, (5) sending the capped syringe to the laboratory for analysis in the blood-gas analyzer without delay,

and (6) calculation of steady-state PCO_2 using a correction factor for each dwell time that is less than needed for full equilibration (figure 2). With the help of the PCO_2, the arterial blood bicarbonate content and the Henderson-Hasselbalch equation, a regional, mucosal pH (pHi) can be calculated. It is likely that the sources of error involved in manual fluid tonometry have limited its wide scale clinical application [28,46].

Table 2. Sources of error associated with manual fluid tonometry.

Problem	***Result***	***Solution***
Blood-gas analyzer bias	Error, dependent on fluid and analyzer	Evaluate and correct
Measurement error	in vitro 3%, in vivo 6-8%	-
Poor anaerobic technique	Decrease in PCO_2 of 8%	Careful anaerobic technique
Improper storage of syringe	Decrease in PCO_2 after 60 min of at least 8%	No delay before analysis
Imprecise dwell time	Error	Instructions and training, or dwell times >60 min
Dead space contamination	Error of 6-10 % at 10 or 20 min dwell times	Rinse tonometer 4 times prior to fluid installation
Incorrect correction factors	Error	Use correct correction factors

Figure 2. Manual saline tonometry: the correction factor is obtained for use in calculating steady state PCO_2 from measured PCO_2 when a dwell time is used which is less than that needed for full equilibration. Gastric- and sigmoid-type tonometers are shown.



Catheter dead space

With each tonometer measurement, the balloon fluid is aspirated and measured in a blood-gas analyzer. However, as the volume of tonometer tube itself is approximately 1.0 ml, the last 1 ml from the balloon resides in this dead space. With a new measurement, this 1.0 ml dead space volume is then pushed into the balloon and mixed with freshly infused fluid. Thus the PCO_2 in the balloon at the start of the dwell time is variable and depends partly on the last measured PCO_2. We found that with dwell times of 10 and 20 min, this phenomenon may cause errors in measured PCO_2 of 10% and 6%, respectively, at a dead space PCO_2 of 4.0 kPa. At longer dwell times this error becomes negligible [124]. The dead space error can be avoided either by calculation based on the last measured PCO_2 and the dwell time or by flushing the tonometer four times with fresh saline in order to remove all remaining carbon dioxide containing saline in the catheter dead space, thus ensuring a stable PCO_2 of 0 kPa in the tonometer balloon before each subsequent measurement [124]. Errors associated with an unrecognized dead space effect may have influenced the manufacturer's correction factors for short dwell times.

Blood gas analyzer bias and dwell time-dependent correction factors

It has become apparent that blood-gas analysers, calibrated for blood or calibration fluid, may underestimate the PCO_2 measured in saline (or air) by 5-50% [72,80,82,114,129]. The magnitude of the error depends on the fluid and blood-gas analyzer used, and potentially on the absolute PCO_2 [72,82,114,129]. The mean error among analyzers (at PCO_2 40 torr) is 12%, ranging from 5 to 29% (Table 3). Consequently, other fluids have been evaluated and used, including succinylated gelatine [8,82,114], albumin [72], Hartmann's solution [114], phosphate-bicarbonate [82], and phosphate or citrate buffer [3,72,82,128,129]. Buffered solutions, including succinylated gelatine may have the advantage over non-buffered solutions that the conversion of carbon dioxide to bicarbonate in the buffer decreases the propensity for accidental losses to the environment, either via incompletely aerobic techniques or during processing in the blood-gas analyzer [114]. Their use may thus result in less bias and greater precision and reproducibility than for PCO_2 measurement in non-buffered solutions [72,82,129]. Indeed, the error in PCO_2 measurements in saline and phosphate was approximately 7% after careless syringe handling or after 1 h storage of capped syringes [82]. Measurement bias and handling errors could be reduced to approximately 3 with the use of succinylated gelatine and phosphate-bicarbonate buffer [82]. However, buffered solutions increase the time needed for PCO_2 to equilibrate by a factor 2-5 [82,129]. Non-bicarbonate-based buffered solutions could share some of the advantages without these disadvantages. Indeed, saline and phosphate had similar PCO_2 build up kinetics and similar propensity for accidental errors, while the bias for phosphate was smaller [72,82,129]. Nevertheless, saline and phosphate may be equally suitable as tonometer fluid, provided strict anaerobic techniques are used and the blood-gas analyzer bias is known and taken into account [72,82].

Table 3. Blood gas analyzer bias for P_{CO_2} measurements in saline.

Manufacturer	***First author and source***	***Bias***
Radiometer		
ABL2	Knichwitz, Anaesthesia 1995	-10
ABL3	Temmesfeld, Intensive Care Medicine 1997	-12
ABL130	Knichwitz, Anaesthesia 1995	-12
ABL300	Riddington, Critical Care Medicine 1994	-18
ABL330	Temmesfeld, Intensive Care Medicine 1997	-7
ABL505	Knichwitz, Anaesthesia 1995	-6
ABL520	Takala, Critical Care Medicine 1994	-6
ABL620	Venkatesh, Anaesthesia and Intensive Care 1998	-20
Ciba-Corning		
Ciba238	Takala, Critical Care Medicine 1994	-5
Ciba278	Kolkman, Intensive Care Medicine 1997	-15
Ciba288	Knichwitz, Anaesthesia 1995	-29
Ciba840	Kolkman, Intensive Care Medicine1997	-11
Instrumentation Laboratories		
IL1302	Takala, Critical Care Medicine 1994	-8
Novastat		
Nova4	Takala, Critical Care Medicine 1994	-26
Nova5	Temmesfeld, Intensive Care Medicine 1997	-46
Nova7	Riddington, Critical Care Medicine 1994	-49
Nova9	Knichwitz, Anaesthesia 1995	-57
Eschweiler	Knichwitz, Anaesthesia 1995	-51

Bias = percentage difference from true P_{CO_2} at a P_{CO_2} of approximately 5.3 kPa.

It is hard to asses the value of the manufacturer's correction factors as *in vitro* studies from which they have been derived have not been published and the role of the dead space effect and blood-gas analyzer bias has not taken into account [37]. Blood-gas analyzer bias has evoked debates in literature on the issue whether a correction for the bias should be superimposed on correction for incomplete equilibration via the manufacturer-provided correction factors [37,74,113]. Compared with the manufacturer's correction factors, the correction factors for short dwell times were considerably larger because we avoided the dead space effect by repeated flushing of the tonometer [80]. However, the difference at long dwell times can not be explained by these effects and must be attributed to blood-gas analyzer bias incorporated in the manufacturer's correction factors [74,80]. Indeed, the manufacturer's correction factors for dwell times beyond 90 min are large. But we have shown that after 120 min dwell time, the tonometer P_{CO_2} is 96% of the surrounding value (figure 2) with a corresponding correction factor of 1.03 compared to 1.17 advised by the manufacturer [80]. That this

1.17 does not relate to incomplete diffusion can be appreciated from a study by Fiddian-Green and colleagues documenting the same PCO_2 after dwell times of 60 and 360 min [37]. In fact, correction for both incomplete equilibration using the factors supplied by the manufacturer and blood-gas analyzer bias may result in overestimations of PCO_2 while incomplete correction may result in underestimations [56,63,80].

In vitro corrections factors have been assumed to apply to the *in vivo* situation [27]. However, in comparing PCO_2 equilibration kinetics of tonometers placed in a saline bath and in the stomach of healthy volunteers, the rate of PCO_2 equilibration in the latter proved 31 % slower [80]. This may relate to gastric juice, gastric folds and mucus covering the tonometer balloon *in vivo*. Finally, the rate of PCO_2 build-up depends on the size and diameter of the catheter, because of the sink effect of the dead space [124]. Hence, equilibration may be a few percent slower when using a long, sigmoid-type catheter instead of the shorter gastric type. This is relevant at 10 min dwell times only [124]. When the sources of error are taken into account, manual measurements are not only reproducible but also accurate [80]. The response of the fluid technique, however, remains relatively slow.

Temperature corrections

As with blood PCO_2 and acid-base balance, it is unclear whether tonometer fluid PCO_2 and pHi should be corrected for body temperature if it is not 37 °C, for example during hypothermia or fever, as the correction on the blood gas machine may yield unpredictable results [8,29,63]. Nevertheless, it seems prudent to calculate the PCO_2 blood-tonometer fluid gradient from measurements made at the same temperature.

Air and others types of tonometry

From animal and human (post-cardiac surgery) studies, it has been suggested that PCO_2 determination in gastric air or juice would represent mucosal PCO_2 and could replace the balloon tonometry technique [118]. The balloon technique facilitates and standardizes gastric sampling, and air as opposed to saline tonometry allows more rapid diffusion and thus a shorter response time [129].

The recently introduced semi-continuous automated air tonometry involves a pump which automatically inflates (and deflates) via an airtight circuit, 6-8 ml of air into the tonometer balloon every 5-60 min (standard 10 min). This measures PCO_2 in the aspirated air using a modified infrared capnograph and may eliminate some of the sources of measurement error of the manual fluid tonometry, thereby increasing the clinical applicability of the technique [8,27,58,63,81,127,129]. The device is commercially available (Tonocap, Datex, Finland). The response time of the Tonocap, defined as the time needed to reach a 95% change in PCO_2 at dwell times of 5-10 min dwell times, was 10 to 18 min. Bias was +1 to -3% and precision about 1% [27,58,81,129]. The relatively long response time, particularly at a high PCO_2 and in comparison with the dwell time, may relate to a dead space effect. PCO_2 measurements by the air tonometry technique may underestimate (high) saline tonometric PCO_2, even if they are highly correlated [27,58,63,80,118]. This may relate to "overcorrection" of the latter. Air tonometry may also overestimate saline

tonometry, possibly as a consequence of wrong correction factors for the saline technique [8,27]. The techniques may have some methodological problems and sources of error in common. This may relate, in part, to the probable need for fasting and gastric acid secretion inhibition and the value of the pHi versus the tonometer-blood PCO_2 gradient. The accuracy of PCO_2 measured by air tonometry is not influenced by temperature corrections [8].

Capnometric recirculating gas tonometry involves a tonometer with two lumina, connected to a circulation pump and an infrared sensor, yielding PCO_2 measurements which correlate highly with those obtained by the manual saline technique [50,51,52]. Compared with the latter, recirculating gas tonometry has a more rapid response time (5 min), allows on line measurements and is more sensitive during haemorrhage and endotoxaemia [50,51,52]. A new method involves a fiberoptic PCO_2 sensor which allows monitoring of pH and PO_2 [73]. The sensor proved faster and more accurate than saline tonometry, both *in vitro* and *in vivo*. The potential for using this probe nasogastrically needs further study. Other techniques that may become available for direct mucosal PCO_2 measurements include the ion sensitive field effect transistor sensor [101,104,119,126]. Finally, tonometry can also be used to measure gastrointestinal luminal nitric oxide concentrations [1].

CLINICAL APPLICATIONS

Diagnostic aid in symptomatic celiac and mesenteric vascular disease

Some patients with otherwise unexplained abdominal signs of dyspepsia and pain (abdominal angina) may have chronic gastrointestinal vascular disease, but it is hard to establish a relation between signs and symptoms on the one hand and objective indicators of gastrointestinal hypoperfusion, such as abnormal angiographic findings, on the other [81]. The management of these patients and the effect of reconstructive vascular surgery may be hard to predict. A diagnostic test for gastrointestinal hypoperfusion, that also predicts the success of surgery is therefore needed [81,85]. It has been suggested that gastric tonometry during a test meal may be used [16,39]. However, feeding may confound tonometry in the stomach and may thereby yield negative results, even in patients with otherwise proven splanchnic hypoperfusion [43,77]. Alternatively, during exercise, the perfusion of the splanchnic organs is at risk because of the "steal" effect of the increased blood flow to skeletal muscle. Hence, vascular disease in the splanchnic region and diminished vasodilator reserve could increase the risk for hypoperfusion during exercise. Indeed, many patients with presumed gastrointestinal vascular disease may have abdominal complaints on exercise. We therefore assessed the value of gastric exercise tonometry in managing patients with suspected gastrointestinal hypoperfusion. When the patients were divided on the basis of normal angiograms and those with stenotic lesions in the celiac or superior mesenteric artery, the PCO_2 gradient during exercise did not increase in the former but increased to about 2.7 kPa in the latter group, with only a minority of patients

exhibiting a supranormal gradient at rest. Furthermore, the exercise tonometric findings correlated with a symptom score, the extent of angiographic abnormalities and the presence of discrete mucosal lesions on gastroscopy, consistent with mucosal hypoperfusion and damage. In some patients re-examined after reconstructive surgery, the exercise tonometry test had normalized [78]. Gastric tonometry could help to diagnose acute mesenteric vascular disease resulting in bowel hypoperfusion and necrosis, provided that the stomach is also partly involved and some metabolism remains [10,73,118].

Estimating prognosis from pHi or the PCO_2 gradient and pHi in critically ill patients

The conditions wherein (gastric) tonometric variables proved prognostically significant for the development of multiple organ failure and subsequent death are: orthotopic liver transplantation [136]; acute pancreatitis [17]; cardiopulmonary bypass and other types of major, emergency vascular surgery [29,30,41,49,54,95,115]; sepsis; trauma [25,26,49,62,65,68,84]; and mechanical ventilation [31,59,94,97]. Furthermore, an elevated PCO_2 gradient and a low pHi were predictive of failure to wean mechanically ventilated patients, independently of arterial blood and ventilatory variables, presumably because of splanchnic diversion of blood flow to exercising respiratory muscles with an increased workload [18,31,97].

The fact that tonometric PCO_2 depends partly on arterial PCO_2, and that the bicarbonate content is shared between arterial pH and calculated pHi, may explain the correlation observed between arterial pH and pHi, and the approximate similar predictive value of both indices [19,23,41,45]. Although splanchnic hypoperfusion and lactate production may influence the systemic indicators, tonometric variables may nevertheless correlate only poorly with systemic factors [40,48]. As hyperlactataemia-associated metabolic acidosis is prognostically unfavourable in critically ill patients, it can be questioned if tonometry is of additive predictive value [4,19,48,59,62,65,84]. A low (subnormal) pHi or elevated PCO_2 gradient may be superior or have additive value in the prediction of morbidity, that is multiple organ failure and mortality, to global haemodynamic and metabolic variables, including the lactate concentration and acid-base variables in the systemic blood of critically ill patients [25,26,32,40,42,56,59,62,68,84,94,95,97,99]. A subnormal gastric pHi may predict circulating markers of an inflammatory response and a poor outcome with postoperative complications and multiple organ failure, after major cardiac, vascular and abdominal surgery [30,99]. After cardiopulmonary bypass surgery, however, neither the pHi nor the PCO_2 gradient in the stomach may constitute an early predictor of increased permeability, endotoxaemia and death in the ICU, whereas global haemodynamics and the systemic lactate level may predict a downhill disease course [6,14,54,115].

Even though the PCO_2 or pH gradients may be more specific indicators of gastric hypoperfusion than the pHi, it may be questioned if the former are equally useful prognostic parameters as the pHi, which incorporates a systemic variable [25,26,40,42,45,59,62,68,94]. In recent studies in critically ill patients pHi, but not pH or PCO_2 gradients, proved prognostic indicators [45,59], suggesting an additive value of systemic acid-base disorders in predicting outcome. In addition, a low pHi may predict occurrence of stress ulcer

bleeding and ischaemic colitis, when measured in the stomach and sigmoid colon of critically ill patients [12,37,71,123,131]. Hence pHi may be superior to the PCO_2 gradient in predicting stress ulcer (bleeding) in the stomach, since the development of stress ulcers may not only relate to local factors but also to systemic acidosis [69]. In fact, lowering of the blood bicarbonate content is a risk factor and systemic alkalinization protects against stress ulcer development during haemorrhagic shock and mucosal hypoperfusion in animals [69]. Taken together, it emerges that the components of pHi, PCO_2 as measure of alveolar ventilation and gastric hypoperfusion, and bicarbonate concentration as measure of general circulation status, are of varying importance in different patients and disease stages.

Children

In a study in paediatric patients with sepsis, lactate content, but not pHi or PCO_2 gradients, predicted outcome, suggesting superiority of systemic over regional abnormalities [32]. In contrast, in many other studies on critically ill (septic) children, pHi and PCO_2 (or pH) gradient were better predictors than systemic haemodynamic and metabolic variables, including the blood pH, bicarbonate and lactate concentrations, for haemodynamic complications, multiple organ failure and survival [23,24,31,32,56,84].

Sigmoid colon

Even though the appropriate methodology of sigmoid tonometry has still to be established, studies have suggested that the technique may be helpful in predicting tissue hypoxia and injury leading to ischaemic colitis, the main cause of morbidity and mortality after major abdominal vascular surgery [12,37,71,123,131]. Colonic hypoperfusion detected by tonometry may be associated with endotoxaemia and cytokine release that might contribute to mortality [123]. Gastric tonometry may also be of predictive value after (emergency) major vascular surgery [12,89,95].

Effect of interventions

As a low gastric pHi or elevated PCO_2 gradient may be prognostically important, studies have examined the effect of various interventions on the tonometric variables, but the beneficial effect on morbidity and mortality of "pHi guided" treatment is still controversial [7,49,105,109]. A variety of treatment procedures consisting of fluid and drug therapy, such as dopamine, dopexamine, epinephrine and norepinephrine, aimed at restoration of splanchnic blood flow, have been evaluated after cardiopulmonary bypass surgery [11,42,100,111,112,130], trauma and sepsis [15,48,49,68,87,88,102,103,122,128]. Colloid fluids may be superior to crystalloids but different types may differ in their capability to increase global oxygen delivery and uptake, and to ameliorate a low gastric pHi, in septic and postoperative patients [15,92]. Some catecholamine treatments in haemodynamically compromised patients may benefit the splanchnic circulation and others may not, as judged from a fall in the gastric PCO_2, an increase in pHi, or both, in a variety of conditions [7,11,42,48,87,88,92,103,108,111,122,128,130]. For example, norepinephrine and dobutamine decreased the (elevated) gastric PCO_2 gradient and increased the

(subnormal) pHi. Dopamine, dopexamine, or epinephrine treatment had no effect or tended to further decrease the pHi in the treatment of sepsis and shock, even if systemic haemodynamics were unchanged or improved [48,87,88,92,103,128]. Dopexamine or dobutamine treatment may not prevent a decrease in pHi during and after cardiopulmonary bypass surgery, even if they increase systemic and hepatosplanchnic blood flow and oxygen delivery [11,42,111,130]. In other critically ill patients, dopexamine appeared to improve splanchnic blood flow and a subnormal pHi, independently of systemic haemodynamics, suggesting selective splanchnic vasodilation, while dopamine had no such effect [122].

Vasodilator therapy by infusion or inhalation of prostacyclin may improve hepatosplanchnic blood flow and decrease the tonometric gastric PCO_2 gradient during septic shock [34]. Administration of nitroprusside or angiotensin converting enzyme (ACE) inhibitors did not change the gastric PCO_2 gradient or pHi after cardiac surgery and this argues against a role for angiotensin in splanchnic vasoconstriction [110,112]. ACE inhibition may ameliorate an increased PCO_2 gradient and a low pHi in trauma, even if systemic haemodynamic variables do not change [67]. Pulsatile blood flow may better preserve gastric mucosal perfusion adequacy than non-pulsatile flow during cardiopulmonary bypass [41]. Inducing muscular paralysis in mechanically ventilated patients may increase a reduced pHi, suggesting redistribution of blood flow from respiratory to splanchnic organs [90]. Treatment of sepsis and trauma patients with antioxidants may prevent a decrease in oxygen extraction abilities, and gastric pHi, particularly during transient hyperoxia [7]. During large intestinal surgery, gastric PCO_2 increased relative to blood values, independent of unchanged global haemodynamics; adjunctive clonidine administration did not attenuate this increase [134]. Abdominal decompression in trauma-related intra-abdominal hypertension may normalize a low pHi, particularly in patients who survive [61].

CONCLUSION

Gastrointestinal tonometry of the luminal to blood PCO_2 gradient can be used to assess adequacy of mucosal perfusion provided that, if applied to the empty stomach, acid buffering and carbon dioxide generation are avoided. Appropriate use may improve the accuracy of manual fluid tonometry until the semi-continuous automated air tonometry technique, which may eliminate some sources of error inherent to the manual technique, becomes widely available. This may broaden the clinical applicability of gastrointestinal luminal tonometry as a monitoring tool in a variety of conditions.

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Chapter 3

Exercise Induces Gastric Ischemia in Healthy Volunteers. A Tonometry Study.

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ABSTRACT

Heavy physical exercise may cause gastrointestinal signs and symptoms, and even though splanchnic blood flow may decrease through redistribution by more than 50 %, it is unclear whether these signs and symptoms relate to gastrointestinal ischemia. In ten healthy volunteers, we studied the effect of exercise on gastric mucosal perfusion adequacy using air tonometry. Two relatively short (10-min.) exercise stages were conducted on a cycle ergometer, aiming for 80% of maximum heart rate and 100% of maximum heart rate, respectively. The gastric intragastric-arterial P_{CO_2} gradient (ΔP_{CO_2}) was elevated (by 1.1 ± 1.0 kPa) over baseline values (-0.1 ± 0.3 kPa) only after maximal exercise ($p<0.001$). The ΔP_{CO_2} positively correlated with the arterial lactate level, taken as an index of exercise intensity (Spearman's rank test: $r=0.76$, $p<0.0001$). By bilinear regression analysis, a lactate level of 12 mmol/l above which a sharp rise in the ΔP_{CO_2} occurred, was calculated. We conclude that in healthy volunteers with normal splanchnic vasculature, gastric ischemia may develop during maximal exercise, as judged from intragastric P_{CO_2} tonometry.

INTRODUCTION

During heavy physical exercise, up to 80 per cent of the increase in cardiac output may be directed to the working muscles to match the increased metabolic demands, thereby curtailing blood flow to splanchnic organs [43]. Using Doppler-ultrasonography, a decrease in splanchnic blood flow of up to 50% has been observed following physical exercise [32,34]. The consequences of such a decrease in blood flow are unclear, but may lead to gut mucosal ischemia, as observed in animal models of shock [15].

It is well established that strenuous exercise may lead to gastrointestinal abnormalities and cause symptoms such as abdominal pain or discomfort, nausea, vomiting, and diarrhoea. Numerous studies have focused on gastrointestinal disorders during exercise [2,21,24,25,28,29,33,35,41]. The majority of these studies addressed the subject of gastrointestinal motility but few have investigated the possible role of ischemia as underlying cause [3,8,12,22,36,38,42]. This may be partly explained by the lack of an accurate test to assess actual ischemia, independent of metabolic rate and absolute perfusion.

Changes in perfusion per se do not necessarily indicate changes in oxygen supply to demand balance, when demand decreases as a consequence of fasting, for instance. The intragastric luminal PCO_2 as measured by tonometry, however, is considered to reflect the mucosal oxygen supply to demand balance [18], so that hypoperfusion increases the intragastric-arterial PCO_2 gradient (ΔPCO_2), following a decreased washout and increased production of CO_2 in ischemic tissue, by liberation of CO_2 from HCO_3^- buffering of anaerobically produced metabolic acids [10]. In fact, heavy exercise may result in an increase of ΔPCO_2 [31]. The latter study, however, does not give insight into the level of exercise inducing gastric mucosal ischemia. This is of importance since exercise tonometry has been suggested in a previous paper by the authors to be a non-invasive diagnostic tool for stenotic splanchnic vascular disease [17], but the specificity of abnormal exercise tonometry for vascular disease should be confirmed by normal tonometric values at a similar level of exercise in healthy volunteers with normal splanchnic blood vessels. The cited study was done with help of the slow manual saline tonometry system, while the introduction of air tonometry thereafter has allowed for more rapid and accurate intragastric PCO_2 tonometry [20].

In consideration of above data, we hypothesised that maximal rather than submaximal exercise in healthy volunteers with normal splanchnic blood vessels causes gastric mucosal ischemia as judged from intragastric air PCO_2 tonometry.

MATERIALS AND METHODS

Subjects

Ten healthy untrained and non-smoking volunteers (5 males and 5 females, mean age 25.4 range 23-28 years), taking no medication other than oral contraceptives, were included in the study. All subjects were informed about the nature, purpose and possible risks involved in the study before giving their consent. The study was

performed according to the ethical guidelines of our institution after approval of the Institutional Ethics Committee.

Duplex sonography

To exclude splanchnic arterial abnormalities, all subjects underwent Duplex sonography of the splanchnic vessels. In the week prior to the exercise studies, following an overnight fast, Duplex sonography was performed by an experienced investigator (B.H.G.) using a Diasonics VST-master ultrasonography device. After identifying the vessels and confirming patency and antegrade flow, the peak-systolic and end-diastolic flow velocities during in- and expiration were measured in the celiac (CA) and superior mesenteric (SMA) arteries and the aorta. Peak-systolic flow velocities below 200 and 275 cm/sec and end-diastolic flow velocities below 55 and 45 cm/sec were regarded as normal for the CA and SMA, respectively [26,30].

Tonometry

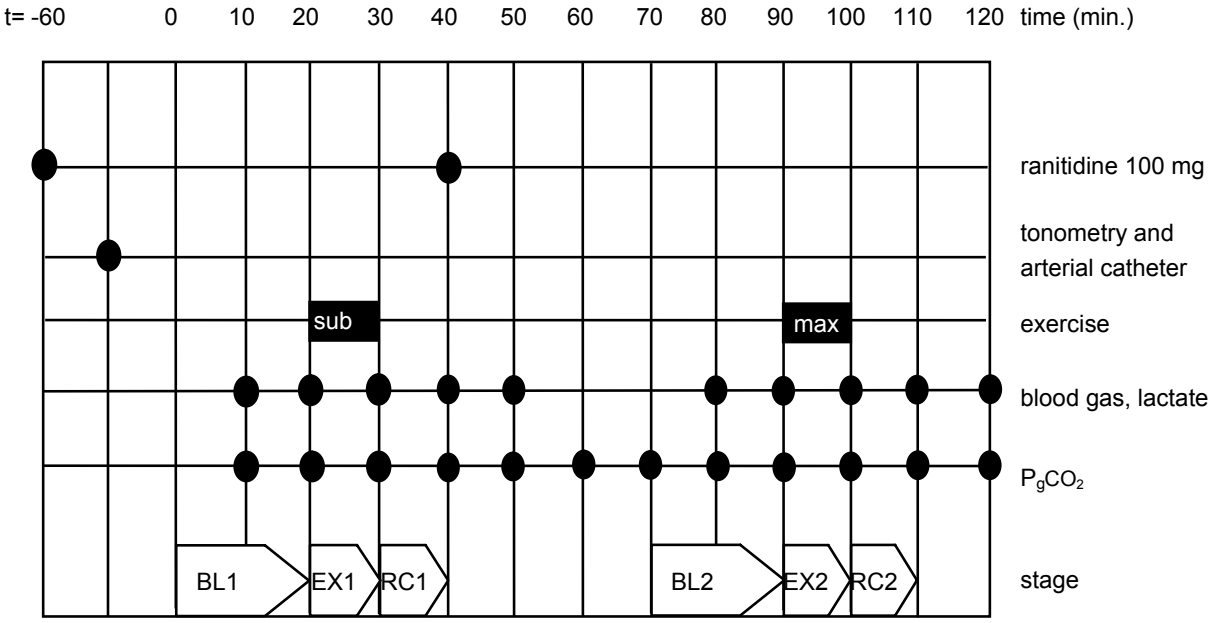
The subjects were studied in the afternoon, after a fasting episode of at least four hours following a light breakfast. One week prior to tonometry exercise testing, the maximum workload and heart rate (HR_{max}) were determined utilizing an incremental exercise protocol (cycle ergometry, work rate increment 25Watt/min) until exhaustion [11]. A standard balloon-tipped tonometry catheter (Trip sigmoid catheter, Tonometrics, Helsinki, Finland) was inserted nasogastrically and placed at 55 cm from the tip of the nose. The catheter was attached to an automated air tonometry device (Tonocap, Datex-Engstrom, Finland) which uses a pump to automatically inflate and deflate the tonometer balloon via an airtight circuit, and analyzes PCO_2 of the aspirated gas by infrared capnography. The tonometry device was set up to measure intragastric PCO_2 (P_gCO_2) every ten minutes. To prevent CO_2 production by buffering of gastric acid, 100 mg of ranitidine was administered intravenously one hour prior to the baseline tonometry measurements (t=-60 min) and again immediately after the first exercise episode (t=30 min). This dose of ranitidine sufficiently suppresses gastric acid production within one hour [19,39].
A radial artery catheter was inserted in the non-dominant arm to allow blood sampling.

Exercise testing

We applied two exercise periods (EX1 and EX2), ten minutes of duration each, with 60 minutes of rest between the two periods. The two exercise periods were aimed to result in steady state exercise at a submaximal (80% of HR_{max}) and maximal work rate level (100% of HR_{max}), respectively. To achieve this, the workload was gradually increased during the first 5-min of EX1 and 7-8 min of EX2, and remained constant thereafter. Exercise was performed on an electromagnetically braked bicycle ergometer (Lode, Groningen, Netherlands). During the exercise stages a 12-lead electrocardiogram was recorded (Case 12, Marquette Electronics Inc., Milwaukee, USA) and in all but one subject breath-by-breath oxygen uptake (VO_2), and respiratory gas exchange ratio (RQ)

were measured by a respiratory gas analyzer system (Oxycon-α Jaeger, Bunnik, the Netherlands).

Figure 1. Schematic time frame of the exercise tonometry study.



Protocol

In figure 1 the time frame of the study protocol is schematically displayed. Baseline measurements of blood and tonometric variables were done at t=10 and t=20 min. (BL1). The submaximal exercise period (EX1) was from t=20 to 30, with measurements at t=30 min. Recovery measurements (RC1) were done at t=40 min. After a wash-out period, the second baseline period measurements were done and at t=70 and t=80 (BL2), followed by the maximal exercise period (EX2) from t=80 to 90, with measurements at t=90 min. A second recovery measurement (RC2) was done at t=100 min. During exercise, the heart rate (HR) was recorded and the percentage of HR_{max} was calculated every 30 seconds. VO_2 and RQ were averaged and stored every 30 sec during the exercise periods. VO_2 is expressed as percentage of predicted maximum VO_2 (VO_{2max}). Predicted VO_{2max} was calculated using equations by Wasserman [44]. At t=10, t=20, t=30, t=40, t=70, t=80, t=90, and t=100 min, arterial blood samples were drawn for determination of arterial PCO_2 (P_aCO_2), base excess, and bicarbonate (blood gas analyzer; Radiometer ABL520, Copenhagen, Denmark), and lactate (enzymatic assay; Cobas Fara, Roche Diagnostics, Branchburg, USA). Every ten minutes the Tonocap® measured P_gCO_2. The gastric-arterial PCO_2 gradient ($\Delta PCO_2 = P_gCO_2 - P_aCO_2$) was calculated.

Statistics

Values are given as mean ± SD unless otherwise stated. For all baseline values the mean of the two consecutive measurements was taken. Differences between study periods for any given parameter were tested by one way analysis of variance (ANOVA) for repeated measurements, followed by a Tukey-Kramer multiple comparison test. For the pooled results of both exercise periods, the relation between maximal lactate levels and ΔP_{CO_2} was calculated using Spearman's rank correlation coefficient. Bilinear regression analysis was done to evaluate a lactate level threshold for P_gCO_2 rises [7]. A p-value < 0.05 was considered statistically significant.

RESULTS

Duplex sonography

All subjects had normal patent CA and SMA with antegrade flow in both vessels. Due to intestinal gas, reliable flow measurements were not possible in the CA in one subject and in both vessels in another subject. All others had normal flow velocities.

Exercise tonometry

Cardiopulmonary measurements. There were no differences in HR, VO_2, and RQ between the two baseline episodes (Table 1). At the end of both exercise stages all cardiopulmonary parameters differed from baseline. HR increased from 78 ± 14 at baseline to 162 ± 6 beats/min (83 ± 3 % of HR_{max}) after EX1 ($p<0.0001$) and to 189 ± 8 beats/min (97 ± 4 % of HR_{max}) after EX2 ($p<0.0001$). The VO_2 rose to 91 ± 23 % of predicted VO_{2max} at the end of EX1 and to 130 ± 20 % of predicted VO_{2max} at the end of EX2 ($p<0.0001$ for both *vs.* baseline).

Table 1. The study parameters at different baseline, exercise and recovery periods.

	BL1	EX1	RC1	BL2	EX2		RC2
HR (/min)	78±14	162±6**		83±12	189±8**	††	
% of HR_{max}		83±3			97±4	††	
VO_2 (l/min)	0.43±0.17	2.12±0.64**		0.43±0.18	3.04±0.75**	††	
RQ	0.72±0.04	0.99±0.07**		0.72±0.06	1.11±0.08**	††	
P_aCO_2 (kPa)	5.1±0.7	5.0±0.5	4.9±0.4	5.0±0.6**	4.4±0.7**	†	4.3±0.5**
HCO_3^- (mmol/l)	23.9±2.2	19.1±1.6**	20.4±1.3**	23.7±1.9	14.2±2.5**	†	14.9±2.9**
BE (mmol/l)	-0.3±1.6	-6.0±1.8**	-3.8±1.6**	-0.1±1.5	-11.8±3.0**	†	-10.5±3.9**
lactate (mmol/l)	0.5±0.1	6.5±2.4**	3.3±1.6**	0.7±0.2	12.8±3.2**	†	8.7±3.2**
P_gCO_2 (kPa)	4.9±0.6	5.3±0.6*	4.9±0.5	4.9±0.6	5.5±0.6**		5.0±0.4

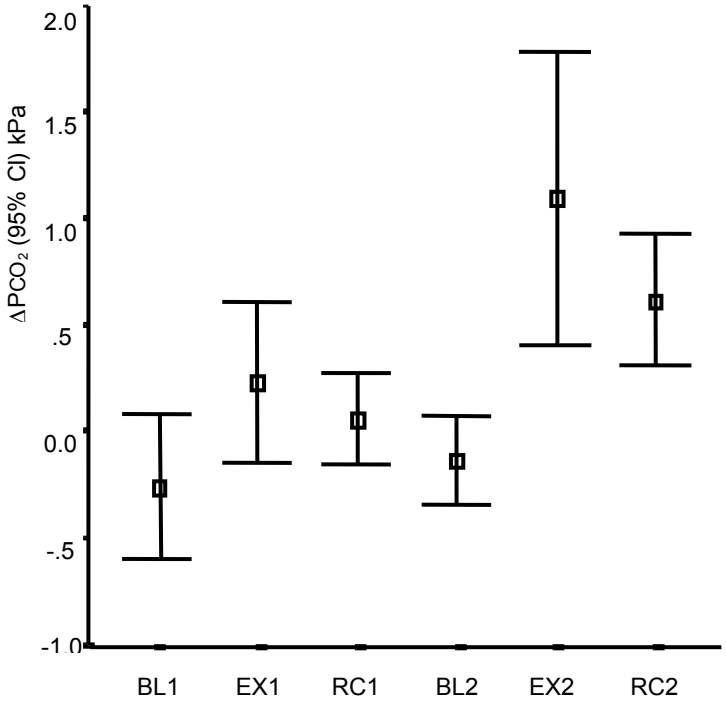
Values in mean ± SD; for abbreviations see text
* $p< 0.05$ for value *vs.* baseline value, ** $p< 0.001$ for value *vs.* baseline value,
† $p<0.001$ for value comparing EX1 *vs.* EX2, †† $p<0.0005$ for comparing EX1 *vs.* EX2

Blood parameters. There were no differences between the two baseline episodes. P_aCO_2 did not change after EX1 but decreased after EX2 and remained below baseline in RC2. The lactate increased and the bicarbonate and BE levels decreased during both exercise periods, but more during EX2 than EX1.

Tonometry parameters. The baseline P_gCO_2 did not differ between both baseline periods. During EX1, P_gCO_2 increased, whereas the ΔPCO_2 did not change significantly (figure 2). During EX2, P_gCO_2 and ΔPCO_2 increased. During RC2 P_gCO_2 returned to baseline but ΔPCO_2 remained elevated over baseline. The mean P_gCO_2 in both baseline periods was 4.9 ± 0.2 kPa, the coefficient of variation 4.3%. The ΔPCO_2 during both baseline periods was –0.2 ± 0.4 kPa, with an upper limit of normal (mean + 2 SD) 0.6 kPa.

Tonometry variables vs. exercise level. A positive correlation was observed between both P_gCO_2 and ΔPCO_2 with exercise level, as indicated by serum lactate at the end of the exercise stage ($r = 0.50$, $p<0.05$ and $r = 0.76$, $p<0.0001$). No increase of ΔPCO_2 over the normal upper threshold of 0.8 kPa was seen during exercise with lactate levels below 8 mmol/l, while in 5 out of 6 tests resulting lactate levels above 14 mmol/l the ΔPCO_2 exceeded this threshold [19]. In figure 3 the relationship between serum lactate level at the end of the exercise stage and ΔPCO_2 is shown. Using bilinear regression analysis, a lactate threshold value of 12 mmol/l was calculated above which ΔPCO_2 started to rise ($r^2 = 0.73$).

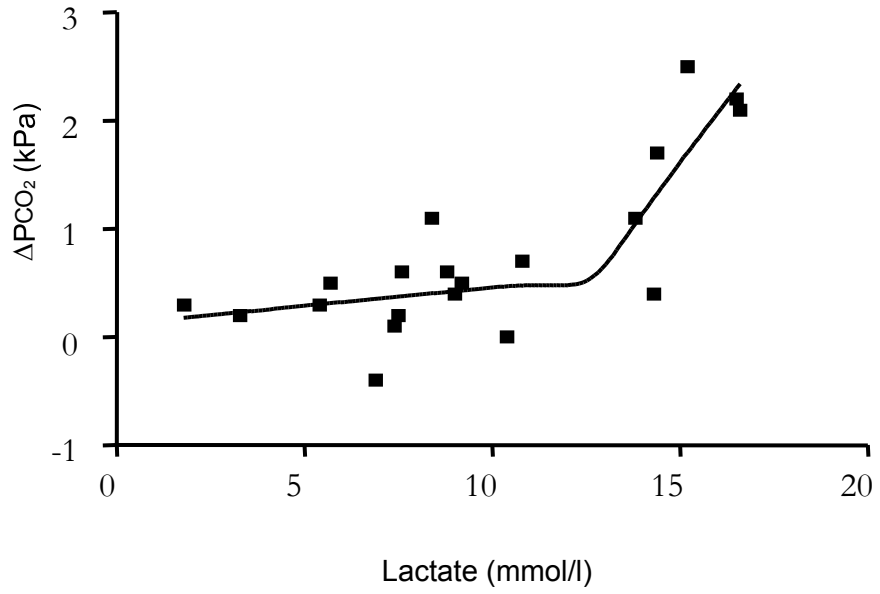
Figure 2. ΔPCO_2 in the different test episodes. Values are means ± SD.



	BL1	EX1	RC1	BL2	EX2	RC2	
ΔPCO_2	-0.3±0.5	0.2±0.5	0.1±0.3	-0.1±0.3	1.1±1.0*†	0.6±0.4*	kPa

*p< 0.05 for value *vs*. baseline value; †p<0.001 for value comparing EX1 *vs*. EX2

Figure 3. Gastric-blood PCO_2 gradient *vs.* lactate level after 10 min. exercise



DISCUSSION

The results of the present study show that in subjects with normal splanchnic vasculature, gastric ischemia can develop after only 10 minutes of maximum physical exercise. The development of gastric ischemia strongly depended upon the exercise intensity. Furthermore, our study demonstrates that air tonometry can be used for assessment of the adequacy of gastric mucosal perfusion during physical exercise.

The bilinear pattern of the gastric-blood PCO_2 gradient during exercise, with a marked increase above a threshold exercise intensity, is in agreement with studies indicating that tonometric measurement of gastric intramucosal PCO_2 is a reliable index of the adequacy of splanchnic mucosal perfusion [16,18]. If tonometry results depend on blood flow only, a linear pattern between PCO_2 gradient and lactate should have been observed [13]. In contrast, it was previously shown in animal models that a small reduction in gastrointestinal blood flow did not influence the P_gCO_2, but when the blood flow fell to less than 50% of baseline, hypoperfusion caused an increased P_gCO_2 in parallel with a fall in tissue O_2 tension and consumption [15,40]. Indeed, the gastric-blood PCO_2 gradient may be the most sensitive and specific tonometric parameter of gastrointestinal perfusion, independent of systemic metabolic and respiratory changes [18].

The increase in ΔPCO_2 during maximal exercise is partly caused by a decrease in P_aCO_2. The latter is the result of increased alveolar ventilation in response to metabolic acidosis due to anaerobic muscular metabolism [11]. However, in mechanically ventilated patients is has been shown that changes in P_aCO_2 are closely and swiftly followed by changes in P_gCO_2, thereby not influencing ΔPCO_2 [23]. But, even if neglecting the decrease in P_aCO_2, the relationship between the increase in P_gCO_2 during exercise and arterial lactate level shows a similar bilinear pattern as ΔPCO_2 *vs.* lactate level: no increase of P_gCO_2 up to a

threshold lactate level of 12 mmol/l and an increase above this lactate threshold ($r^2 = 0.36$).

Our present study confirms the findings of the study of Nielsen et al. which showed that gastric ischemia occurred during heavy exercise in trained rowers at exercise levels close to their maximum aerobic capacity [31]. Using fluid tonometry they observed, similar to our present study, a gradual increase in P_gCO_2 during exercise with a concomitant decrease in P_aCO_2. A direct comparison of both studies is difficult since the Nielsen study reported on the previously advocated but now largely abandoned pHi, a calculated value incorporating arterial bicarbonate levels as well. With profound metabolic acidosis, the pHi might be a poorer predictor of mucosal ischemia than ΔPCO_2. Another potential confounding factor might have been insufficient acid suppression, as one of their baseline P_gCO_2 already measured up to 8.5 kPa. Similar to previous studies by our group, we used high dose intravenous ranitidine to ensure adequate acid suppression in our subjects [19].

Automated air tonometry offers several advantages over manual fluid tonometry, including superior accuracy, speed and reproducibility [18]. It is less laborious and involves less error-prone steps, and the faster diffusion of CO_2 in air results in shorter equilibration times. In our study, air tonometry may have slightly underestimated P_gCO_2 values, leading to negative ΔPCO_2 baseline values in the majority of measurements (28 of 40 baseline measurements). In one subject in our study, all P_gCO_2 values were lower than arterial PCO_2 values, resulting in negative gradients, even at maximal exercise. The most likely explanation is the occurrence of air swallowing causing dilution of intragastric gas.

The ΔPCO_2 threshold for anaerobic metabolism is still unclear [18]. The range of normal P_gCO_2 and ΔPCO_2 in our study is in close agreement with the study by Creteur et al. on air tonometry showing a normal upper limit of normal of 0.8 kPa for the gradient [4]. Schlichtig et al. demonstrated that a fall in tissue O_2 tension and consumption, development of anaerobic metabolism and production of lactic acid, occurred at a ΔPCO_2 of 3.5 kPa or greater, a value that can be regarded as the critical gradient [40]. Thus, it may be questioned whether the increased ΔPCO_2 as shown in this study indeed indicate ischemia rather then hypoperfusion of the gastric mucosa. Nevertheless, we cannot exclude ischemia and anaerobic metabolism in the gastric mucosa even at gradients lower than the critical values reported by Schlichtig et al. The 10-minute measurement interval of air tonometry may have resulted in an underestimation of the actual peak P_gCO_2 during exercise periods of 10 min. Indeed, the first minutes of the exercise periods were used to gradually increase the workload. Therefore, anaerobic CO_2 production could have occurred only in the last minutes of the exercise episode, not lasting long enough for full PCO_2 equilibration in the tonometry balloon and resulting in a measured intragastric PCO_2 underestimating the actual intraluminal PCO_2 at the end of the exercise. Moreover, exercise-induced hypoperfusion might result in patchy ischemia with anaerobic areas surrounded by still well perfused areas, similar to the ischemic pattern demonstrated in hypovolemic shock [6,27].

An alternative explanation for increasing ΔP_{CO_2} after strenuous exercise, other than splanchnic vasoconstriction and ischemia, could be an increase in intraabdominal pressure, leading to increased wall tension in the digestive tract and even reduced mucosal flow and ischemia. Indeed, in pigs it was demonstrated that prolonged increase in intraabdominal pressure of 1.5 to 3 kPa may decrease mucosal blood flow by 30-40% [5]. Similar intraabdominal pressures have been measured during exercise [14]. However, as during exercise the intraabdominal pressure is not continuously elevated, but changing during each respiratory cycle between approximately 0 and 3 kPa it is unlikely that these short (1-2 seconds) periods of intraabdominal peak-pressure will lead to mucosal ischemia. Moreover, if gastric mucosal ischemia would have been caused by an increase in abdominal pressure during exercise, a rapid normalization in the recovery phase would be expected. In the present study however, in the recovery phase ΔP_{CO_2} remained elevated in four subjects and in one subject even further increased. This result is in agreement with the finding that during recovery after exercise the splanchnic flow may be impaired for as much as 30 minutes [34].

An interindividual difference in the response of ΔP_{CO_2} to the two exercise intensities was noted. In three subjects, the ΔP_{CO_2} after maximal exercise (with lactate levels increasing to 14.3 mmol/l) was not or only slightly higher than after submaximal exercise and still well below the normal threshold of 0.8 kPa. In contrast, in one subject ΔP_{CO_2} was already elevated after submaximal exercise (lactate 8.4 mmol/l) and increased greatly after maximal exercise (lactate 15.2 mmol/l), resulting in the highest ΔP_{CO_2} of all subjects. Although splanchnic arterial abnormalities were excluded by Duplex sonography, differences in microvascular anatomy and physiology might very well explain this interindividual susceptibility to gastric mucosal ischemia. This might result from differences in training status as, although none of the subjects were competitive athletes, all were recreationally active up to different degree [9].

Our results demonstrate a threshold in exercise intensity, as judged from the arterial lactate level, above which a marked increase in ΔP_{CO_2} as a reflection of gastric mucosal ischemia. This finding of a lactate threshold in individuals with normal splanchnic vasculature beyond which gastric ischemia may develop has important implications when using exercise gastric tonometry as a diagnostic tool in patients suspected for having splanchnic arterial disease. In these patients, in contrast to control patients, exercise of even moderate intensity has shown to lead to gastric ischemia as judged from a rise in the tonometric intragastric P_{CO_2} [17]. Our current results in healthy volunteers suggest that for optimal performance of the test in patients and in order to prevent false positive results, it is mandatory to continuously monitor and, if necessary, adjust the exercise intensity to keep the lactate level below 8 mmol/l.

In many studies, exercise led to a variety of gastrointestinal abnormalities. The etiology of these abnormalities is still unclear, however. Exercise has been shown to lead to delayed liquid gastric emptying [21,25,35], the magnitude of the delay depending on the exercise intensity [29]. Using ultrasonography it has been shown that impaired motility may be explained by exercise-induced closure of the pylorus and a decreased gastric

antral area [2]. Exercise has also shown to affect intestinal postprandial motor activity [41]. The intestinal epithelial barrier function may be impaired since heavy exercise may result in increased intestinal permeability and impaired water absorption [24]. Apart from these functional alterations, heavy exercise, especially marathon running, is also known to cause gastrointestinal blood loss, gastritis, and colitis, which are –at least partially- ascribed to gastrointestinal ischemia [3,8,12,22,36,38,42]. Although often suggested as playing a key role in the development of exercise-induced gastrointestinal abnormalities, gastrointestinal hypoperfusion has not yet been proven to be the cause of these exercise-induced abnormalities. Several investigations using Doppler ultrasound and thermodilution techniques, have shown an exercise-induced decrease of splanchnic blood flow, but failed to address the issue of metabolic demand [1,32,34,37,43]. Our present study using air tonometry shows that in subjects with normal splanchnic vasculature gastric ischemia may indeed develop early during maximum physical exercise, and that the development of gastric mucosal ischemia is strongly dependent upon the exercise intensity.

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Chapter 4

Triggering for Submaximal Exercise Level in Gastric Exercise Tonometry: Serial Lactate, Heart Rate or Respiratory Quotient?

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Submitted

ABSTRACT

Background and aims. Gastric exercise tonometry can be used for as a functional test in the diagnosis of gastrointestinal ischemia. To achieve maximal diagnostic accuracy the exercise build-up should be controlled to reach submaximal exercise levels, because maximal exercise levels can result in false-positive tests. This study evaluates three different parameters for monitoring and adjustment of exercise levels.

Methods. From 1997 – 2000, 178 exercise tests were performed in healthy volunteers as well as patients suspected of gastrointestinal ischemia. The parameters used were: heart rate monitoring (HRM), RQ-monitoring (RQM) and serial rapid lactate measurements (RLM).

Results. Exercise levels above submaximal were reached in 20% of HRM, 2% of RQM, and 5% of RLM ($p<0.05$ for HR *vs.* RQ and lactate). Low exercise levels were seen in 5%, 10% and 41% in HRM, RQM and RLM, respectively ($p<0.01$ for RLM *vs.* HRM and RQM). Low exercise levels did not result in an increase in false negative gastric exercise tonometry (5% compared to 6% of all tests, n.s.), whereas high levels resulted in 43% false-positives (compared to 19% in all tests, $p<0.001$).

Conclusion. Maximal exercise levels leads to increased false-positivity; lower exercise levels did not influence tonometry accuracy. Although RQ-monitoring resulted in the greatest proportion of optimal exercise tests, rapid serial lactate would be our method of choice, as it combines optimal diagnostic accuracy, low-cost and simplicity and allows for accurate gastric exercise tonometry in daily clinical practice.

INTRODUCTION

For diagnosis in patients with suspected chronic gastrointestinal ischemia, we have previously shown that gastric exercise tonometry can be used as a functional test providing information about the adequacy of the gastrointestinal mucosal perfusion [3,8]. In these studies it was demonstrated that during 10 minutes of submaximal exercise gastric ischemia occurred only in patients with splanchnic artery stenosis. An extreme exercise level may cause false-positive tests, as was shown in a study in healthy volunteers, where lactate levels exceeding 8 mmol/l resulted in gastric ischemia in 50% [9]. Furthermore, it may be conceivable that exercise of very low intensity can lead to false-negative results in exercise tonometry used for diagnosing chronic gastrointestinal ischemia. In order to prevent false positive and false negative tonometry tests, the exercise intensity should be monitored throughout the test and if necessary adjustments of the workload should be made in order to obtain an optimal exercise test.

Exercise intensity can be monitored by various parameters including arterial plasma **lactate** concentration, decrease in serum arterial **base excess** or **bicarbonate** concentration (which both are directly related to lactate level), **heart rate,** and **respiratory parameters** (respiratory gas exchange ratio: $RQ = V\dot{C}O_2/V\dot{O}_2$) [13].

In this study we evaluated and compared three consecutive time periods in each of which a different parameter was used for monitoring the exercise intensity and adjusting the workload in order to obtain a submaximal exercise test. Initially heart rate monitoring was used, in the second period exercise intensity monitoring and adjustment was guided by monitoring of RQ. In the final period exercise intensity was monitored by serial rapid lactate measurements.

SUBJECTS AND METHODS

In ten volunteers (5F, 5M; mean age 25, range 23-28 yr.) and 157 patients (59M, 98F; median age 55, range 13-82 yr.) 178 tonometry exercise tests were performed. The volunteers were tested as part of a more extensive study investigating the effect of two different exercise levels on gastric tonometry [9]. All patients were suspected for having symptomatic chronic gastrointestinal ischemia. Their clinical presentation was that of unexplained abdominal pain, weight loss, diarrhoea or gastric ulcers. Gastric tonometry exercise testing was performed as a diagnostic function test in addition to duplex sonography and selective angiography of the splanchnic vessels. A part of the patients in this study have been previously described in a publication of our group investigating the diagnostic potential of gastric exercise tonometry [8].

The procedure of gastric tonometry exercise testing was described in detail in a previous study [9]. In short, a standard nasogastric tonometry catheter was inserted and connected to an automated air tonometry device that was set up to measure intragastric $P\dot{C}O_2$ every ten minutes. All subjects were studied after a fasting episode of 4 hours. Ranitidine 100 mg was given intravenously 90 minutes prior to exercise testing. A radial artery catheter was introduced in the non-dominant arm to allow sequential arterial

blood sampling. Exercise was performed on an electromagnetically braked bicycle ergometer (Lode, Groningen, Netherlands).

Monitoring exercise intensity and adjusting the workload

The maximal workload (W_{max}) was estimated by using standard criteria, using age, sex, and weight. [1] The exercise episode was started at 10% of W_{max} and in the first 4-6 minutes the workload was increased every minute with 10% of W_{max}. The workload was intended to remain constant thereafter at a submaximal exercise level. Three different approaches for monitoring the exercise intensity and -if necessary- guiding additional adjustments of the workload were evaluated in consecutive periods.

First period: HR-triggered tests. Exercise intensity was monitored by measuring HR, aiming for a HR in the last 4-5 minutes of 80% of maximal predicted heart rate ($HR_{maxpred}$). $HR_{maxpred}$ was calculated by the following formula: $HR_{maxpred}$ = 210 – 0.65*age [12].

Second period: RQ-triggered testing. The workload adjustments were guided by measurement of the RQ, aiming for an RQ of 1.0 in the last 4-5 minutes of the exercise episode. This RQ was chosen as it indicates the anaerobic threshold

Third period: lactate-triggered. In 40 of the RQ-triggered tests serial rapid lactate measurements were done during exercise at t=0, 4, 6, 8 and 10 min. These measurements were not used for guiding the exercise intensity, but to develop a lactate-based exercise triggering protocol. From the results of rapid serial lactate measurements in the RQ-triggered period, an algorithm was developed for triggering the exercise intensity (see table 1). We aimed for a lactate concentration of 4 mmol/l in the last 4 minutes of the test. In parallel with RQ-triggering at an RQ-value of 1.0, this lactate level resembles the anaerobic threshold, at which redistribution of blood flow patterns is initiated.

Table 1. Algorithm for lactate-guide exercise intensity adjustments.

start at 10% of predicted Wmax
increase workload by 10% of Wmax every minute (at t=1, 2, 3, 4, 5, 6 min)
lactate measurements at t= 4, 6, 8 and 10 minutes
if lactate > 3 mmol/l: decrease workload by 10% of Wmax
if lactate not > 1 mmol/l: increase 2x 10% of Wmax

In the first two periods (HR- resp. RQ-triggering) the tests were performed at the pulmonary function department of our hospital. During these exercise tests a 12-lead electrocardiogram was recorded (Case 12, Marquette Electronics Inc., Milwaukee, USA). Heart rate (HR) was recorded every minute. Breath-by-breath oxygen uptake (VO_2), and respiratory gas exchange ratio (RQ) were measured by a respiratory gas analyzer system (Oxycon-α Jaeger, Bunnik, the Netherlands) and recorded every 30 sec.

In the third time frame (rapid serial lactate triggering) the test was performed at the gastroenterology function department, HR was monitored, but respiratory parameters were not monitored.
Arterial blood samples for determination of base excess (BE) and bicarbonate (blood gas analyzer; Radiometer ABL520, Copenhagen, Denmark), and lactate (enzymatic assay; Cobas Fara, Roche Diagnostics, Branchburg, USA) were drawn, in parallel with the 10 min. tonometry interval, before and immediately at the end of the 10 min. exercise episode. Rapid serial lactate measurements were performed using a small portable lactate analyser (Accutrend, Roche Diagnostics, Almere, the Netherlands), specifically developed for use during exercise testing. Using this device, measurement results were available within 60 sec. after blood sampling.
The tests evaluated in the present study were all aimed at a submaximal level: lactate level (or BE-decrease) at or just above 4 mmol/l (the anaerobic threshold) and not exceeding 8 mmol/l. After comparison with arterial lactate measurements (see results section), BE-decrease during exercise was used as the parameter assessing the exercise intensity. The optimal exercise level was a BE-decrease between 3 and 7 mmol/l. Less than 3 mmol/l and more than 7 mmol/l were regarded as low resp. high exercise levels.
For comparing the results of HR- and RQ-measurements with BE-decrease as the indicator of the exercise intensity reached, the following parameters were used: maximum RQ reached (RQ_{max}), total time of RQ>1 ($RQ_{t>1}$), maximum heart rate reached (HR_{max}) as percentage of $HR_{maxpred}$, and total time of HR>80% of $HR_{maxpred}$ ($HR_{t>80}$).

Statistics

All values are given as mean ± SD unless otherwise stated. P-values < 0.05 were considered statistically significant. Correlations between lactate and BE- respectively bicarbonate-decrease, and between both HR-and RQ-parameters and exercise intensity as measured by BE-decrease, were calculated using Spearman's rank test. For comparison of HR- and RQ-parameters with exercise level (as divided in low, optimal or high) one-way ANOVA with Bonferroni post-hoc analysis was used. Group comparisons of the tonometry results of high and low exercise levels *vs.* all tests and the diagnostic accuracy of tonometry in the different monitoring episodes were performed using chi-square testing.

RESULTS

HR-triggering

In 39 tests (10 in healthy volunteers and in 29 patient tests) HR-triggering was used. In 22 (56%) of these HR-triggered tests the mean HR in the last 4 minutes equalled the target HR of 80% (± 5%) of $HR_{maxpred}$. In 9 tests (23%) the target HR was not reached; in five of these the subjects were using beta-blocking medication. In 8 tests (20%) HR was greater than 85% of $HR_{maxpred}$. The resulting exercise levels as measured by BE-decrease are shown in table 2. In three tests the exercise intensity was too low. In two

the target HR was not reached; one of the subjects used beta-blockers. Two tonometry results were true negative, the other false positive.
Of the 9 tests with an erroneously high exercise level, in only one test HR was too high. The other 6 tests in which HR was too high resulted in the submaximal exercise levels aimed for. When analysing the 110 tests in which both HR and RQ were recorded, only a weak correlation was observed between both HR_{max} and $HR_{t>80}$ and exercise intensity as measured by BE-decrease ($r=0.23$ resp. 0.20, $p<0.05$). There was no significant difference for the HR-derived parameters when comparing low, target and high exercise intensity. Figure 1 displays the comparison of HR_{max} for the three exercise intensity groups.

Figure 1. HRmax (95% confidence intervals) in low, target and high exercise level.

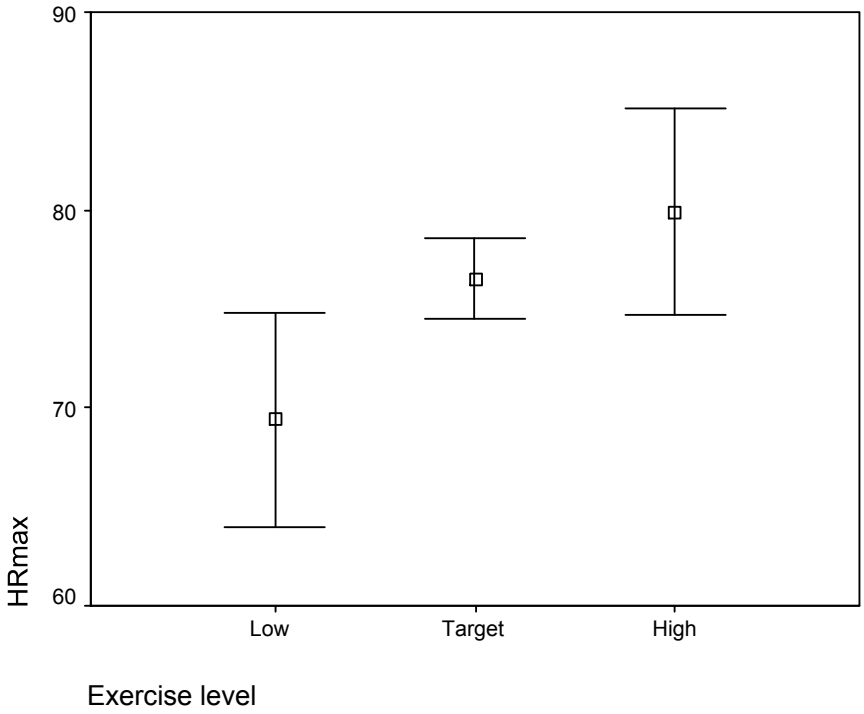


Table 2. Resulting exercise intensities for the three triggering regimes.

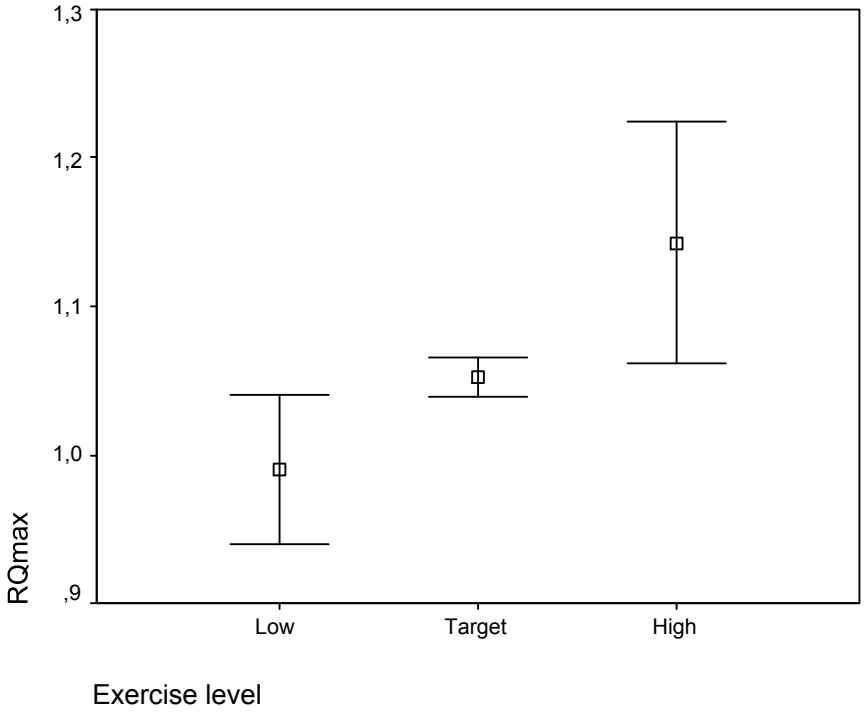
	Exercise level	***Low***	***Target***	***High***
Triggering method	***BE-decrease:***	<3 mmol/l	3-7 mmol/l	>7 mmol/l
HR (39 tests)		3 (8%)	27 (69%)	9 (23%)*
RQ (84 tests)		8 (10%)	74 (88%)	2 (2%)
Lac (55 tests)		23 (41%)†	29 (53%)*	3 (5%)

values are given as numbers (percentage of total of triggering method);
*$p<0.05$, † $p<0.001$ comparing the three different triggering regimes

RQ-triggering

In 84 tests RQ-triggering was used. In 67 (80%) of these tests the target RQ of 1.0 was reached while the mean RQ in the last 4 minutes was 1.0 (± 5%). In 11 tests (13%) the target RQ was not reached and in 6 tests (7%) the mean RQ in the last 4 minutes exceeded the target RQ by more than 5%. Of the 8 tests with a low exercise level, the target RQ was not reached in 4. In both tests with a too high exercise intensity mean RQ in the last 4 minutes was greater than 1.05.
When analysing all 110 tests in which RQ was monitored, positive correlations were found for comparing RQ_{max} and $RQ_{t>1}$ and BE-decrease ($r=0.34$ and 0.38 resp., $p<0.0005$). When divided in low, target and high exercise intensity groups, both RQ_{max} and $RQ_{t>1}$ showed significant differences between these three groups ($p<0.0005$; one-way ANOVA with Bonferroni post-hoc analysis). Figure 2 displays the comparison of RQ_{max} for the three exercise intensity groups.

Figure 2. RQmax (95% confidence intervals) in low, target and high exercise level.



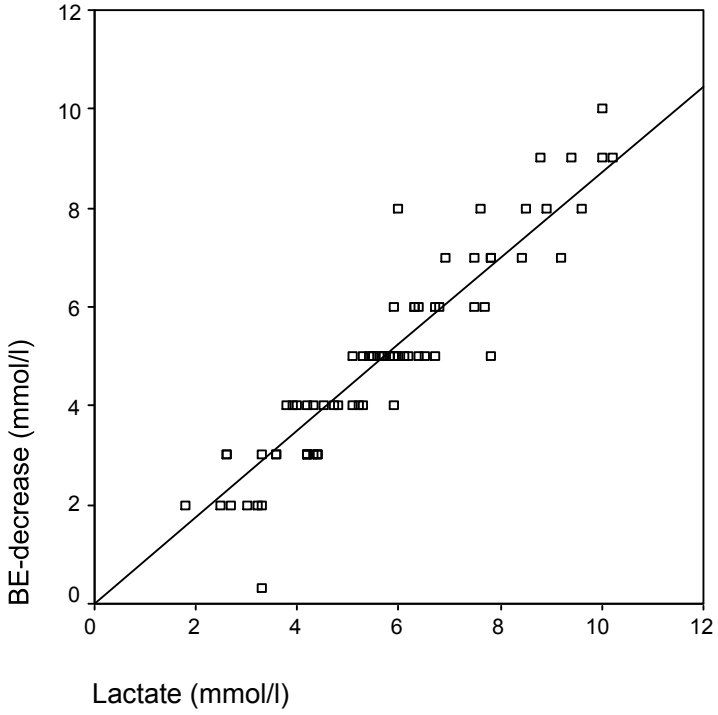
Lactate-triggering

In 55 tests lactate triggering was used. In 26 of these tests the target lactate level of 4.0 mmol/l in the last 2-4 minutes was not reached. This resulted in BE-decrease below 3 mmol/l in 19 tests. In two tests the rapid lactate measurements exceeded 8 mmol/l at t=6 or 8 min. In one, the resulting exercise level was too high (BE-decrease >7 mmol/l). Of the 27 tests in which the target lactate levels were reached (at least 4 mmol/l at t=6 or 8, and remaining below 8 mmol/l), the resulting exercise levels were too low in 7 and too high in 2.

Arterial lactate *vs.* BE- and bicarbonate decrease

In 78 tests both arterial lactate levels and blood gas parameters were obtained. A high degree of correlation between both BE- and bicarbonate-decrease and lactate level after exercise was found: r=0.93 resp. r=0.89 ($p<0.0005$). Figure 3 displays the relation between arterial lactate and BE-decrease after exercise. Mean paired differences between lactate and BE-decrease were 0.7 (SD 0.7) mmol/l and between lactate and bicarbonate-decrease 1.4 (SD 0.9) mmol/l.

Figure 3. Relationship between arterial lactate concentration after exercise and BE-decrease at the end of the exercise period.



Comparison accurateness of exercise tonometry at low, target and high exercise levels

As shown in table 2, lactate triggering resulted in significantly more low exercise levels compared to the other two regimes ($p<0.001$).

False negative tonometry results were found in 10 (6%) of all tests. Low exercise levels did not result in an increase in false negative tonometry tests: in only 2 of 10 (5%) false negative tests the exercise level was too low; one test was RQ-triggered, the other lactate-triggered.

Tonometry results were false positive in 34 of all 178 tests (19%). Of the 14 tests with a too high exercise level, in 6 (43%) the tonometry tests were false positive ($p<0.001$ comparing high exercise level *vs.* all tests). Three of these tests were HR-triggered (but HR did not exceed the target HR), 2 RQ-triggered and one was lactate-triggered.

The sensitivity and specificity of tonometry exercise testing for gastrointestinal ischemia did not differ among the three groups (82% and 73%, respectively).

DISCUSSION

For optimal diagnostic accuracy, the exercise level in gastric exercise tonometry can be monitored and adjusted by RQ-measuring, or alternatively by serial arterial lactate measurement. Although the latter resulted in more tests with lower than desired exercise levels, this had no influence on diagnostic accuracy.

The greatest problem relating to exercise level in gastric exercise tonometry is the above submaximal, or maximal, test as this is associated with 43% false-positive tests in this study. In maximal exercise, splanchnic blood flow is severely reduced, and can be lead to reduction below the level required to maintain aerobic metabolism. Although data on the splanchnic vascular responses to maximal exercise have not been established, ischemia has been established frequently under these circumstances [6,9]. In a study on splanchnic blood flow in trained volunteers, mean SMA blood flow fell by 38-49% after a 10 min. exercise test at 70% of maximal workload [11]. It has been shown that the flow reduction in the celiac artery exceeds that of the superior mesenteric artery, but still does not exceed around 50% [10]. Therefore the normal splanchnic flow after sub-maximal exercise remains well above the normal lower level of normal splanchnic blood flow, which is estimated at approximately 30% of the normal baseline value [2]. This explains why submaximal exercise does not result in ischemia in subjects with normal splanchnic vessels. Gastric ischemia during submaximal exercise can be seen in patients with splanchnic stenoses or in patients with reduced cardiac output [5,8]. Thus, for practical clinical purposes 10 min of submaximal exercise seems adequate to distinguish between normal and pathological gastrointestinal vascular responses.

Some exercise should be performed to allow for blood flow redistribution and reduction of the splanchnic blood flow, and thus provocation of ischemia. However, the minimally required level is currently unknown. Even with very low intensity exercise in healthy humans a significant shift in blood flow from the abdominal viscera to the exercising muscles was observed [7]. Thus submaximal exercise as currently advocated might not be necessary, and lower lactate levels may suffice for diagnostic testing.

Triggering on RQ-measurements resulted in the highest proportion of tests within the target range, but has disadvantages. It requires a pulmonary function lab with specific devices for measurement of exhaled carbon dioxide and inhaled oxygen, making the test expensive and more complicated. The advantage of RQ-monitoring in minimizing the proportion of below-target exercise level did not result in a lower number of false negative tests in this study.

The major advantages of the serial lactate measurement are its simplicity and low cost. This rapid test can be performed by paramedic personnel and enables determination of blood lactate levels within 60 seconds. This enables adequate monitoring and triggering of exercise levels. A gastric tonometry exercise test, a routine procedure in our hospital in patients suspected of chronic gastrointestinal ischemia, takes 15 min of doctor's time,

and 2 hours time for a registered nurse. Moreover, the currently available air tonometry device allows for accurate and reproducible measurements without the hassle and problems associated with classically used saline tonometry [4].

In conclusion, by using RQ and serial lactate measurements adequate exercise levels for gastric exercise tonometry can be achieved. Rapid lactate measurements and the presented algorithm for gastric exercise tonometry are feasible for the daily clinical practice.

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Chapter 5

Jejunal Tonometry for the Diagnosis of Gastrointestinal Ischemia. Feasibility, Normal Values and Comparison of Jejunal with Gastric Tonometry Exercise Testing.

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Submitted

ABSTRACT

Background and aims. In most patients with chronic gastrointestinal ischemia the celiac artery is involved, enabling the use of gastric exercise tonometry as a diagnostic function test. In this study we investigated the feasibility of combining gastric and jejunal exercise tonometry and determined the normal values. We investigated the potential diagnostic value of combining gastric with jejunal exercise tonometry.

Materials and methods. Between 1998 and 2000, combined gastric and jejunal exercise tonometry tests was performed in a healthy volunteer and in patients suspected of chronic gastrointestinal ischemia. Using automated air tonometry, gastric (P_gCO_2) and jejunal PCO_2 (P_jCO_2) were measured before, during and after 10 min. exercise. Luminal-arterial PCO_2 gradients (Δ_gPCO_2 resp. Δ_jPCO_2) were calculated. Final diagnosis of chronic ischemia was made by our institutional multidisciplinary working group on gastrointestinal ischemia.

Results. Jejunal tonometry was possible in 25 of 27 subjects. The healthy volunteer was tested twice, yielding a total of 26 combined tests. Mean normal basal P_jCO_2 was 0.9 kPa higher than P_gCO_2. The calculated upper threshold (mean + 2SD) of normal Δ_jPCO_2 was 1.4 kPa. In five of 8 patients with chronic gastrointestinal ischemia gastric exercise tonometry was abnormal, in one both gastric and jejunal tonometry were abnormal, in two only jejunal exercise tonometry was abnormal.

Conclusion. Combined gastric and jejunal exercise tonometry is a feasible procedure that is relatively easy to perform. Based on this pilot study, jejunal tonometry seems to have a small additional value in the diagnosis of chronic gastrointestinal ischemia.

INTRODUCTION

Gastric exercise tonometry has been shown to be a valuable diagnostic function test for suspected chronic gastrointestinal ischemia [4,8]. For detection of chronic gastrointestinal ischemia, which usually involves the celiac artery (CA), the easily performed gastric tonometry measurement may suffice. Although in most patients with symptomatic ischemia the celiac artery is stenotic or occluded, doubt remains whether exercise tonometry testing in the stomach alone is sufficient for determining ischemia if the celiac artery is not involved or not the only vessel involved. It might be expected that jejunal tonometry measurement -in the flow region of the superior mesenteric artery (SMA)- could have additive value in patients with (isolated) SMA stenosis or occlusion.
Jejunal tonometry dates back to 1991 when Boley and Brandt described a single case of chronic gastrointestinal ischemia (3-vessel disease), which was demonstrated by increased jejunal PCO_2 after a test meal [1]. Unfortunately, no study determining the normal values of jejunal tonometry and comparing its results with gastric tonometry has been performed until now.
We therefore investigated the feasibility of jejunal tonometry, with focus on the determination of normal values in comparison with gastric tonometry, and comparison of the results of jejunal with gastric tonometry exercise testing in the evaluation of patients suspected of having chronic gastrointestinal ischemia.

MATERIAL AND METHODS

Subjects

The combined gastric and jejunal exercise tonometry tests were performed between 1998 and 2000. First, a healthy volunteer (male 25 years) was tested twice: before, during, and after a 10-min. episode of submaximal as well as maximal exercise. Thereafter, combined gastric and jejunal tonometry exercise testing was planned in 26 patients (12 male, 14 female; median age 51 yr.; range 34-75) with suspected chronic gastrointestinal ischemia. All patients were referred to the multidisciplinary working group on gastrointestinal ischemia in our hospital. Chronic gastrointestinal ischemia was suspected because of persistent symptoms of abdominal pain, weight loss, diarrhoea or unexplained gastric ulceration for which no other explanation could be found despite additional investigations such as endoscopy of upper digestive tract, colonoscopy, abdominal ultrasound, and abdominal CT-scan.
All patients were evaluated by this working group for clinical suspicion of chronic gastrointestinal ischemia using a standard protocol. Gastric and jejunal exercise tonometry, duplex ultrasonography and visceral angiography were performed.
For the presence or absence of splanchnic stenoses the selective visceral angiography was used as the gold standard. As there is no gold standard for diagnosing ischemia we decided to rely on a panel decision [2]. Upon discussing each case in the gastro-intestinal working group a consensus diagnosis was made. As has been described earlier, a careful follow-up program of all patients irrespective of diagnosis was part of this process [8].

Thus, the panel had access to all results, including angiograms, duplex and tonometry. The main criterion was the clinical history (pain provoked by a meal or exercise, weight loss), exclusion of other causes, and the presence of significant hemodynamic stenosis [3,4]. On follow-up the consensus diagnosis could change based on the clinical course, treatment results, or alternative diagnosis.

Angiography

The patients underwent multiplane arterial digital subtraction angiography of the abdominal aorta, in AP and lateral projections in in- and expiration (Philips 3000 Integris system, Philips, Eindhoven, the Netherlands) during injection of 25-40 ml contrast medium (Ioxaglate, Hexabrix®, Mallinkrodt). The luminal filling of the abdominal aorta, the celiac, superior, and inferior mesenteric artery was measured. Also selective catheterisation was performed of the CA, the SMA and the inferior mesenteric artery (IMA) to detect collateral vessels. Stenoses were graded in consensus by two independent investigators who were blinded to the patients' symptoms and the results of the duplex sonography and exercise tonometry.

Duplex sonography

In all subjects duplex sonography was performed. After a fasting episode of six hours, the patients were scanned using a 3.5 MHz convex sector probe with a Diasonics VST-master ultrasonography device. After identifying the vessels and confirming patency and antegrade flow, the peak-systolic and end-diastolic flow velocities during in- and expiration were measured in the celiac (CA) and superior mesenteric (SMA) arteries and the aorta. The Doppler measurements were made with a sample size of 5 mm. Velocity measurements were taken with the smallest, most accurate flow-to-beam angle possible. No measurements were accepted if the angle was greater than 60°. Peak-systolic flow velocities below 200 and 275 cm/sec and end-diastolic flow velocities below 55 and 45 cm/sec were regarded as normal for the CA and SMA, respectively [7].

Tonometry

Two standard tonometry catheters (in the first 15 patients: Trip tonometer, sigmoid model with a blind tip and no central lumen; in the remaining subjects: Datex 8F pediatry/gastroenterology tonometry catheter with a central lumen allowing insertion of a guide wire; Datex-Engstrom, Hoevelaken, the Netherlands) were inserted nasogastrically and placed at 50 cm from the tip of the nose. Under fluoroscopic guidance, one of these catheters was further inserted and positioned in the jejunum with its tip past the ligament of Treitz, while ensuring proper placement in the proximal corpus of the stomach of the second catheter.

Both catheters were attached to automated air tonometry devices (Tonocap, Datex-Engstrom, Finland), which use a pump to automatically inflate and deflate the tonometer balloon via an airtight circuit, and analyze PCO_2 of the aspirated gas by infrared capnography. The tonometry devices were set up to measure intragastric PCO_2 (P_gCO_2) and intrajejunal PCO_2 (P_jCO_2) every ten minutes.

All measurements were made in the afternoon after a fasting episode of 6 hours. One hour prior to starting tonometry measurements, 100 mg ranitidine was administered intravenously to prohibit gastric acid formation [11]. A radial artery catheter was inserted in the non-dominant arm to allow arterial blood sampling.
The exercise test was performed on an electromagnetically braked bicycle ergometer (Lode, Groningen, Netherlands). During the exercise testing a 12-lead electrocardiogram was recorded (Case 12, Marquette Electronics Inc., Milwaukee, USA) and breath-by-breath oxygen uptake (VO_2) and respiratory gas exchange ratio (RQ) were measured by a respiratory gas analyzer system (Oxycon-α Jaeger, Bunnik, the Netherlands).
Baseline measurements of arterial blood sampling and gastric and jejunal tonometry PCO_2 were obtained 10 minutes and immediately before the exercise period. The exercise period lasted 10 minutes and was started immediately after completing the last baseline tonometry measurement cycle. The workload was increased gradually during the first 4-5 minutes and targeted at a submaximal work rate level [8,9]. RQ was monitored as an indicator for exercise level and was used to taper the workload, aiming for an RQ at 1.0. In the healthy volunteer a second exercise test was done aiming at maximal exercise intensity, as part of a larger volunteer study [9]. Arterial and tonometry parameters were obtained immediately at the end of the exercise period and ten and twenty minutes after the exercise period. Arterial blood was analyzed immediately for pH, PCO_2, PO_2, base excess (BE) and bicarbonate content using a standard blood gas analyzer (Radiometer ABL520, Copenhagen, Denmark).

Statistics

All tonometry variables are expressed as mean ± standard deviation (SD). Where appropriate the 95% confidence intervals (95% CI) are given. The normal upper threshold for $\Delta_i PCO_2$ was calculated from the normal resting values (mean + 2 SD). Correlation between tonometry variables was calculated using Pearson's correlation coefficient. Differences between the tonometry variables were calculated using the paired Student's t-test. Comparison of the tonometry variables for the different test episodes (baseline, exercise, recovery) was performed using one-way ANOVA. P-values <0.05 were considered statistically significant.

RESULTS

Feasibility

In 25 of 27 subjects combined gastric and jejunal tonometry was successfully performed. The time for the total procedure from the moment of the nasal insertion of the catheters until achieving proper placement of both catheters varied between 12 and 20 min (median 15 min). Total transillumination time was between 2 and 5 minutes. In one patient proper placement of the jejunal catheter was not possible because of persistent curling of the catheter in the proximal duodenum. In one subject the jejunal

catheter appeared to leak very small amounts of air which made the jejunal tonometry results unreliable.

Tonometry variables in subjects with normal splanchnic vasculature and perfusion

For determining normal values only the 12 tests in subjects without splanchnic stenoses and ischemia and without other possible confounding disorders were taken into account.

Baseline measurements. In table 1 the normal resting values for P_gCO_2 and P_jCO_2 and luminal-arterial PCO_2 gradient (Δ_gPCO_2 resp. Δ_jPCO_2) are given. The calculated upper threshold of normal Δ_jPCO_2 was 1.4 kPa. As already observed with air tonometry in healthy volunteers, P_gCO_2 was slightly lower than arterial PCO_2 resulting in negative Δ_gPCO_2 [9]. Mean baseline P_jCO_2 was 0.9 kPa (95% CI 0.6 - 1.2 kPa) higher than mean P_gCO_2 ($p<0.0001$). A significant correlation between P_gCO_2 and P_jCO_2 (figure 1) was observed (Pearson's correlation coefficient 0.70, $p<0.0001$). There was no significant correlation between Δ_gPCO_2 and Δ_jPCO_2 (figure 2).

Table 1. Normal resting values (in kPa) for gastric and jejunal tonometry parameters.

	Mean	SD	95% CI
P_gCO_2	5.0	0.7	4.7 - 5.3
P_jCO_2	5.9	0.9	5.5 - 6.3
Δ_gPCO_2	-0.5	0.5	-0.7 - -0.3
Δ_jPCO_2	0.4	0.5	0.2 - 0.6

Exercise and recovery measurements. In 10 subjects a proper submaximal exercise test (BE-decrease < 8 mmol/l) was obtained. One test in the healthy volunteer was deliberately aimed at being maximal (BE-decrease 14 mmol/l) and in one patient the exercise intensity was increased too fast, also resulting in a nearly maximal test (BE-decrease 9 mmol/l). The course of the tonometry variables before, immediately after exercise and during recovery is displayed in figure 3. For all parameters there were no significant differences between baseline, exercise and recovery values in the 10 submaximal tests. The P_gCO_2 was 4.9 ± 0.7 kPa at baseline (mean of the two baseline measurements), 5.3 ± 0.8 kPa immediately after exercise and 5.0 ± 0.7 kPa after the first 10-min. recovery. For the P_jCO_2 the baseline, exercise and recovery values were 5.8 ± 1.0 kPa, 6.1 ± 1.3 kPa, and 5.8 ± 1.3 kPa respectively. The Δ_gPCO_2 was -0.6 ± 0.5 kPa before, -0.1 ± 0.7 kPa immediately after and -0.1 ± 0.8 kPa in the first 10 minutes recovery after exercise. The corresponding values for Δ_jPCO_2 were 0.4 ± 0.5 kPa, 0.7 ± 0.7 kPa, and 0.7 ± 0.9 kPa respectively. In none of the subjects with normal vasculature the normal upper thresholds for Δ_gPCO_2 of 0.8 kPa and for Δ_jPCO_2 of 1.4 kPa were exceeded.

Figure 1. Normal resting (baseline) gastric *vs.* jejunal PCO_2

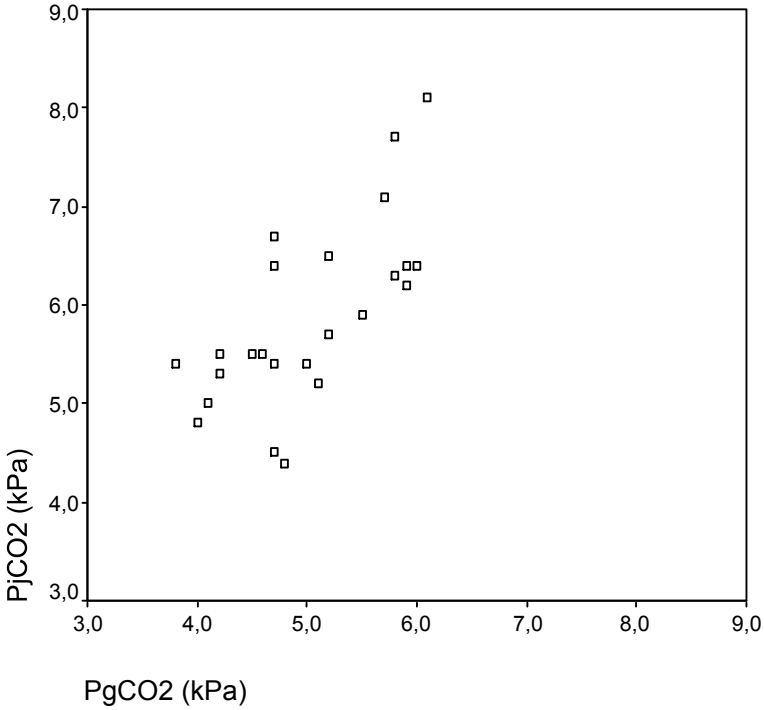


Figure 2. Normal resting $\Delta_g PCO_2$ *vs.* $\Delta_j PCO_2$ (values in kPa)

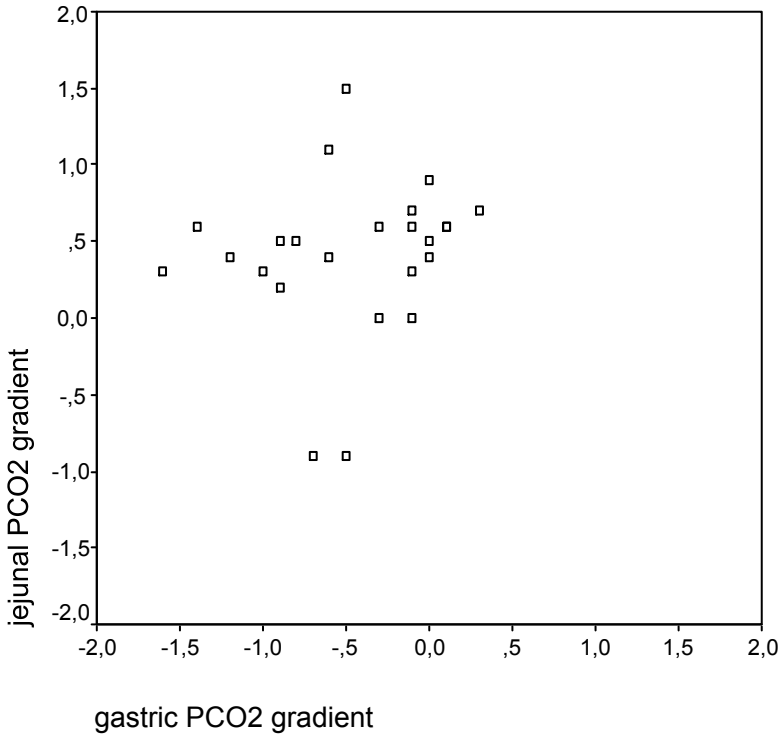
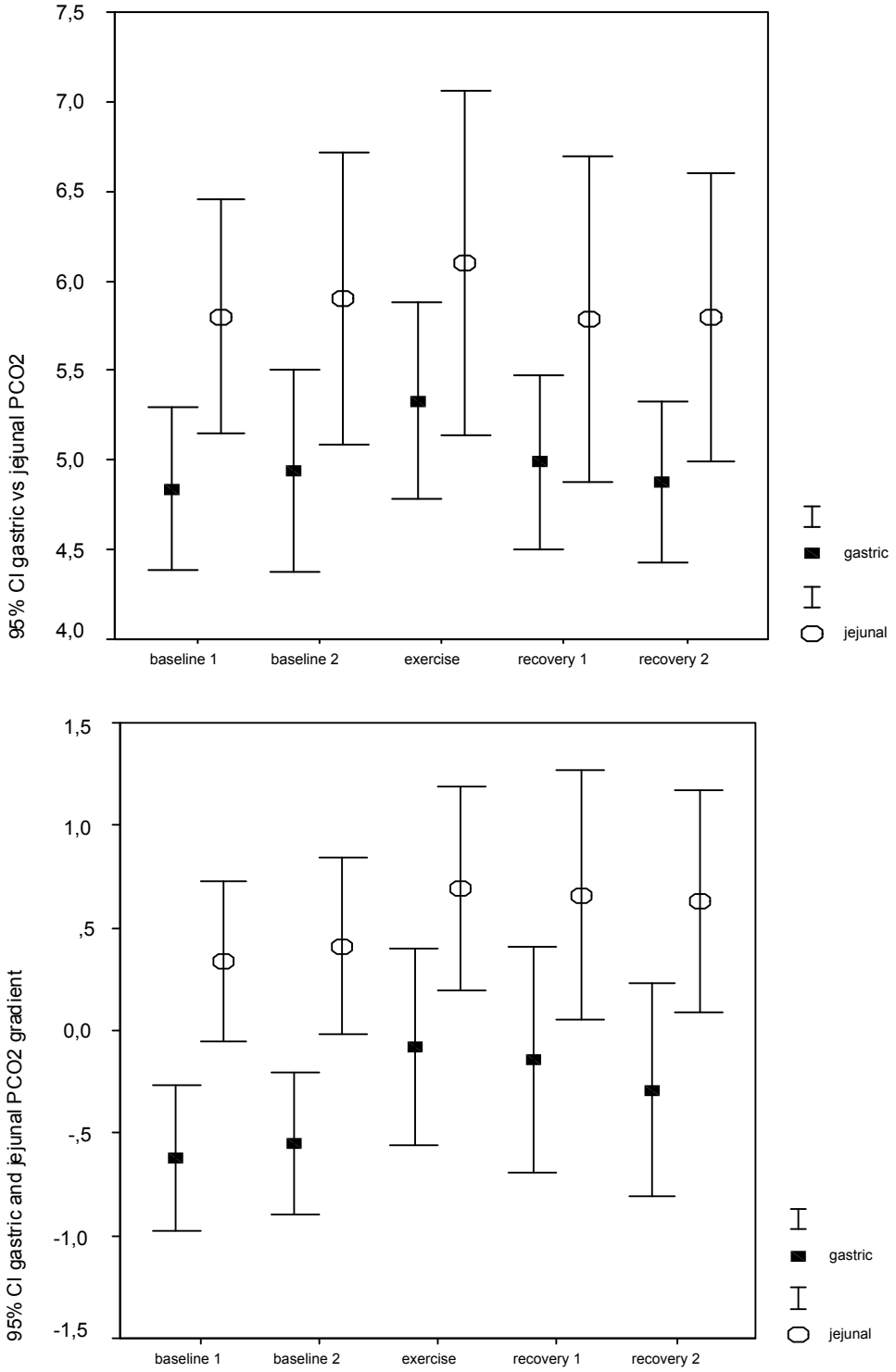


Figure 3. Course of gastric and jejunal PCO_2 and ΔPCO_2 at baseline (1 resp. 2), during 10 min. submaximal exercise, and after 10 and 20 min. recovery (1 and 2) in subjects with normal splanchnic vasculature. Values are in kPa.



Tonometry variables in patients with splanchnic artery stenosis or symptomatic chronic gastrointestinal ischemia

In table 2 the maximal $\Delta_g PCO_2$ and $\Delta_j PCO_2$ in patients (n=8) with symptomatic chronic gastrointestinal ischemia (7 with ischemia due to splanchnic artery stenosis, one with NOMI) and in patients (n=3) with asymptomatic splanchnic artery stenosis. Of the eight patients with ischemia, gastric exercise tonometry detected six. Two patients with a negative gastric exercise test were found only with jejunal tonometry: one with CA stenosis only (suggesting intrasplanchnic steal) and one with both CA and SMA stenosis. The other way around, jejunal tonometry was abnormal in only three of the eight patients with symptomatic gastrointestinal ischemia.
In one subject isolated SMA stenosis was found. This patient had no symptomatic ischemia and both gastric and jejunal tonometry was normal.
In the subject with NOMI vascular spasms (without fixed stenosis) were demonstrated by angiography. In this subject gastric but not jejunal ischemia was found with exercise tonometry.

Table 2. Tonometry results in eleven patients with splanchnic artery stenosis and/or symptomatic chronic gastrointestinal ischemia.

	M/F	age	Stenosis	Ischemia	Max $\Delta_g PCO_2$	Max $\Delta_j PCO_2$
1	M	55	CA/SMA	Yes	↑ (0.9)	**n** (1.3)
2	M	48	CA/SMA	Yes	**n** (0.3)	↑ (1.4)
3	F	58	CA/SMA	Yes	↑ (1.3)	**n** (1.3)
4	F	64	CA/SMA	Yes	↑ (1.5)	↑ (2.5)
5	F	58	CA	Yes	↑ (0.8)	**n** (0.0)
6	M	34	CA	Yes	**n** (-0.4)	↑ (1.8)
7	F	37	CA	Yes	↑ (0.9)	**n** (0.5)
8	F	37	CA	No	**n** (0.5)	**n** (1.0)
9	M	48	CA	No	**n** (0.0)	**n** (1.2)
10	M	68	SMA	No	**n** (0.7)	**n** (0.7)
11	M	40	none (NOMI)	Yes	↑ (1.3)	**n** (1.0)

Max. $\Delta_g PCO_2$ and max. $\Delta_j PCO_2$ are displayed as: normal (n) or elevated (↑), the values are enclosed in parentheses.

Tonometry variables in other disorders

Table 3 displays maximal gastric and jejunal ΔPCO_2 in 3 subjects with various other conditions leading to impaired gastrointestinal perfusion. One patient had ischemic colitis as presenting complaint; no splanchnic stenoses were found on angiography. Later analysis revealed cardiac disease leading to forward failure analysis, which was previously not recognized. This forward failure led to gastrointestinal ischemia during

exercise [6]. A second patient was treated with iloprost because of suspected vasospasms. During exercise he became hypotensive, which probably resulted in the gastrointestinal ischemia we observed. In one subject with small bowel Crohn's disease a marked increase of an already elevated resting jejunal P_{CO_2} gradient (mean baseline $\Delta_j P_{CO_2}$ of 3.2 kPa) was observed, while gastric tonometry variables were normal.

Table 3. Tonometry results in other disorders.

	M/F	age	Diagnosis	Max $\Delta_g P_{CO_2}$	Max $\Delta_j P_{CO_2}$
12	F	68	Ischemic colitis, cardiac failure (forward failure, hypotension)	2.6	2.6
13	F	65	Crohn's disease of small bowel	0.6	4.3
14	M	53	Iloprost infusion, hypotension	1.8	2

DISCUSSION

The present study suggests that combining gastric and jejunal exercise tonometry may have additional value in the diagnosis of chronic gastrointestinal ischemia as compared to gastric tonometry only. However, in this small study, gastric exercise tonometry would have detected 6 of 8 patients, while jejunal tonometry alone would have detected only 3 of 8. Thus, its role is probably confined to additive of gastric tonometry, not a replacement.

It might be expected that jejunal measurement is abnormal in patients with ischemia due to isolated SMA stenosis or occlusion. But as none of the patients in the present study had isolated due to SMA stenosis this hypothesis could not be proven. However, in two of the eight subjects with symptomatic chronic gastrointestinal ischemia gastric tonometry testing showed normal results, while jejunal exercise tonometry parameters were abnormal. In one subject an isolated CA occlusion was found, in the other stenosis of both CA and SMA. In the latter patient it may be postulated that ischemia occurs in the flow area of the SMA whereas in the stomach (the flow area of the CA) no ischemia is provoked by exercise. The finding that exercise induced jejunal but not gastric ischemia in the case of isolated CA stenosis, might be explained by the occurrence of intrasplanchnic steal, where -in response to exercise- the jejunal blood flow is compromised if favor of the collateral gastric perfusion. Alternatively, it may be postulated that gastric tonometry values were erroneously low (by air swallowing for example) yielding false-negative gastric tonometry results.

Our present study demonstrates that jejunal placement of a standard nasogastric tonometry catheter is a feasible procedure. Although the procedure is easily performed, most patients experienced mild to moderate discomfort in the nasopharyngeal area when the jejunal catheter was manipulated to further advance it into the small bowel. In one subject minuscule leakage of air from the closed tonometry circuit (via the jejunal

tonometry catheter) was observed, yielding very low P_jCO_2 values of 0.1 – 0.2 kPa. The results from this patient were discarded from analysis in this study.

In a previous study of our group, a normal upper threshold for Δ_gPCO_2 after submaximal exercise of 0.8 kPa was found [5,9]. For jejunal tonometry an upper normal threshold of 1.4 kPa was calculated. Indeed, in the present study in none of the subjects with normal vasculature during and after exercise the normal upper thresholds for Δ_gPCO_2 and Δ_jPCO_2 were exceeded in this study.

It was found that normal resting P_jCO_2 values were 0.8 (SD 0.7, 95% CI 0.6 – 1.2) kPa higher than P_gCO_2. Several possible explanations may be postulated to explain this discrepancy between gastric and jejunal PCO_2.

Duodenal bicarbonate secretion via the bile together with small amounts of acid passing from the stomach may result in excess formation of carbon dioxide in the small bowel. In the fasting state the intraluminal duodenal pH varies between 2 and 6 [10]. These fluctuations are reduced or even completely buffered in the distal duodenum and proximal jejunum. The PCO_2 measured in the proximal jejunum might be the result of propulsion of carbon dioxide produced in the duodenal bulb by peristalsis. Alternatively, swallowing of air may result in dilution of the CO_2 concentration of intragastric gas, while not affecting PCO_2 of the jejunum. This phenomenon may also explain the finding that intragastric PCO_2 is slightly lower than arterial PCO_2, resulting in negative baseline Δ_gPCO_2 values. Similar as previously observed in one subject in a volunteer study, in the present study in one subject all intragastric PCO_2 values were lower than arterial PCO_2 values [9]. Indeed, air-swallowing may be the most plausible explanation for this finding.

Apart from being an additional diagnostic tool in (suspected) chronic gastrointestinal ischemia, jejunal tonometry might be of interest in several other conditions. In situations of "global" hemodynamic instability it was found that jejunal tonometry closely paralleled gastric tonometry results. Interesting observations were made in a patient with Crohn's disease of the small bowel. Gastric tonometry results were normal whereas jejunal tonometry demonstrated that already at rest ischemia was present, which worsened during exercise. These findings support the hypothesis of significant local vascular involvement in Crohn's disease [12].

In conclusion, this study demonstrates that combining gastric with jejunal exercise tonometry testing is a feasible procedure that is relatively easy to perform and may contribute to the diagnosis of gastrointestinal ischemia. Normal resting jejunal PCO_2 values were 0.8 kPa higher than gastric PCO_2. The calculated normal upper threshold of the jejunal-arterial PCO_2 gradient of 1.4 kPa was not exceeded during and after exercise in subjects with normal splanchnic vasculature. Apart from having additional value in demonstrating jejunal ischemia in subjects with chronic gastrointestinal ischemia, the technique may be used to demonstrate ischemia in other disorders such as hemodynamic instability and Crohn's disease.

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Chapter 6

Clinical Impact of Gastric Exercise Tonometry on Diagnosis and Management of Chronic Gastrointestinal Ischemia

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ABSTRACT

Background and aims. Chronic gastrointestinal ischemia or chronic splanchnic syndrome is a difficult diagnosis. The use of a physiological test, combined with clinical and anatomical data should improve diagnostic accuracy. This study evaluates the diagnostic accuracy, and clinical impact of gastric exercise tonometry in a patient cohort suspected of chronic splanchnic syndrome.

Methods. From 1997 – 2000, 102 patients with chronic abdominal pain were analysed. The workup included gastric exercise tonometry and selective biplane angiography. The diagnosis chronic gastrointestinal ischemia was based on consensus in a multidisciplinary working group and sustained on follow-up.

Results. Gastrointestinal ischemia was diagnosed in 38 patients. In 33 patients chronic splanchnic syndrome was found, with single vessel involvement in 20 (17 celiac artery, 3 mesenteric superior), and multivessel disease in 13. In 5 patients nonocclusive ischemia was found. By using receiver operator curve analysis, the difference between gastric and arterial partial pressure of carbon dioxide (P_{CO_2} gradient) proved to be the best exercise tonometry parameter. The criteria for diagnosing ischemia in gastric exercise tonometry were: P_{CO_2} gradient > 0.8 kPa and increase gastric P_{CO_2}, with base excess decrease < 8 mmol/l during exercise. Gastric exercise tonometry had 78% sensitivity and 92% specificity. Twenty-five patients underwent vascular treatment (19 operative, 6 stent / PTA). After 4 years of follow-up 83% of patients were alive and free of symptoms.

Conclusions. Gastric exercise tonometry is an accurate diagnostic tool to show gastrointestinal ischemia. Including gastric exercise tonometry into clinical decision making enabled selecting patients with ischemia, who benefited from vascular and medical treatment. These benefits were sustained during 4-year follow-up. Gastric exercise tonometry should be considered in the workup of patients with a suspected diagnosis of gastrointestinal ischemia.

INTRODUCTION

The diagnosis of chronic gastrointestinal ischemia is notoriously difficult. Many patients with splanchnic stenoses remain asymptomatic and have no indication for treatment. Other patients develop typical symptoms, including postprandial pain, fear of eating, and weight loss, a condition referred to as chronic splanchnic syndrome or chronic mesenteric ischemia. Another patient group consist of those with ischemia and apparently normal splanchnic vessels, a condition referred to as non-occlusive mesenteric ischemia (NOMI), caused by local vasoconstriction related to circulatory (pre)-shock.
It has been shown that the main contributor to the diagnosis is a high degree of clinical suspicion [2,6], and that detection of a stenosis alone does not prove ischemia [4,5,21]. It is widely accepted that the gastrointestinal tissue is resistant to ischemia because of the extensive collateral circulation between the three main arteries [16,19]. Common clinical knowledge thus dictates that at least two of the three major splanchnic arteries have to be stenotic to give ischemic symptoms. Studies that reported the rarity of an isolated stenosis of the celiac artery (CA) as cause of complaints [3,20] coincide with series showing disappearance of symptoms after treatment of isolated CA stenoses [13,15].
Therefore, some but not all patients with splanchnic stenoses benefit from treatment. It was acknowledged over a decade ago that "a functional and physiological test distinguishing symptomatic ischemia, the chronic splanchnic syndrome from non-ischemic stenoses, the chronic splanchnic disease, was urgently warranted" [1]. None of the currently available diagnostic modalities, including angiography, duplex ultrasound and magnetic resonance angiography, could provide that functional information. Measurement of intraluminal partial pressure of carbon dioxide (PCO_2) by tonometry has been shown to provide exactly that information, the presence or absence of ischemia. In a small pilot study we have shown that gastric exercise tonometry was able to detect actual ischemia [9]. We have recently validated this exercise test in healthy volunteers and established the optimal exercise intensity level as well as normal threshold values [14].
The current study was performed to establish the role of gastric exercise tonometry testing for detection of gastrointestinal ischemia in a cohort of patient with unexplained chronic abdominal symptoms and to establish its clinical impact for these patients.

PATIENTS AND METHODS

In our institution a multidisciplinary working group on gastrointestinal ischemia was instituted in 1997. All patients were evaluated for clinical suspicion of chronic gastrointestinal ischemia, or because of an incidental finding of splanchnic stenosis on abdominal angiography. A standard protocol was used including a detailed history of complaints by two experienced physicians, duplex ultrasound, splanchnic angiography and gastric exercise tonometry.
The severity of complaints (upper abdominal pain at "rest", worsening after meal or exercise, and diarrhoea) was scored by one of the authors (J.A.O.) using a symptom score: 0 = no complaints, 1 = minor complaints not interfering daily activities, 2 = moderate

complaints, some restrictions in daily activities, 3 = severe complaints, normal activities impossible. The body mass index was calculated (weight/square of length), and the weight loss during the last 6 months was recorded.

Splanchnic angiography

All patients underwent multiplane intra-arterial digital subtraction angiography of the abdominal aorta and its branches (Philips 3000 Integris system, Philips, Eindhoven, the Netherlands) during injection of 30 to 40 ml contrast medium (Ioxaglate, Hexabrix®, Mallinkrodt). First a non-selective anterior-posterior and lateral aortic angiography was performed, followed by selective canulation of the splanchnic arteries. The luminal filling of the abdominal aorta, the CA, SMA, and IMA was determined. Stenoses were graded by consensus of two investigators who were blinded to the patients' symptoms and the results of the other investigations. For comparison we graded these stenoses as absent (no stenoses), insignificant (<50%), mild (50-70%), major (70-99%) and occlusion (100%). Furthermore, the presence or absence of collateral circulation was scored.

Gastric exercise tonometry

Gastric exercise tonometry was performed in the afternoon, after a light breakfast followed by at least four hours of fasting. To prevent intragastric CO_2 production by buffering of gastric acid, 100 mg of ranitidine was administered intravenously one hour prior to the baseline tonometry measurements. A standard balloon-tipped tonometry catheter (Trip sigmoid catheter, Tonometrics, Helsinki, Finland) was inserted nasogastrically and placed at 55 cm from the tip of the nose. The catheter was attached to an automated air tonometry device (Tonocap, Datex-Engstrom, Finland) that uses a pump to automatically inflate and deflate the tonometry balloon via an airtight circuit. PCO_2 of the aspirated gas is analyzed by infrared capnography. The tonometry device measures gastric PCO_2 (P_gCO_2) every ten minutes.
An intravenous catheter was placed in the forearm for IV administration of ranitidine. A radial artery catheter was inserted in the non-dominant arm to allow arterial blood sampling. The exercise period lasted 10 minutes and followed the last baseline tonometric measurement cycle. Exercise was performed on an electromagnetically braked bicycle ergometer (Lode, Groningen, Netherlands). During the exercise test a 12-lead electrocardiogram was recorded (Case 12, Marquette Electronics Inc., Milwaukee, USA) and breath-by-breath oxygen uptake (VO_2) and respiratory gas exchange ratio (RQ) were measured by a respiratory gas analyzer system (Oxycon-α Jaeger, Bunnik, the Netherlands) in all but the first 19 subjects. The workload during was gradually increased and targeted at submaximal work rate level. [14] The maximal workload (W_{max}) was estimated using standard criteria, using age, sex, weight and forced expiratory volume. The exercise episode was started at 10% of W_{max} and in the first 4-6 minutes the workload was increased every minute with 10% of W_{max}. The workload was intended to remain constant thereafter at a submaximal exercise level. The exercise intensity was monitored by measuring HR, aiming for a HR in the last 4-5 minutes of 80% of maximal predicted heart rate ($HR_{maxpred}$) and RQ, aiming for an RQ of 1.0 in

the last 4-5 minutes of the exercise episode. This RQ was chosen as it indicates the anaerobic threshold.
At these same time points the P_gCO_2 was measured by the Tonocap, and the gastric-arterial PCO_2 difference or PCO_2-gradient was calculated: PCO_2 gradient = P_gCO_2 – P_aCO_2. The normal upper threshold value for PCO_2 gradient during exercise is 0.8 kPa [14] The mean of both baseline measurements were taken as baseline values (BL). The decrease in base excess (baseline - exercise BE value) was used as a measure of exercise intensity as it is closely correlated to arterial lactate levels. All tonometry test results were reviewed by two investigators blinded for the other clinical data for determination of interoperator variability.

The gold standard for chronic gastrointestinal ischemia

Selective splanchnic arteriography was used as the gold standard for the presence or absence of splanchnic arterial stenosis. Because there is no gold standard for diagnosing chronic splanchnic syndrome we decided to rely on a multidisciplinary panel consensus and sustained with careful follow-up, an approach used earlier for diagnoses lacking a gold standard procedure like rheumatoid arthritis [17]. After completion of all investigations, each case was discussed in the multidisciplinary gastro-intestinal working group and a consensus diagnosis was made. Due to the nature of this procedure, blinding was impossible. As mentioned, a careful follow-up program of all patients irrespective of diagnosis was an important part of this process. On follow-up, the consensus diagnosis could change based on the clinical course, treatment results, or alternative diagnosis. In the results, the group referred to as "chronic gastrointestinal ischemia" contains those subjects with a final, unchanged diagnosis. The patients in whom the diagnosis was changed on follow-up will be reported separately.

Follow-up

All patients with an initial diagnosis of ischemia are seen in our outpatient clinic at least 1-yearly. For the follow-up of the resumed non-ischemic patient group the physicians of these patients were contacted by letter. The required information consisted of current health status, abdominal symptoms, the cause of death in the case patient expired, and the presence of any signs, symptoms or diagnostic procedures indicating gastrointestinal ischemia.

Statistics

Values are given as mean ± SD unless otherwise stated. P-values < 0.05 were considered statistically significant. The Mann Whitney test was used for comparing symptom scores between the groups with and without chronic gastrointestinal ischemia. For all baseline values the mean of the two consecutive measurements was taken. Interobserver variability for angiographic stenosis of CA and SMA and for gastric exercise tonometry results was determined using the Cohen's kappa test. Differences in tonometry variables between patients with and without stenosis and ischemia were calculated using the unpaired Student's T-test. Association between gastric exercise

tonometry result and the presence or absence of stenosis and ischemia was tested using the Fisher exact test. The diagnostic accuracy of gastric exercise tonometry for chronic gastrointestinal ischemia was measured by ROC-analysis. The differences between curves were determined by comparison of the area under the curve and standard error. The sensitivity, specificity, positive and negative predictive values, as well as likelihood ratios were calculated. The outcome of patients treated for stenoses were determined by the life-table analysis according to Kaplan-Meier, using a log rank test.

Table 1. Demographics and clinical presentation (diagnosis gastrointestinal ischemia)

	all subjects (n=102)	chronic GI ischemia# (n=38)	no ischemia (n=64)
Male / female	34 / 68	7 / 31	26 / 37 **
Age (mean, range)	52 (20 - 81)	52 (24 – 75)	52 (20 – 81)
Abdominal pain % (median score)	66% (0.8)	63% (0.8)	66% (0.8)
Pain after exercise % (median score)	47% (0.7)	55% (0.9)	41% (0.7)
Pain after meal % (median score)	72% (1.4)	82% (1.8)*	64% (1.2)
Weight loss % (median score)	59% (1.3)	66% (1.5)	53% (1.2)
Diarrhoea	18%	24%	14%
Ulcer, non-*Hp*, non-NSAID	11%	13%	9%
Classic trias	32%	42%	27%

symptom scores ranged from 0-3 (see Methods)
patients diagnosed as chronic gastrointestinal ischemia, sustained during follow-up.
**$p<0.05$ comparing ischemic and non-ischemic patients (Chi-Square test)
*$p<0.05$ comparing ischemic and non-ischemic patients (Mann Whitney test)

RESULTS

Patients and symptoms

Between 1997 and 2000, 102 patients (67F/35M, median age 52, range 20-81 yr) were evaluated. The clinical presentation (symptom scores) and demographic data of patients who were finally classified as having chronic gastrointestinal ischemia or no ischemia are summarized in table 1. The presenting complaints were comparable, only postprandial pain was more pronounced in the ischemia group.

The complaints of the 38 patients with chronic gastrointestinal ischemia consisted of abdominal pain in 36 (95%), weight loss in 25 (66%), and diarrhoea in 3 (8%). The abdominal pain was provoked by meals in 83%, by exercise in 60%, and occurred at rest in 67%. In chronic gastrointestinal ischemia more severe postprandial pain was reported: grade ≥ 2 in 71% of the ischemia patients compared to 42% in the non-ischemic group ($p<0.05$). No differences in body mass index (22.5 kg/m² in both groups), BMI below 20 (34.2% *vs.* 29.7%), and weight loss was seen between the

ischemic and non-ischemic group. Gastric or duodenal ulcers, not explained by *Hp*-infection, medication or malignancy, were found in 12% in chronic mesenteric ischemia *vs.* 9% in the non-ischemic group (n.s.).

Splanchnic angiography

In 47 of 102 patients one or more significant stenoses were found; in 42 of 47 the stenosis was > 70%. Collateral vessels were found in 29 of the 47 patients with stenoses and in 11 of the 55 patients with normal vessels ($p<0.0001$). The interobserver agreement for detection of a stenosis in the CA, the SMA and the presence of collaterals was good with kappa values of 0.71, resp. 0.77 and 0.63 ($p<0.001$ for all kappa values).
The vascular abnormalities of the 38 patients with a final diagnosis of chronic gastrointestinal ischemia are summarized in table 2. In 2 of 5 patients without stenoses, abundant vasospasm was seen during angiography.

Table 2. Vascular involvement in gastrointestinal ischemia patients.

	Chronic gastrointestinal ischemia (n=38)
Single vessel	20
CA	17
SMA	3
Multivessel	13
CA/SMA	10*
CA/IMA	0
CA/SMA/IMA	3
No stenosis	5#

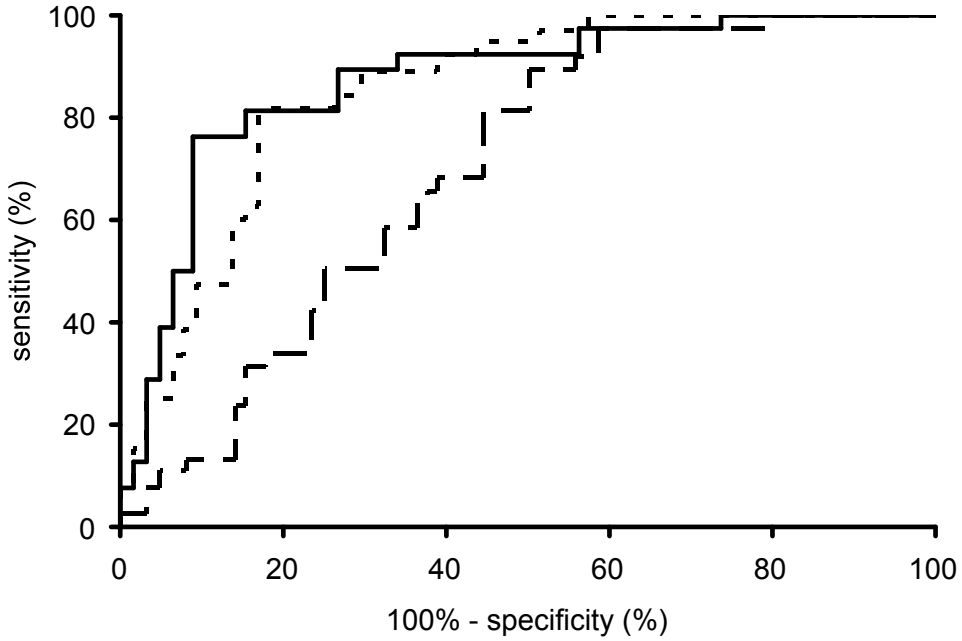
* one subject had SMA-stenosis >70% plus CA-stenosis 50-70%
# 5 subjects with suggested gastric vasospasm; in 2 spasms were seen on angiography

Gastric exercise tonometry

In 98 patients (96%) gastric exercise tonometry was interpretable. In 4 patients the level of exercise was above the goal range (BE-decrease ≥ 8 mmol/l). These four tests were excluded from analysis because we have previously shown false-positive tests in 45% of subjects at these exercise levels [14].
The final diagnosis of GI ischemia was made and sustained in 38 patients. Of these 33 had splanchnic stenoses (chronic splanchnic syndrome) and 5 had NOMI [10]. The P_gCO_2 and PCO_2 gradient differed between patients with chronic splanchnic syndrome, NOMI and those without ischemia ($p<0.0001$). The PCO_2 gradient in patients with chronic splanchnic syndrome was higher compared to those without ischemia: (1.2±0.6 *vs.* 0.3±0.7 kPa, $p<0.0005$), with similar exercise levels (BE-decrease 5.1±1.7 *vs.* 4.5±1.9; n.s.). The PCO2 gradient in patients with NOMI was higher than in the non-ischemic

group (1.3±0.3 *vs.* 0.3±0.7 kPa, p<0.01), but not different from the chronic splanchnic syndrome patients.
The diagnosis of NOMI was explained by pronounced vasospasm, seen on angiography in 2 patients. One patient had ischemia from cardiac failure, a condition known to cause NOMI [12]. In 2 others in whom vasospasm was suspected, nitrates were prescribed; both reported >50% reduction of pain, on a visual analogue scale, sustained after > 4 year follow-up.

Figure 1. ROC (Receiver Operater Curve) of three tonometry parameters used in the diagnosis of splanchnic ischemia.

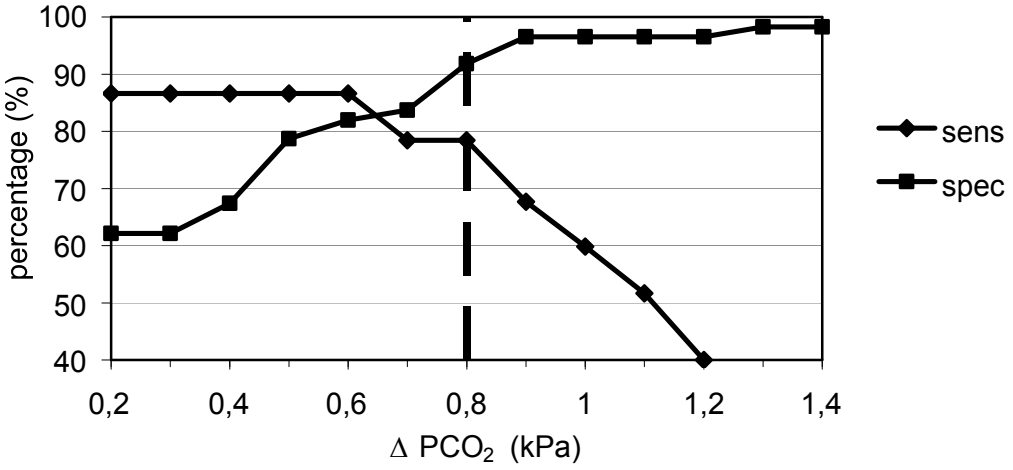


solid line: maximum PCO_2 gradient during exercise, short dashed line: area under the curve of the PCO_2 gradient, long dashed line: gastric PCO_2 during exercise

Gastric exercise tonometry criteria

To establish the best tonometric parameter we compared the maximum gastric PCO_2, the increase of gastric PCO_2, the PCO_2 gradient and the area under the curve of the PCO_2 gradient ($AUC_{PCO2\text{-}gradient}$). ROC analysis demonstrated that ΔPCO_2 and AUC were the best parameters for demonstrating ischemia (figure 1) and proved better than the P_gCO_2 (p<0.001), but not different from the $AUC_{PCO2\text{-}gradient}$ (p=0,71). The $AUC_{PCO2\text{-}gradient}$ was significantly better than the gastric PCO_2 (p<0.05).
In 8 patients the increased PCO_2 gradient during exercise was based on a decreased arterial PCO_2 alone, without concomitant increase in gastric PCO_2. This was caused by exercise-induced hyperventilation. Only 1 of these 8 was diagnosed with chronic gastrointestinal ischemia. Our current data re-establish the previously estimated threshold value of 0.8 kPa as upper level of normal PCO_2 gradient, with an optimal accuracy (figure 2).

Figure 2. Relation between the threshold PCO_2 gradient, sensitivity (sens) and specificity (spec) for detection of gastrointestinal ischemia.



Taken together, an abnormal gastric exercise tonometry result can best be defined by three criteria: an increase in gastric PCO_2 exercise from baseline to exercise, a PCO_2 gradient > 0.8 kPa during exercise, and a BE-decrease < 8 mmol/l during exercise. Using these three criteria, tonometry was abnormal in 29 of 38 patients with final consensus diagnosis of chronic gastrointestinal ischemia and in 5 of 64 patients without (accuracy 86%). The sensitivity and specificity of gastric exercise tonometry for chronic gastrointestinal ischemia were 78% and 92%, respectively; the positive and negative predictive values were 85% and 86%, respectively; the likelihood ratio for detection of gastrointestinal ischemia was 9.6.

Follow-up

The diagnosis on follow-up. Initially gastrointestinal ischemia was diagnosed in 43 patients; after a follow-up of mean 50 months (range 33-81), the diagnosis was abandoned in 5 patients. The reasons to abandon the initial diagnosis were: lack of improvement despite adequate stent placement (n=2), development of complaints typical for IBS and atypical for ischemia (relation to stool passage, bloating and distended abdomen, n=3).
Of the 64 patients without ischemia, 59 with initial classification as non-ischemic and 5 re-assigned to this group during follow-up, follow-up data were available in 55 after mean 5.5 years (range 3.8-7.7 yrs). None of these developed symptoms fitting acute or chronic splanchnic syndrome, three died of an unrelated course. Nine were lost to follow-up because neither we, nor the primary physician or referring physician were informed on their whereabouts.

Treatment results on follow-up. Of the 38 patients with chronic gastrointestinal ischemia 33 had chronic splanchnic syndrome and 5 NOMI. Twenty-five patients with chronic splanchnic syndrome underwent vascular treatment. The 8 non-treated patients

consisted of 3 patients with CA stenosis and mild complaints, who preferred conservative treatment with frequent small meals and proton pump inhibition over surgery. In 5 patients with chronic splanchnic syndrome a vascular procedure was clearly indicated but not performed. Two of these died from bowel infarction within weeks after diagnosis, while waiting for surgery, all had multivessel involvement. Of the remaining three, the operative risk was considered too high, whilst the stenoses were unfitted for stent placement (n=1), or they refused further treatment (n=2).
Of the 25 treated patients 19 were treated operatively, and 6 were treated by endo-vascular stent placement (n=5) or percutaneous transluminal angioplasty (PTA) alone (n=1). All 5 patients treated by PTA/stent placement showed good improvement. The patient treated by PTA alone had only a temporary response, but no further treatment was considered because of serious concomitant disease (metastatic lung cancer). Of the 19 operated patients, 3 died in the perioperative period from multiple-organ failure. One was severely cachectic (body mass index 16.0 $kg/m^{2)}$, and 2 had prolonged periods of abdominal vascular rest pain indicating acute-on-chronic gastrointestinal ischemia. The remaining 16 had uneventful postoperative course and improvement of symptoms was documented in all. Two patients treated for multivessel disease died on follow-up: one had a graft occlusion and subsequent bowel infarction 1.2 years after surgery, another died from unrelated cause 3 years later.
The outcome of the 12 treated single-vessel patients was quite different from the 13 patients with multivessel disease. Of single vessel patients none died, and the 1-yr success in this series was 100%, dropping to 79% after 4 years because of symptom recurrence from stent failure (n=1) or restenosis of the autogenous reconstruction (n=1) after more than 2 years. In the latter patient, endovascular dilatation relieved symptoms again. In the multivessel patients 5 patients died, 3 perioperative and 2 during follow-up. All surviving patients with multivessel chronic splanchnic syndrome were free of symptoms. Thus after 4 years follow-up, all surviving multivessel patients were symptom free; as well as 79% of the single-vessel patients. Taken together 10/12 (83%) of patients alive at 4 years were free of symptoms.

DISCUSSION

The current study was performed to establish the role of gastric exercise tonometry for detection of gastrointestinal ischemia in a cohort of patient with unexplained chronic abdominal symptoms, and to establish its clinical impact for these patients. This study confirmed that gastric exercise tonometry test can indeed detect gastrointestinal ischemia, both chronic splanchnic syndrome and NOMI. This is the first study to show the clinical impact of gastric exercise tonometry, because the inclusion of the results of this functional test to standard clinical and anatomical data in treatment decision, resulted in pain relief in 83% of patients sustained after 4-years of follow-up
Tonometry has the unique capability that it can show actual ischemia, for whatever cause, and regardless of blood flow and metabolic activity [10,11]. During ischemia the tissue P_{CO_2} rises over the normal levels from reduced tissue CO_2 washout by the

lowered blood flow and increased CO_2 production during anaerobic metabolism. Thus, an increased gastric-arterial PCO_2 level indicates local production, and therefore ischemia in practically all shock and ischemia models [11]. The gastric PCO_2 can be measured conveniently using air tonometry with small nasogastric catheters and a semi-automated capnograph. The use of test meal as provocative test seems more obvious, it proved unreliable [8], and we therefore explored exercise as provocative test. In a pilot study, gastric exercise tonometry could successfully detect ischemia in 7 chronic splanchnic syndrome patients [9] and was later validated by us in healthy volunteers [14]. The current study underscores the clinical usefulness and applicability of gastric exercise tonometry, with 96% interpretable tests, 86% accuracy, and no complications.

In 9 patients gastric exercise tonometry was normal, despite gastrointestinal ischemia. Two of these patients were unfit to exercise because of underlying severe pulmonary emphysema. In one patient with isolated SMA stenosis, a second tonometer, placed in the jejunum as part of a feasibility test to small bowel tonometry, showed a peak jejunal PCO_2 gradient 1.9 kPa, indicating small bowel ischemia. In another patient 24-hour tonometry, as part of another pilot study, showed repeated peaks in both gastric and jejunal PCO_2 gradients up to 8.0 kPa, correlating with abdominal pain episodes. Also, the higher frequency of false-negative tonometry among patients who did report exercise-induced pain indicates that measurement after meals still might be worthwhile. These findings indicate that the accuracy of exercise tonometry testing may further improve with 24-hour measurements, and small bowel tonometry.

In the current study most patients with chronic splanchnic syndrome had single-vessel disease, whereas many others reported this syndrome predominantly in 2- or 3-vessel disease [2]. The 1- and 2- to 3-vessel involvements represent different clinical entities. In our series, approximately 50% of 1-vessel patients had chronic splanchnic syndrome, compared to 90% of subjects with 2- to 3-vessel stenoses. Complications, especially bowel infarction, were common in 2- to 3-vessel patients and absent in those with 1-vessel stenosis. The symptomatic response to treatment, however, was comparable with disappearance of symptoms in both groups. This difference might have a major impact on diagnosis and treatment options. Diagnosing ischemia in patients with 2- to 3-vessel stenoses often will be right, even without a proper ischemia-specific test. In 1-vessel disease, diagnosing chronic splanchnic syndrome without a test like gastric exercise tonometry can feel like tossing a coin, a 50% chance and no clue on how it will turn out. Thus, especially in this group, gastric exercise tonometry has additional value over angiography.

The perioperative mortality was rather high in this study, with 3 of 19 patients dying days to weeks after operation. Three factors could be identified explaining this mortality figure. First, two of three patients were operated for acute-on-chronic chronic splanchnic syndrome, with prolonged and intensified bowel pain, increased lactate levels and leukocyte counts. During surgery a pale-bluish bowel was notably present in these patients; the procedures itself went well, but all died from multiple organ failure within 21 days after surgery. It could therefore be argued if these are still chronic ischemia

patients or already acute infarction or acute on chronic ischemia, known for its very high mortality of 80% or above [18]. Second, the third patient was extremely cachectic, she had an uneventful surgical procedure, but died from multiple organ failure 2 weeks post-procedure. Probably, the surgical procedures which consisted of aortic clamping above the level of the splanchnic arteries may just have been too much for this patient group. The third factor may thus be the procedure of choice. It is conceivable that less invasive procedures, like stent placement [22] or retrograde bypasses coming from the iliac vessels, could reduce this mortality figure in this high-risk patient group.

It seems unlikely, but can not fully be excluded, that the patient group whom we considered asymptomatic might have benefited from vascular treatment as well. During follow-up we found no evidence of progressive gastrointestinal ischemia, although admittedly the observation period was relatively short in relation to such developments [21]. The fact that tonometry represents a physiological test for gastrointestinal perfusion adequacy, and most of the "non-ischemic" patients had normal tonometry seems a strong argument against treatment of these patients. Still, to rule out a beneficial effect of vascular treatment in these patients, randomized controlled trials would be needed, blinded to tonometry results. From an ethical view point, ignoring physiological data for choosing optimal treatment options in this disorder seems hardly defendable.

In five patients NOMI was diagnosed because the complaints fitted ischemia, tonometry was abnormal and vessels on angiography were normal. It might be argued that these patients represent merely false-positive tonometry tests, but several arguments favour NOMI as diagnosis. NOMI is regularly observed in intensive care patients, where splanchnic vasoconstriction is an adaptive response to circulatory (pre)-shock [10]. This low-flow mechanism could explain findings in one patient with a cardiac failure. In 2 others profound vasospasm of smaller branches of the CA during angiography coincided with abdominal pain, indicating NOMI [2,11]. We hypothesized that vascular spasm might be involved in the complaints of the other patients as well. In fact, in many vascular beds symptomatic vasospasms are known to cause symptoms, such as Prinzmetal angina or syndrome X, Raynaud's disease, and hemiplegic migraine. Therefore, patients were treated with vasodilators (nitrates in 3, ketanserin in one) and 3 of them showed remarkable improvement of symptoms with more than 50% reduction of pain within weeks, sustained during follow-up.

CONCLUSION

We have shown that gastric exercise tonometry test is an accurate diagnostic test for chronic gastrointestinal ischemia in a large cohort of patients, using rigid diagnostic criteria and careful follow-up. The P_{CO_2} gradient during submaximal exercise enabled correct diagnosis in 86% of patients. Gastric exercise tonometry enabled identification of patients with ischemia and normal vessels, due to vascular spasm, which responded to vasodilator treatment. The clinical impact of incorporating tonometry results in decision making was very significant because 83% of patients treated for ischemia were free of symptoms after 4 years follow-up.

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Chapter 7

What is the Best Diagnostic Approach for Chronic Gastrointestinal Ischemia?

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Submitted

ABSTRACT

Background. Chronic gastrointestinal ischemia is still a difficult diagnosis to establish. The diagnosis depends on a high degree of clinical suspicion as well as selective angiography. Duplex sonography may serve as a screening tool, providing information on splanchnic vessel patency and flow patterns. Gastric exercise tonometry is a minimally invasive test that can be used for diagnosis in patients with chronic gastrointestinal ischemia, and can differentiate between symptomatic and asymptomatic splanchnic artery stenosis. In the present study we compared four different diagnostic approaches.

Methods. Between 1997 and 2000 84 patients were evaluated for suspected chronic gastrointestinal ischemia. All underwent splanchnic arterial angiography, duplex sonography and gastric exercise tonometry. For the presence or absence of stenosis angiography was used as golden standard. For diagnosing ischemia we relied on a panel decision. The diagnostic approaches studied were: 1) angiography, only in patients with classic abdominal angina, 2) screening with duplex sonography, angiography if sonography abnormal or unreliable, 3) screening with gastric tonometry and angiography if tonometry not normal, 4) both gastric tonometry exercise and duplex sonography, angiography if one of both screening tests not normal.

Results. In 28 patients chronic gastrointestinal ischemia was diagnosed. Using clinical suspicion only, 16 patients (57%) would have been missed. Screening by duplex sonography or gastric tonometry only would have missed 4 respectively 6 patients. Screening with combined gastric tonometry and duplex sonography would not have missed patients with symptomatic ischemia, while 21% of angiographies would have been avoided.

Conclusion. Screening by combined gastric exercise tonometry and duplex sonography has excellent diagnostic accuracy. Currently, this approach represents the best diagnostic work-up strategy in patients with suspected chronic gastrointestinal ischemia.

INTRODUCTION

Chronic gastrointestinal ischemia is a relatively rare disorder, which is difficult to establish and often has considerable doctor's delay. Its diagnosis is currently based on a high degree of clinical suspicion, e.g. the recognition of the classical clinical presentation of abdominal angina and requires angiography [2]. The use of duplex sonography of the celiac artery (CA) and superior mesenteric artery (SMA) is commonly advocated as an alternative, non-invasive, screening test [5]. Although generally available it is still sparsely used for this purpose however, partly because duplex of the splanchnic arteries is operator dependent and mainly because the presence of a stenosis does not automatically indicate ischemia. It is assumed that many patients with splanchnic stenoses never develop ischemia and stay asymptomatic.

Gastrointestinal tonometry is at present the only available test modality that can demonstrate actual ischemia [2,11]. In gastrointestinal tonometry luminal PCO_2 is measured and compared to blood values. In even the earliest stages of ischemia luminal PCO_2 rises over arterial blood PCO_2 [9]. This physiological background makes tonometry a unique and very sensitive measurement technique for ischemia. We have previously demonstrated the optimal conditions for tonometry, including acid suppression, use of meals and normal values in humans [9]. Tonometry after food provocation as diagnostic test for chronic mesenteric ischemia resulted in varying and disappointing accuracies [1,3,4]. These poor results were explained by volunteer studies showing poorly predictable tonometry parameters during and after meals, due to acid secretion, CO_2 dilution and gastric volume effects [6]. We therefore shifted our efforts to an alternative provocative manoeuvre for tonometric detection of ischemia and used a standardised exercise protocol instead with promising results [7,11,12].

In our clinic we perform duplex ultrasound, selective multi-plane visceral angiography, and gastric exercise tonometry in all patients suspected for chronic gastrointestinal ischemia. Still, for future use it is unclear if all of these techniques should indeed be used, and in which order or combination, for optimal accuracy and minimal costs and patient burden.

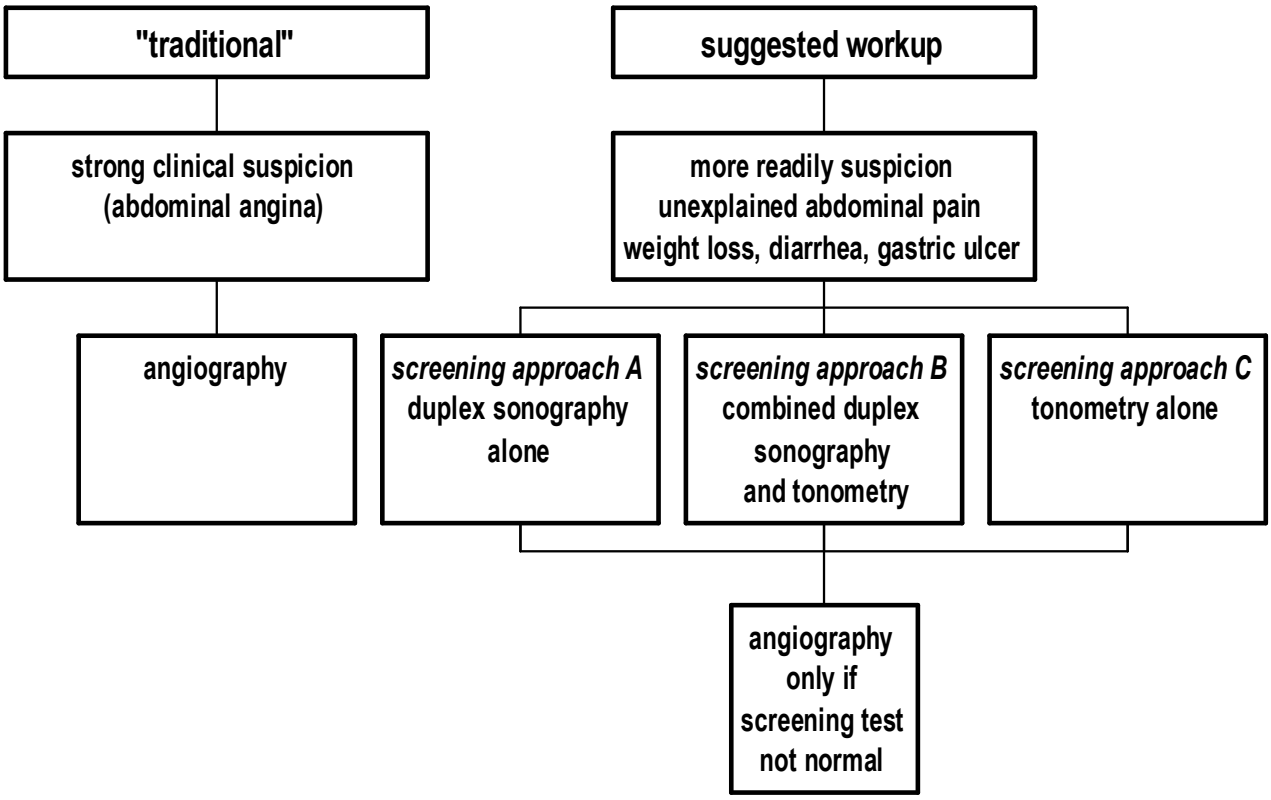
Using the results of our patient cohort we studied four different approaches using these test modalities (see figure 1).

PATIENTS AND METHODS

Eighty-four patients (58F, 26M; mean age 52, range 20-81 yrs) were examined between 1997 and 2000 for suspected chronic gastrointestinal ischemia. Most of the patients in this study have been previously described in a publication of our group investigating the diagnostic value of gastric exercise tonometry [11]. All patients had a clinical presentation of abdominal pain, weight loss and diarrhoea not explained by other investigations (including esophagogastroduodenoscopy and upper abdominal ultrasound) or gastroduodenal ulcer not associated with *Helicobacter pylori* infection or NSAID-use. All subjects underwent splanchnic arterial angiography, duplex sonography and gastric tonometry exercise testing.

For the presence or absence of splanchnic arterial stenosis selective splanchnic arteriography was used as the gold standard.
As there is no gold standard for diagnosing ischemia we decided to rely on a panel decision. Upon discussing each case in the gastro-intestinal working group a consensus diagnosis was made. Due to the nature of this procedure, blinding was impossible. A careful follow-up program was part of this process, and the consensus diagnosis was corrected if the data in the follow-up period necessitated this.

Figure 1. Diagnostic approach: suspected chronic splanchic syndrome



Angiography

The patients underwent multiplane arterial digital subtraction angiography of the abdominal aorta, in AP and lateral projections in in- and expiration (Philips 3000 Integris system, Philips, Eindhoven, the Netherlands) during injection of 25-40 ml contrast medium (Ioxaglate, Hexabrix®, Mallinkrodt). The luminal filling of the abdominal aorta, the celiac, superior, and inferior mesenteric artery was measured. Also selective catheterisation was performed of the CA, the SMA and the inferior mesenteric artery (IMA) to detect collateral vessels. Stenoses were graded in consensus by two independent investigators who were blinded to the patients' symptoms and the results of the duplex sonography and exercise tonometry.

Duplex ultrasonography

After a fasting episode of six hours, the patients were scanned using a 3.5 MHz convex sector probe with a Diasonics VST-master ultrasonography device. The duplex examinations were performed by operators who had no prior knowledge of the angiographic or tonometry results. After identifying the vessels and confirming patency and antegrade flow, the peak-systolic and end-diastolic flow velocities during in- and expiration were measured in the celiac (CA) and superior mesenteric (SMA) arteries and the aorta. The Doppler measurements were made with a sample size of 5mm. Velocity measurements were taken with the smallest, most accurate flow-to-beam angle possible. No measurements were accepted if the angle was greater than 60. Peak-systolic flow velocities below 200 and 275 cm/sec and end-diastolic flow velocities below 55 and 45 cm/sec were regarded as normal for the CA and SMA, respectively [10].

Gastric tonometry exercise testing

Gastric exercise tonometry was performed in the afternoon, after a fasting episode of at least four hours following a light breakfast. To prevent intragastric CO_2 production by buffering of gastric acid, 100 mg of ranitidine was administered intravenously one hour prior to the baseline tonometry measurements. A standard balloon-tipped tonometry catheter (Trip sigmoid catheter, Tonometrics, Helsinki, Finland) was inserted nasogastrically and placed at 55 cm from the tip of the nose. The catheter was attached to an automated air tonometry device (Tonocap, Datex-Engstrom, Finland), which was set up to measure intragastric PCO_2 (P_gCO_2) every ten minutes.
A radial artery catheter was inserted in the non-dominant arm to allow arterial blood sampling.
Baseline measurements of arterial blood and gastric tonometry PCO_2 were obtained 10 minutes and immediately before the exercise period. The exercise period lasted 10 minutes and started immediately after the last baseline tonometric measurement cycle. Exercise was performed on an electromagnetically braked bicycle ergometer (Lode, Groningen, Netherlands). During the exercise test a 12-lead electrocardiogram was recorded (Case 12, Marquette Electronics Inc., Milwaukee, USA) and breath-by-breath oxygen uptake (VO_2) and respiratory gas exchange ratio (RQ) were measured by a respiratory gas analyzer system (Oxycon-α Jaeger, Bunnik, the Netherlands). The workload during was gradually increased and targeted at submaximal work rate level [12]. Arterial and tonometry parameters were obtained immediately at the end of the exercise period. Ten and 20 minutes after the exercise period recovery measurements of arterial blood gases and tonometry parameters were done. Arterial blood was analyzed immediately for pH, PCO_2, PO_2, bicarbonate content, and base excess (BE) using a standard blood gas analyzer (Radiometer ABL520, Copenhagen, Denmark).
Gastric-arterial PCO_2 gradients (ΔPCO_2) were calculated: $\Delta PCO_2 = P_gCO_2 - P_aCO_2$. The normal upper threshold value for ΔPCO_2 was considered 0.8 kPa. The decrease in base excess (BL-BE minus EX-BE) was used as a measure of exercise intensity. Exercise tonometry testing was considered to be "positive" if 1) P_gCO_2 after exercise increased

over baseline P_gCO_2, 2) ΔPCO_2 exceeded the threshold value of 0.8 kPa in exercise or recovery measurements (provided that baseline measurements were normal), and 3) exercise intensity was submaximal (BE-decrease <8 mmol/l).

Comparison of different algorithms

Four potential diagnostic approaches were considered for analysis:
1. to perform angiography only in patients with classic abdominal angina
2. to screen with duplex sonography and perform angiography after an abnormal or unreliable test
3. to screen with gastric exercise tonometry and perform angiography after an abnormal or unreliable test
4. to screen with both gastric exercise tonometry and duplex sonography and perform angiography in those with at least one of these screening tests abnormal or unreliable.

Statistics

Values are given as mean ± SD unless otherwise stated. P-values < 0.05 were considered statistically significant. Association between tonometry test result and the presence or absence of stenosis and ischemia was tested using the Fisher exact test. The diagnostic accuracy of duplex sonography and exercise tonometry testing for symptomatic chronic ischemia were assessed by calculation of sensitivity, specificity, positive and negative predictive values, as well as likelihood ratios.

RESULTS

Duplex ultrasonography

In 12/84 (18%) patients duplex was not reliable because flow measurement in one or both vessels (CA alone in 6, CA and SMA in 6) was impossible due to insufficient visualisation (intestinal gas, circumferential calcifications, or large abdominal wall-splanchnic artery distance) or wide measurement angle. Consequently 72 splanchnic duplex ultrasounds were interpretable.
In 24/72 both vessels had normal flow velocities and were regarded as "negative duplex tests". In 48/72, a "positive duplex" was found. Significant stenoses were found in CA and SMA in 13 patients, in the CA alone in 29 and in the SMA alone in 3 patients. In 3 of these 72 patients duplex showed stenosis or occlusion in one vessel, while the other vessel (CA in 2, SMA in 1) could not be visualized. This did not change the classification however, as these patients were already considered "abnormal" based on the stenosis in one vessel.

Gastric exercise tonometry

In 4 tests the exercise level was too high for reliable interpretation with base excess decrease after exercise exceeding 8 mmol/l [12]. In 54/80 gastric exercise tonometry was normal, the remaining 26 were considered abnormal ("positive tonometry exercise

test") with a gastric-arterial P_{CO_2} gradient >0.8 kPa, and an increase after exercise of P_gCO_2 over baseline.

Angiography

Splanchnic arterial stenoses >50% were found in 34 patients: 22 had isolated CA-stenosis, 3 had isolated SMA-stenosis, 7 had stenosis of both CA and SMA, and 2 had stenosis of all three splanchnic vessels (CA, SMA, and IMA).

Final diagnosis

Initially, the working group categorised 32 patients as chronic mesenteric ischemia. With 50 months (range 35-80 months) follow-up in 4 patients the diagnosis was changed to asymptomatic stenosis. Thus, in 28 patients the diagnosis chronic ischemia was confirmed and maintained on follow-up. Of these patients 12 had isolated CA-stenosis, 3 had SMA stenosis, 6 had stenosis of CA and SMA, 2 had stenosis of all three vessels and 5 had NOMI.

Analysis of work-up regimens / diagnostic strategies

1. *Clinical presentation.* The classical clinical presentation of abdominal angina (both moderate to severe pain after food intake unexplained by other causes, and weight loss) was present in 27/84 subjects. Of these 27 patients 12 had chronic mesenteric ischemia. Sixteen patients with chronic ischemia had an "incomplete" clinical presentation: only moderate-severe postprandial pain but no or only mild weight loss in 9, only weight loss but lacking postprandial pain in 2, and both lacking postprandial pain and weight loss in 5. The latter patients did present with abdominal pain but this was not typically food-intake-related. Ten patients with a "non-classical" presentation were treated by either surgery or PTA/stent placement and were symptom free afterwards. Using the classical presentation as the only criterion, 57% of all chronic ischemia patients would have been missed.

2. *Duplex ultrasound.* Of the 12 patients in whom one or both vessels could not be adequately visualized for flow measurements, 8 had stenosis (7 in CA and 1 in SMA), and 5 of them had ischemia.
Of the 72 reliable duplex ultrasound tests, 25 patients had abnormal duplex, confirmed by angiography (true-positive for stenosis). In 23 patients with abnormal flow velocities on ultrasound, the angiography was normal (false-positive for stenosis). In 22 patients normal vasculature on duplex ultrasound was confirmed by angiography (true-negative for stenosis). In 2 patients duplex ultrasound was normal, but angiography showed stenosis of the CA in both (false-negative for stenosis). The diagnostic accuracy of duplex ultrasound is summarised in table 1.
If duplex ultrasound had been used as the only screening test, and both positive and unreliable tests were followed by angiography, two patients with stenoses would have been missed, and a total of four patients with ischemia would remain undiagnosed (one with chronic ischemia due to splanchnic artery stenosis, three with NOMI). Thus, 14%

of all patients with ischemia would have been missed, while 24 (=29%) angiographies could have been avoided.

3. *Tonometry.* One of the four patients with a non-diagnostic gastric exercise tonometry test was finally diagnosed as having chronic mesenteric ischemia. In ten patients gastric exercise tonometry was abnormal but angiography showed normal vasculature. Five of these had nonocclusive mesenteric ischemia (NOMI), leaving 5 false-positive tonometry tests. If we had relied on tonometry as the only screening method, 6/28 (21%) patients with ischemia would have been missed (gastric exercise tonometry false-negative for ischemia). 54 (64 %) angiographies would have been avoided.

Table 1. Sensitivity, specificity, positive and negative predictive value and likelihood ratio for duplex sonography and tonometry in stenosis and ischemia.

	% assessable tests	stenosis					ischemia				
		sens	spec	PPV	NPV	LR	sens	spec	PPV	NPV	LR
duplex	86	93	49	52	92	1.8	81	39	35	83	1.3
tonometry	95	48	79	62	69	2.3	78	91	81	89	8.2

sens = sensitivity, spec = specificity, PPV = positive predictive value, NPV = negative predictive value, LR = likelihood ratio

4. *Combined duplex ultrasound and tonometry.* Screening by combining duplex ultrasound and gastric exercise tonometry, only followed by angiography if one of the screening test is not normal (i.e. abnormal or inconclusive), would have yielded no false negative results (negative predictive value 100%; 95% confidence interval: 73%-100%). In all 26 of the 28 patients with chronic ischemia one or both screening tests was abnormal, in 1 both duplex ultrasound and gastric exercise tonometry were unreliable, in 1 duplex ultrasound was unreliable and gastric exercise tonometry was normal. Combined screening resulted in 38 false-positive results (either one or both tests abnormal or unreliable). The approach of combined non-invasive screening would have resulted in 18 (= 21%) true-negative results and thus in not performing splanchnic arteriography in these patients.

DISCUSSION

From this study it can be concluded that relying on only one screening test for excluding chronic symptomatic gastrointestinal ischemia does not suffice. Using clinical presentation as "trigger" and angiography as diagnostic tool, as currently advocated [2],

would have resulted in detection of less then 50% of all patients with ischemia. Duplex ultrasound has the limitation of incomplete assessability, the 15% of this study is in line with literature [10]. Still, relying on duplex alone would have resulted in 14% missed ischemia, albeit only one (4%) with chronic mesenteric ischemia, reconfirming its capability of stenosis detection. Tonometry with its unique capability of showing actual ischemia (defined as inadequate blood flow for the metabolism) is not suitable as primary screening alone with miss-rates of 21%. Combining duplex ultrasound, as best stenosis screening tool, and exercise tonometry, as only available diagnostic test for detecting ischemia, leads to very accurate detection of symptomatic chronic mesenteric ischemia. Moreover, the latter may be used to separate chronic mesenteric ischemia from asymptomatic stenosis and demonstrate NOMI.

It might be questioned whether our approach of combined screening methods resulted only in diagnosing clinically insignificant cases of chronic ischemia. In other words: are those with less typical complaints of any importance. This is not the case, as these less typical presentation, 10 patients were treated by revascularisation and were free of symptoms thereafter. Interestingly, a difference was noted between those with typical abdominal angina and those with an "incomplete clinical picture". The former seem to present more advanced stages of gastrointestinal ischemia with 63% 2-3 vessel disease compared to only 9% of 2-3 vessel disease in the latter group.

Most authors focused on more advanced disease and indeed reported typical presentation in most patients while only few patients with single vessel disease [2]. Therefore, it seems that current literature on abdominal angina focuses on late stages of chronic mesenteric ischemia, and consequently early presentation is relatively underappreciated. This notion is supported by the delay of many years before diagnosis in most patients. The extreme was a patient with CA stenosis, who developed a gastric ulcer 31 years earlier, and had postprandial pain ever since, disappearing immediately after stent placement. Thus, chronic gastrointestinal ischemia can be found in more than typical abdominal angina, and should include patients with unexplained epigastric pain after meals and exercise.

Several explanations may be postulated for the fact that one patient may have complaints with only single vessel stenosis and others have minimal complaints with much more extensive vascular pathology. As in functional disorders such as irritable bowel syndrome and non-ulcer dyspepsia, visceral sensitivity may vary widely between individuals and explain marked differences in susceptibility for abdominal symptoms. Furthermore, collateral circulation may be extensive in the gastrointestinal vascular bed. It may well be that in longstanding and slowly progressive multi-vessel disease abundant collateral circulation has developed securing the gastrointestinal perfusion, while in newly developed single vessel stenosis -and especially occlusion- no adequate collateral circulation is present yet, thus giving rise to ischemic symptoms.

In some patients ischemia was diagnosed despite normal vascular anatomy. This was suspected in 5 patients with typical clinical presentation and abnormal tonometry. In these patients NOMI (non-occlusive mesenteric ischemia) or vasospasm is the most

likely cause of symptoms (and abnormal tonometry). It is widely recognised that tonometry is the optimal diagnostic for NOMI detection [8]. NOMI can be seen as an exaggeration of normal adaptive response to low flow states. In our patients, NOMI was caused by cardiac failure in one patient. In the remaining four, splanchnic vascular spasms were thought to occur giving resulting in recurrent episodes of ischemia. In two of these patients abundant spasms were visualized during angiography, an otherwise rare phenomenon. All four patients were treated with vasodilating medication and showed remarkable and longstanding improvement of symptoms.

The introduction of new minimally invasive techniques including MR angiography, CT angiography, and portal vein flow measurement, may improve screening -or definite diagnosis- of ischemia. Combining MRA with portal flow measurement seems attractive, although anatomic resolution of MRA is still inferior compared to state of the art splanchnic artery angiography and assessment of collaterals and influence of respiration is not possible. Portal flow increment after a meal may be considered a function of splanchnic vessel reserve. To date, the clinical experience with the latter technique is sparse. Whatever diagnostic tool is used, combining a diagnostic test aimed at vascular morphology and/or blood flow with a diagnostic test for actual GI-ischemia is in our opinion mandatory.

The present study demonstrates that suspicion for chronic gastrointestinal ischemia should include patients with unexplained longstanding abdominal pain eventually provoked by meals or exercise, in which other more common causes were excluded. The approach of performing angiography only in patients with a high degree of clinical suspicion would have resulted in missed diagnosis in over 50% in our cohort of patients with chronic mesenteric ischemia. Combining non-invasive screening with exercise tonometry and duplex ultrasonography in this cohort of patients has excellent diagnostic accuracy, while still avoiding 21% of angiographies.

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Chapter 8

Summary and Conclusions

This thesis investigates the role of gastrointestinal exercise tonometry as a functional diagnostic test in patients suspected of chronic gastrointestinal ischemia. In contrast with all other diagnostic modalities (angiography, duplex sonography, CT- and MR-angiography) that only provide information about vessel anatomy, vessel patency or blood flow, tonometry can actually demonstrate end-organ ischemia.
Measurement of gastrointestinal luminal to blood PCO_2 by means of tonometry has been shown to provide exactly that information: the presence or absence of ischemia. Until now it is the only clinically feasible, i.e. minimally invasive and bedside, technique for monitoring the adequacy of gastrointestinal (mucosal) perfusion in a wide variety of conditions such as (hemorrhagic) shock, sepsis, trauma, pancreatitis, cardiovascular and gastro-esophageal surgery. In **chapter two** a review of the current thoughts on tonometry is given. Uncertainties about physiological background, methodology, and clinical use have hindered tonometry from gaining the status of a routine diagnostic technique. Most of the initial problems however have been addressed and solved, for instance by the introduction of automated air tonometry, and recognizing that measurements have to be done in an empty stomach and after adequate gastric acid suppression.

Gastric tonometry after food provocation has been used as diagnostic test for chronic gastrointestinal ischemia. This has resulted in varying and disappointing accuracies. In a pilot study by J.J. Kolkman, using physical exercise as an alternative provocative manoeuvre, gastric (saline) tonometry showed to be a promising test for the detection of symptomatic chronic gastrointestinal ischemia. In chapters two, three and four of this thesis questions arising from this pilot study are addressed, including the intensity of exercise needed for provocation of gastrointestinal ischemia, the best way to monitor this exercise intensity and the best location in the gastrointestinal tract for tonometric measurements.
In **chapter three** the relationship between exercise intensity and gastric mucosal perfusion adequacy as measured by gastric (air) tonometry is investigated in a volunteer study with two different exercise levels. The results of this study show that in these subjects with normal splanchnic vasculature, gastric ischemia can develop after only 10 minutes of (maximum) physical exercise. The intragastric-arterial PCO_2 gradient (ΔPCO_2) was elevated (by 1.1 ± 1.0 kPa) over baseline values (-0.1 ± 0.3 kPa) only after maximal exercise ($p<0.001$). The development of gastric ischemia strongly depended upon the exercise intensity: using Spearman's rank test a positive correlation between ΔPCO_2 and arterial lactate level, taken as an index of exercise intensity was found ($r=0.76$, $p<0.0001$). By bilinear regression analysis, a lactate level of 12 mmol/L above which a sharp rise in the ΔPCO_2 occurred, was calculated. Furthermore, this study demonstrates that air tonometry can be used for assessment of the adequacy of gastric mucosal perfusion during physical exercise.
As maximum exercise levels can lead to gastric mucosal ischemia in healthy subjects, in patients suspected of chronic gastrointestinal ischemia the exercise build-up should be

controlled to reach submaximal exercise levels, thus achieving maximal diagnostic accuracy by avoiding false-positive tests. In **chapter four** three different monitoring regimes (monitoring of heart rate, respiratory gas exchange ratio -RQ-, and rapid serial arterial lactate measurements) for determining exercise intensity are compared. Exercise levels above submaximal were reached in 20% of heart rate monitoring, 2% of RQ-monitoring and 5% of rapid serial lactate measurements ($p<0.05$ for HR *vs.* RQ and lactate). Low exercise levels were seen in 5%, 10% and 41% in heart rate monitoring, RQ-monitoring, and rapid lactate monitoring, respectively ($p<0.01$ for lactate *vs*. heart rate and RQ). However, low exercise levels did not result in an increase in false negative tonometry tests (5% in low exercise level compared to 6% in all tests), whereas high levels resulted in 43% false-positive tests (compared to 19% in all tests, $p<0.001$). RQ-monitoring resulted in the greatest proportion of optimal exercise tests, but rapid serial lactate emerged as our method of choice, combining good diagnostic accuracy, low-cost and simplicity, and allowing accurate gastrointestinal exercise tonometry easily to be performed in daily clinical practice.

In most patients with chronic gastrointestinal ischemia the celiac artery (CA) is stenotic or occluded, either as the single vessel involved or in multivessel disease. This enables the use of gastric exercise tonometry as a diagnostic function test. It may be questioned whether jejunal tonometry measurement -in the flow region of the superior mesenteric artery (SMA)- could have additive value in patients with (isolated) SMA stenosis or occlusion. In **chapter five** we investigated the feasibility of combining gastric and jejunal exercise tonometry and determined the normal values. Furthermore we investigated the potential diagnostic value of combining gastric with jejunal exercise tonometry.
This study demonstrated that combining gastric with jejunal exercise tonometry testing is a feasible procedure that is relatively easy to perform. Normal resting jejunal PCO_2 values were 0.8 kPa higher than gastric PCO_2. The calculated normal upper threshold of the jejunal-arterial PCO_2 gradient is 1.4 kPa. This threshold was not exceeded during and after exercise in subjects with normal splanchnic vasculature. Of 8 patients with chronic gastrointestinal ischemia, gastric exercise tonometry was abnormal in five, both gastric and jejunal tonometry were abnormal in one, and only jejunal exercise tonometry was abnormal in two. Gastric exercise tonometry would thus have detected 6 of 8 patients, while jejunal tonometry alone would have detected only 3 of 8. Thus, combining jejunal with gastric exercise tonometry may contribute to the diagnosis of gastrointestinal ischemia. Apart from having an additional value in demonstrating jejunal ischemia in subjects with chronic gastrointestinal ischemia, the technique may be used to demonstrate ischemia in other disorders such as hemodynamic instability and Crohn's disease.

In **chapter six**, gastric exercise tonometry testing is validated as a diagnostic tool in a cohort of 102 patients with unexplained chronic abdominal symptoms, suspected for

chronic gastrointestinal ischemia. The diagnostic workup included gastric exercise tonometry and angiography. The diagnosis gastrointestinal ischemia was based on consensus in a multidisciplinary working group, sustained on follow-up. Gastrointestinal ischemia was diagnosed in 38 patients. In 33 chronic gastrointestinal ischemia (with single vessel involvement in 20 (17 CA, 3 SMA), and multivessel disease in 13). In 5 patients non-occlusive ischemia was found. Using ROC-analysis, gastric-arterial ΔP_{CO_2} proved the best gastric exercise tonometry parameter. The criteria for diagnosing ischemia were: $\Delta P_{CO_2} > 0.8$ kPa, and increase of gastric P_{CO_2} (with base excess decrease < 8 mmol/l) during exercise. Using these criteria gastric exercise tonometry had a sensitivity of 78% and specificity of 92% for diagnosing chronic gastrointestinal ischemia. It is concluded that gastric exercise tonometry is an accurate diagnostic tool to show gastrointestinal ischemia, both chronic splanchnic syndrome and NOMI. Including gastric exercise tonometry in clinical decision making enabled selecting patients with ischemia who benefited from vascular or medical treatment. These benefits were sustained during 4-yr follow-up. Gastric exercise tonometry should be considered in the work-up of patients suspected of gastrointestinal ischemia.

In **chapter seven**, various diagnostic approaches for suspected chronic mesenteric ischemia are compared: 1) angiography, only in patients with classic abdominal angina, 2) screening with duplex sonography, angiography if sonography abnormal or unreliable, 3) screening with gastric tonometry and angiography if tonometry not normal, 4) both gastric tonometry exercise and duplex sonography, angiography if one of both screening tests not normal.
In 28 of 84 patients suspected of chronic gastrointestinal ischemia and who underwent both angiography, duplex sonography, and gastric exercise tonometry the consensus diagnosis chronic gastrointestinal ischemia was made by an expert panel. Using clinical suspicion only, 16 patients (57%) would have been missed. Screening by duplex sonography or gastric tonometry alone would have missed 4 respectively 6 patients. Screening with combined gastric tonometry and duplex sonography would not have missed patients with symptomatic ischemia, while 21% of angiographies would have been avoided. From this study it can be concluded that relying on only one screening test for excluding chronic symptomatic gastrointestinal ischemia does not suffice. Using clinical presentation as "trigger" and angiography as diagnostic tool, as currently advocated, would have resulted in detection of less than 50% of all patients with ischemia. Duplex ultrasound has the limitation of incomplete assessability (15% in this study which is in line with literature). Still, relying on duplex sonography alone would have resulted in 14% missed patients with ischemia, albeit only one (4%) with chronic splanchnic syndrome, reconfirming its capability of stenosis detection. Tonometry with its unique capability of showing actual ischemia (defined as inadequate blood flow for the metabolism) is not suitable as primary screening alone with miss-rates of 21%. Tonometry may be used to separate chronic mesenteric ischemia from asymptomatic stenosis and to demonstrate NOMI. Combining duplex ultrasound, as best stenosis

screening tool, and exercise tonometry, as currently the only available diagnostic test for detecting ischemia, leads to very accurate detection of symptomatic chronic mesenteric ischemia. Currently, the approach of combined screening by duplex sonography and gastric exercise tonometry represents the best diagnostic work-up strategy in patients with suspected chronic gastrointestinal ischemia.

Chapter 9

Samenvatting en Conclusies

In dit proefschrift wordt de rol onderzocht van inspanningstonometrie van de maag als diagnostische functietest bij patiënten met verdenking op chronische maagdarm-ischemie. Gastrointestinale tonometrie is tot op heden de enige klinisch toepasbare, minimaal invasieve, 'bedside' techniek om de doorbloeding van het maagdarmkanaal te beoordelen. In tegenstelling tot alle andere diagnostische tests bij verdenking op vaatlijden van het maagdarmkanaal, zoals angiografie, duplex echografie, en CT- en MRI-angiografie, die slechts informatie geven over vaatanatomie (stenose of occlusie) en bloedstroom kan tonometrische bepaling van de luminale PCO_2 informatie geven over het aan of afwezig zijn van ischemie in het eindorgaan (maag- of darmslijmvlies).
Tonometrie van de maag wordt in de klinische praktijk onder meer gebruikt om de adequaatheid van de mucosale perfusie van het maagdarmkanaal te beoordelen bij bijvoorbeeld (hemorrhagische) shock, sepsis, trauma, pancreatitis, cardiovasculaire chirurgie en slokdarm- en maagchirurgie. Door onduidelijkheid over de fysiologische achtergrond, methodologie en klinische toepasbaarheid is tonometrie tot op heden echter nog geen routinematig toegepaste techniek. In **hoofdstuk 2** wordt een overzicht gegeven over de huidige inzichten in tonometrie. In dit overzicht worden de fysiologische en methodologische achtergronden besproken, evenals nieuwe ontwikkelingen zoals geautomatiseerde luchttonometrie (welke de arbeidsintensieve en foutgevoelige handmatige vloeistoftonometrie vervangt en tonometrie daarmee veel eenvoudiger uitvoerbaar maakt), de waarde van de luminale-bloed PCO_2 gradiënt versus de intramucosale pH en de noodzaak van maagzuurremming en het meten in een lege maag.

Tonometrie van de maag na maaltijdprovocatie is in het verleden gebruikt als diagnostische test bij chronische maagdarmischemie. De resultaten hiervan waren wisselend met vaak teleurstellende accuratesse van deze diagnostische test. Tonometrie van de maag waarbij lichamelijke inspanning als alternatieve provocatietest voor ischemie werd door Kolkman et al. in 1999 beschreven. De conclusie van deze pilot studie was dat inspanningstonometrie van de maag een veelbelovende diagnostische test voor symptomatische chronisch maagdarmischemie leek. In hoofdstukken twee, drie en vier van dit proefschrift worden vragen die naar aanleiding van die pilot studie rezen verder onderzocht. Welk inspanningsniveau is nodig voor provocatie van gastrointestinale ischemie? Wat is de beste manier om de hoogte van dit inspanningsniveau te bewaken? Wat is de beste plaats in het maagdarmkanaal voor tonometrie?

In **hoofdstuk 3** wordt de relatie onderzocht tussen het niveau van lichamelijk inspanning en de doorbloeding van de maag zoals gemeten met (lucht-)tonometrie. Dit werd onderzocht bij gezonde vrijwilligers tijdens twee verschillende inspanningsniveaus (submaximaal en maximaal). De resultaten van deze studie laten zien dat bij gezonde personen met normale maag- en darmvaten ischemie van de maag kan optreden na slechts 10 minuten (maximale) inspanning. De intragastrische-arteriële PCO_2 gradiënt

(ΔPCO_2) was alleen bij maximale inspanning hoger (1.1 ± 1.0 kPa) dan baseline waarden (-0.1 ± 0.3 kPa; $p<0.001$). Het optreden van ischemie van de maag hing sterk af van het inspanningsniveau. Met behulp van Spearman's rank test werd een positieve correlatie tussen ΔPCO_2 arterieel lactaat (als maat voor inspanningsintensiteit) gevonden ($r=0.76$, $p<0.0001$). Met bilineaire regressie analyse werd een lactaat van 12 mmol/L berekend, waarboven een scherpe toename van ΔPCO_2 werd gezien.
Aangezien maximale inspanning kan leiden tot ischemie van de maag bij gezonde personen, moet bij het gebruik van inspanningstonometrie van als diagnostische test bij patiënten met verdenking op chronische gastrointestinale ischemie om vals-positieve tests te voorkomen het inspanningsniveau zodanig gecontroleerd zijn dat dit submaximaal blijf.
In **hoofdstuk 4** worden drie verschillende manieren om het inspanningsniveau te bewaken vergeleken: monitoring van hartfrequentie (HR), respiratoir quotiënt (RQ) en snelle arteriële lactaatbepalingen. Aan de hand van meting van de hartfrequentie werd bij 20% van de tests een inspanningsniveau boven submaximaal verkregen. Dit was slechts 2% bij RQ-monitoring en 5% bij lactaatmetingen ($p<0.05$ voor HR *vs.* RQ en lactaat). Een laag inspanningsniveau werd gevonden bij 5% van de HR-gemonitorde tests, 10% bij RQ-monitoring en 41% bij lactaat monitoring ($p<0.01$ voor lactaat *vs.* HR en RQ). Een laag inspanningsniveau resulteerde echter niet in een toename van vals-negatieve tonometrietests (5% bij laag inspanningsniveau vergeleken met 6% in alle tests). Te hoge inspanningsniveaus resulteerden daarentegen in 43% vals-positieve tests (vergeleken met 19% in alle tests, $p<0.001$). RQ-monitoring resulteerde in de grootste proportie van optimale inspanningstests, maar monitoring aan de hand van snelle lactaatmetingen heeft toch onze voorkeur omdat dit in de dagelijkse praktijk eenvoudig uitvoerbaar is, lage kosten heeft en een goede diagnostische accuratesse van inspanningstonometrie van de maag oplevert.

Bij de meeste patiënten met chronisch splanchnicus syndroom is de truncus coeliacus (CA) stenotisch of geoccludeerd, hetzij als enig betrokken vat, hetzij bij meertakslijden. Dit maakt het mogelijk dat inspanningstonometrie van de maag wordt gebruikt als diagnostische functietest. De vraag die zich dan aandient is of metingen in het jejunum -in het stroomgebied van de arteria mesenterica superior (SMA)- wel of geen meerwaarde hebben bij patiënten met (al dan niet geïsoleerde) SMA stenose. In **hoofdstuk 5** wordt de uitvoerbaarheid van gecombineerde maag- en jejunum-tonometrie bij inspanning onderzocht en worden de normaalwaarden van inspannings-tonometrie van het jejunum vastgesteld. Daarnaast werd de diagnostische waarde van gecombineerde inspanningstonometrie van maag en jejunum onderzocht.
Gecombineerde inspanningstonometrie van maag en dunne darm bleek relatief eenvoudig uitvoerbaar. De normale jejunum PCO_2 waarde was in rust 0.8 kPa hoger dan de maag PCO_2. De berekende bovengrens van normaal van de jejunale-arteriële PCO_2 gradiënt is 1.4 kPa. Bij personen met normale maag- en darmvasculatuur werd deze bovengrens tijdens (en na) submaximale lichamelijke inspanning niet overschreden. Van

acht patiënten met chronische gastrointestinale ischemia, was inspanningstonometrie van alleen de maag afwijkend bij vijf, van zowel maag als jejunum bij één en van alleen jejunum bij twee. Inspanningstonometrie van de maag alleen zou dus zes van de acht patiënten hebben gedetecteerd, terwijl jejunumtonometrie alleen dit slecht bij drie van de acht zou doen. Het combineren van metingen in het jejunum bij inspanningstonometrie van de maag kan dus bijdragen bij de diagnostiek van chronische intestinale ischemie. Los van deze additionele waarde van het aantonen van jejunumischemie bij patiënten met chronisch splanchnicus syndroom, kan deze techniek ook gebruikt worden om ischemie aan te tonen bij andere aandoeningen zoals hemodynamische instabiliteit en de ziekte van Crohn.

In **hoofdstuk 6**, wordt inspanningstonometrie van de maag gevalideerd als diagnostische test in een cohort van 102 patiënten met onbegrepen chronische buikklachten, verdacht voor chronische maagdarmischemie. Het diagnostische traject omvatte naast inspanningstonometrie van de maag onder andere angiografie. De consensusdiagnose chronische maagdarmischemie werd gesteld door een Multidisciplinaire werkgroep (expert panel), het beloop tijdens de follow-up periode werd hierin betrokken. Chronische gastrointestinale ischemie werd gediagnostiseerd bij 38 patiënten. Bij 33 betrof het chronisch splanchnicus syndroom (met eentakslijden bij 20 patiënten (17 CA, 3 SMA), and meertakslijden bij 13). Bij 5 patiënten werd non-occlusieve ischemie (NOMI) gevonden. Met behulp van ROC-analyse bleek dat de intragastrische-arteriële ΔPCO_2 de beste parameter was voor inspanningstonometrie. De criteria voor de diagnose ischemie waren: $\Delta PCO_2 > 0.8$ kPa, een toename van intragastrische PCO_2 tijdens inspanning en submaximale inspanning met een base exces afname < 8 mmol/l. Met deze criteria had inspanningstonometrie van de maag een sensitiviteit van 78% en een specificiteit van 92% voor de diagnose van chronische gastrointestinale ischemie. De conclusie van deze validatietest is dat inspanningstonometrie van de maag een accurate diagnostische test is om gastrointestinale ischemie aan te tonen, zowel chronisch splanchnicus syndroom als NOMI. Wanneer inspanningstonometrie van de maag wordt betrokken bij "clinical decision making" is het mogelijk om patiënten te selecteren die baat hebben bij vasculaire of medicamenteuze behandeling, wat bleek tijdens de follow-up perioden van 4 jaar. Inspanningstonometrie van de maag moet worden overwogen voor de work-up bij patiënten met verdenking op chronische gastrointestinale ischemie.

In **hoofdstuk 7**, worden verschillende manieren van diagnostische aanpak bij verdenking op chronische maagdarmischemie vergeleken: 1) angiografie, alleen bij patiënten met klassieke angina abdominalis, 2) screening met duplex echografie en angiografie alleen als duplex echo afwijkend of niet betrouwbaar, 3) screening met inspanningstonometrie van de maag en angiografie als tonometrie niet normaal, 4) zowel duplex echografie en inspanningstonometrie van de maag als screeningtests, angiografie als een of beide screening tests niet normaal.

Bij 28 van 84 patiënten met verdenking op chronische maagdarmischemie en die allen zowel angiografie, duplex echografie en inspanningstonometrie van de maag ondergingen werd de diagnose chronische maagdarmischemie in consensus gesteld door een expert panel.
Wanneer de diagnose alleen op klinische criteria gesteld zou zijn, zou deze bij 16 patiënten (57%) zijn gemist. Screening door duplex echografie of maagtonometrie alleen zou leiden tot een gemiste diagnose bij 4 respectievelijk 6 patiënten. Bij screening met zowel maagtonometrie als duplex echografie zou bij geen van de patiënten met symptomatische chronische maagdarmischemie de diagnose zijn gemist terwijl 21% van de angiografieën niet nodig zou zijn geweest. Uit de resultaten van dit onderzoek kan worden geconcludeerd dat één enkele screeningtest voor het uitsluiten van de diagnose chronische symptomatische maagdarmischemie onvoldoende is. Een hoge klinische verdenking en dan angiografie doen als diagnostische test, heden ten dage nog algemeen gebruik, zou tot de diagnose hebben geleid bij minder dan 50% van alle patiënten met chronische ischemie. Duplex echografie heeft als beperking dat het onderzoek vrij vaak onvolledig te beoordelen is (15% in deze studie komt overeen met data in de literatuur). Toch, hoewel bij screening met duplex echografie alleen 14% van de patiënten met chronische ischemie gemist zouden zijn, zou slechts één patiënt (4%) met chronisch splanchnicus syndroom zijn gemist. Dit bevestigt opnieuw het vermogen van duplex echografie om stenoses aan te tonen. Tonometrie heeft het unieke vermogen om daadwerkelijk ischemie aan te tonen, maar is niet geschikt als enige screeningtest met een percentage gemiste diagnoses van 21%. Tonometrie kan gebruikt worden om onderscheid te maken tussen symptomatisch maagdarmvaatlijden en asymptomatische stenose en ook voor het aantonen van niet-occlusieve mesenteriaal ischemie (NOMI). Het combineren van duplex echografie als beste screeningtest voor stenoses en inspanningstonometrie van de maag als test om daadwerkelijk ischemie aan te tonen, leidt tot een hoge accuratesse bij het diagnostiseren van chronische maagdarmischemie. Momenteel is gecombineerde screening met duplex echografie en inspanningstonometrie van de maag de beste diagnostische aanpak bij verdenking op chronisch maagdarmvaatlijden.

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Curriculum Vitae

Johannes Adrianus Otte werd op 3 april 1959 geboren te Haarlem. In 1977 behaalde hij het diploma Voorbereidend Wetenschappelijk Onderwijs (gymnasium B) aan het Jacob Roelantscollege te Boxtel. Hij studeerde Wiskunde en Informatica aan de Rijksuniversiteit van Utrecht voordat hij werd ingeloot voor de studie Geneeskunde. In 1987 behaalde hij het artsexamen aan de Rijksuniversiteit van Utrecht. Aansluitend was hij assistent-geneeskundige niet-in-opleiding gedurende een viertal jaren: aanvankelijk in het St. Ignatiusziekenhuis te Breda tot 1990 en vervolgens in het Havenziekenhuis te Rotterdam. In het Havenziekenhuis begon hij in januari 1993 met de opleiding tot internist (opleiders prof.dr. P.C. Stuiver en dr. A.G.C. Bauer). In januari 1995 werd de opleiding voortgezet in het Zuiderziekenhuis te Rotterdam (opleider dr. A. Berghout) om in juli 1995 naar het oosten des lands te trekken. In het Medisch Spectrum Twente te Enschede volgde hij het resterende deel van zijn opleiding (opleiders dr. H. Jordans en prof.dr. D.J. Richel). In het laatste jaar van zijn opleiding werd een aanvang gemaakt met het onderzoek dat heeft geleid tot dit proefschrift. Na zijn opleiding tot internist was hij gedurende drie jaren werkzaam als onderzoeker (en chef de clinique) bij de afdeling gastroenterologie van het Medisch Spectrum Twente. Het onderzoek heeft onder andere geleid tot de volgende onderscheidingen: Gold Medal Award (category "Endoscopy/New Techniques") World Congress of Gastroenterology 1998, Vienna en Eerste Posterprijs Nederlandse Internistendagen 1999, Veldhoven.

In januari 1998 vond zijn registratie als internist plaats. Vanaf januari 2001 is hij werkzaam als internist met als aandachtsgebieden gastroenterologie en hepatologie in het Ziekenhuis Zeeuws-Vlaanderen te Terneuzen.

Hij deelt zijn leven met Ellie Oostveen en samen zijn zij de gelukkige ouders van een geweldige en prachtige dochter Marleen.

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