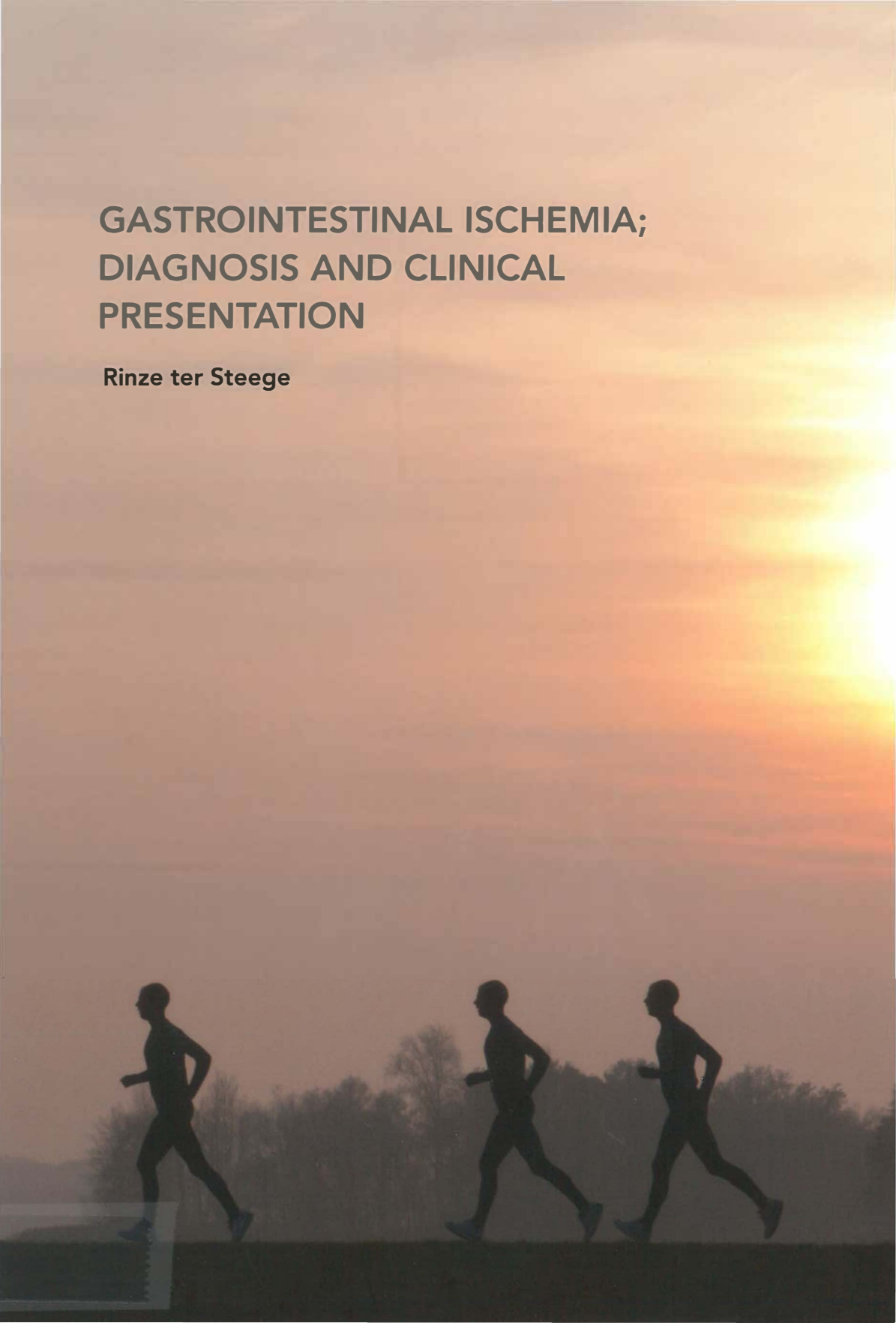
GASTROINTESTINAL ISCHEMIA; DIAGNOSIS AND CLINICAL PRESENTATION

Rinze ter Steege



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Stellingen

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Gastrointestinal ischemia; diagnosis and clinical presentation

door Rinze ter Steege

1) Continue CO_2 meting in de tractus digestivus is technisch uitvoerbaar maar de dient nog te worden geperfectioneerd alvorens dit gebruikt kan worden in de klinische praktijk. *(dit proefschrift)*

2) 11% van de recreatieve hardlopers heeft hinderlijke maagdarmklachten waarbij een jonge leeftijd en vrouwelijk geslacht risicofactoren zijn voor het ontwikkelen van klachten. *(dit proefschrift)*

3) Het maagdarmkanaal dient gewend te worden aan voedselinname tijdens lichamelijke inspanning; op deze wijze kan de kans op maagdarmklachten tijdens hardlopen worden gehalveerd. *(dit proefschrift)*

4) Maagdarmischemie is tijdens maximale inspanning vrijwel altijd aanwezig. Daarom kan de aanwezigheid van maagdarmische niet de enige verklaring zijn van maagdarmklachten tijdens lichamelijke inspanning. *(dit proefschrift)*

5) Atleten met maagdarmklachten tijdens inspanning lijken een meer uitgesproken neiging tot splanchnische vasoconstrictie te hebben in reactie op lichamelijke inspanning. *(dit proefschrift)*

6) De anamnese alleen is niet voldoende betrouwbaar om patiënten zonder maagdarmischemie maar met splanchnische vaatstenosen te onderscheiden van patienten met splanchnische vaatstenosen en maagdarmischemie. *(dit proefschrift)*

7) Het atherosclerotisch risicoprofiel van de patient met stenose van het splanchnisch vaatbed verschilt met die van stenosen in andere vaatbedden; het kenmerkt zich door een uitgesproken dominantie van het vrouwelijk geslacht en de lagere prevalentie van overgewicht. *(dit proefschrift)*

8) Sports do not build character but reveal it. *(Heywood Broun)*

9) The desire to take medicine is perhaps the greatest feature which distinguishes man from animals. *(sr William Ossler)*

10) Het toestaan van Mc-drives in Nederland staat haaks op het overheidsbeleid aangaande voldoende bewegen, gezond eten, bestrijden van files en reductie van de CO_2 uitstoot.

11) Discipline is de wil om te werken, ook al wil je het liever niet.

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Contents

Chapter 1

Introduction and outline of the thesis

The occurrence of gastrointestinal (GI) symptoms during exercise is common with a reported prevalence of up to 70% [1-3]. These complaints may be caused by GI-ischemia due to exercise induced decrease in splanchnic blood flow as has been repeatedly reported [4-8]. We will briefly discuss the normal regulation of systemic and splanchnic blood flow in resting conditions. Changes in the splanchnic blood flow during exercise are outlined in more detail. Thereafter, we will focus on the different diagnostic modalities which have been used to assess the splanchnic blood flow dynamics.

Regulation of splanchnic blood flow

The nervous system and vasoactive substances

The innervation of the gut consists of the extrinsic nervous system and the intrinsic (or enteric) nervous system. The extrinsic nervous system innervates the gut autonomically via two pathways; the craniosacral (or parasympathetic) tract and the thoracolumbar (or sympathetic) tract. The enteric, or intrinsic, nervous system consists of the myenteric and submucosal plexus. The myenteric plexus controls motility, and the submucosal plexus controls secretion and microvascular blood flow. The enteric nervous system is a primary autonomic system, although it can be influenced by the extrinsic nervous system [9]. Sympathetic stimulation is mainly regulated via the vasomotor centre of the medulla oblongata. Its stimulation leads to release of norepinephrine via alpha adrenergic nerves in the vessel wall. This results in vasoconstriction due to contraction of smooth muscle cells in the large arteries and arterioles of the splanchnic vascular bed [10]. The effect of parasympathetic activation on the splanchnic circulation is a down regulation of this basal basal sympathetic splanchnic vasotone. This effect can be mediated by cholecystokinin release and CCK2 receptor stimulation, or via a direct vagal stimulation on the splanchnic vessel wall [11-13]. Other gastrointestinal hormones, like gastrin, secretin, and glucagon, have been shown to increase gastrointestinal blood flow was well [12]. The balance between the activity of sympathetic and parasympathetic nervous system determines the distribution of blood flow between the different splanchnic organs.

Digestive state

The digestive process results in an increased oxygen demand of stomach and gut. In response to ingestion of a meal, cardiac output is increased. Splanchnic vascular resistance is reduced due to process of capillary recruitment where existing but closed vessels open [10]. After a high caloric meal, Superior Mesenteric Artery (SMA) blood flow may increase by 135% and a peak increase in Celiac Artery (CA) blood flow of 70% has been measured [14]. After ingestion of a meal, blood flow is shifted to the mucosal layers of the GI-tract. Oxygen demand in the mucosa is probably the common pathway in the complex process of redistribution of Splanchnic Blood Flow (SBF) to several parts of the GI-tract during the digestive process [10]. For example, oral feeding results in CA dilation first whereas direct placement of food in duodenum

resulted in vasoconstriction in CA and vasodilatation in SMA [15]. Several factors may influence the postprandial changes of the SBF.

1) *Nervous system effects and reflexes:* The caloric value and meal composition results in predominance of the parasympathetic nervous system, which causes increased splanchnic blood flow [16]. The sympathetic nervous system is activated in response of tasting of food. This results in increased blood pressure, cardiac output, heart rate and results in a shortlived increase in splanchnic resistance. At the same time, the taste of food stimulates vagal efferent fibers resulting in increase in blood flow, especially in the celiac artery [14]. The effect of food tasting on the splanchnic blood flow was nicely demonstrated by Gatt et al. They showed that an oral meal resulted in a larger increase in SBF than if a liquid meal was given through a nasogastric tube. Unfortunately, no attempts were made to give isocaloric meals [17].

2) *Direct effect of absorbed nutrients:* Meal composition may affect the macrovascular and microvascular splanchnic blood flow as well [16,18]. Superior mesenteric artery blood flow was increased more by fat and protein in comparison to carbohydrates [18]. In particular micelles (fatty-acids containing particles) have a vasodilatory effect on microvascular flow in the intestinal mucosa, probably because of the fact that micelles absorption is an active process and therefore highly dependent of an adequate oxygen delivery.

Carbon dioxide and hydrogen solution have a regulating influence on the intestinal microvessels. Decrease in pH and increase pCO_2 can reduce small artery sensitivity to the vasoconstricting substance norepinephrine whereas oxygen depletion causes an increase of vasodilating nitric oxide (NO) in the mucosa [10,19]. Mucosal stimulation by mechanic factors and chemical substances like bile acid, micelles and glucose stimulate vasodilatory reflexes via the submucosal plexus, which is part of the intrinsic nervous system. By this reflex, blood flow can be regulated within a distance of 1-2mm from the stimulated area [9].

3) *Locally vasoactive mediators:* Histamine, bradykinin and prostaglandin and gastrin are released by the small intestine in response to meal and can have a locally vasodilatory effect on microvascular splanchnic blood flow [10]. Probably the most important metabolic vasoactive mediators is nitric oxid (NO). Endothelial NO is the most important nitric oxide in regulating blood flow and it plays a crucial role in regulation of the splanchnic blood flow [20]. Endothelial NO (eNO) promotes vasodilatation at mesenteric arteriolar level, which is a key determinant in flow regulation of total and regional intestinal blood flow. eNO is produced in response to different stimuli, like hormonal, paracrine and mechanical factors and has a major role in the development of ischemia-reperfusion injury [10,16,20,21].

4) *Gastrointestinal hormones and peptides:* Ingestion of a meal stimulates the secretion of gastrointestinal hormones and peptides, like secretin, insulin, gastrin. It has been shown that these substances could increase blood flow in the superior mesenteric artery when given in high concentration [12]. However, in physiological concentrations gastrointestinal hormones and peptides seem not to be of quantitative importance in regulating macrovascular postprandial mesenteric blood flow. Should they have an effect on splanchnic blood flow, it is more likely to be on microvascular level [10].

Effects of physical exercise on splanchnic blood flow

During physical exercise, cardiac output rises from 6 l/min up to 20 l/min [22]. The rise in cardiac output and increased heart rate are coordinated by two responses. The first is the *exercise pressor reflex* which consists of 1) Activation of the sympathetic nervous system (SNS) by stimulation of mechanoreceptors in active skeletal muscles and by cutaneous thermoreceptors. [23-25], and 2) decrease in vagal activity [26,27]. The second response is a *feed forward mechanism*. Due to this mechanism, changes in cardiac output, respiration and a splanchnic blood flow emerge before the actual physical exercise has begun. The proposed mechanism to cause this feed forward response involves hypothalamic regulation of changes in blood flow and respiration during exercise. This was demonstrated in an experiment by Eldridge et al. who stimulated the hypothalamus of normal and decorticated cats and observed a marked increase in cardiac output and respiration in both actual (normal cats) and fictive (in decorticated) locomotion. [28].

Splanchnic blood flow

In rest, the splanchnic organs receive 20% of the cardiac output but extract only 10-20% of the available oxygen [29]. During exercise, splanchnic vascular resistance is increased which results redistribution of blood from the splanchnic organs to the working muscle and skin [30]. The net result is a decrease in splanchnic blood flow, despite the massive increase in cardiac output [29,31,32]. During high intensity exercise, splanchnic blood flow may be reduced to 20-30% of baseline values. The splanchnic vasoconstriction during exercise seems to be more outspoken in CA than in the SMA [32,33]. During short-lived exercise at low exercise intensity, SMA blood flow and splanchnic vascular resistance remains largely unchanged [33]. Several studies suggest a direct relation between exercise intensity and decrease in SBF. A negative correlation between exercise intensity and splanchnic blood flow has been shown in dynamic (e.g. cycling) and isometric (knee extension) exercise. In a study with knee extensions for 20 minutes a reduction in visceral blood flow (renal and splanchnic) of 44% was shown [29,34]. Reduced splanchnic blood flow may lead to ischemia because blood flow levels below 40-50% of baseline may induce ischemia, despite a high oxygen extraction rate [29,35-37].

Postprandial splanchnic blood flow can be sufficiently maintained during short bouts of exercise [33,38,39]. During postprandial exercise, cardiac output may increase sufficiently to meet the extra blood flow needed for both exercise and digestion. Interestingly, patients with heart failure have a significantly impaired postprandial exercise tolerance and a blunted response of superior mesenteric artery blood flow in response to a meal due to a limited ability to sufficiently raise the cardiac output [40]. Limited data is available on the role of circulating humoral mediators on splanchnic blood flow during physical exercise in humans. The role of endothelin-1, vasopressin and angiotensin on the regulation of splanchnic blood flow in physical exercise at

normal conditions seems to be limited [41-46].
In conclusion, the splanchnic vascular bed may act as a blood giver to the systemic circulation during exercise. During maximum intensity exercise, splanchnic blood flow may decrease up to 70%. The redistribution of splanchnic blood flow during exercise is the result of increased sympathetic nervous system activity mainly. Fluid/food ingestion might partly counteract the decrease in splanchnic blood flow during exercise.

Assessment of splanchnic blood flow and gastrointestinal ischemia

Changes in splanchnic blood flow can be detected directly by measuring blood flow or indirectly by detection of GI-ischemia or ischemic mucosal damage. We will discuss the potential of several methods for splanchnic blood flow measurement, in particular during physical exercise.

Indocyanin Green Dye elimination

Indocyanin Green Dye (IGD) elimination technique is based on the principle that IGD is exclusively extracted by the liver. Therefore, the plasma clearance rate of IGD reflects the changes in hepatic blood flow during continuous IGD infusion. This is a fair estimation of total splanchnic blood flow. IGD elimination technique involves catheterisation of the portal vein, which is a potentially hazardous procedure. Furthermore, movements during exercise may cause alterations in the position of the liver vein catheter, resulting in variation of measurements [29,32,47]. Nowadays, measurement of splanchnic blood flow by this modality is almost completely replaced by non-invasive measurement methods.

Duplex ultrasound

Duplex Ultrasound (DU) is a non-invasive method for the measurement of arterial and venous splanchnic blood flow. Usually, the first 2-3 cm of the origin of superior mesenteric artery or celiac artery is used to measure blood flow. The blood flow rate is calculated from the product of cross sectional area of a vessel and the mean blood flow velocity. The cross sectional area is often deducted from the diameter of the vessel to enable quick measurement instead of tracing the vessel circumference on the monitor [17,48,49]. The rate of splanchnic vasoconstriction is often expressed in terms of splanchnic vascular resistance which is the ratio of splanchnic blood pressure and the blood flow through the splanchnic vessel [31-33]. A good correlation between DU and IGD-elimination technique has been shown [32].
Several technical challenges with DU measurement during exercise may occur. First, during strenuous exercise the cross sectional area of the splanchnic vessels decreases

which makes fast and reliable measurement of blood flow during exercise more difficult. Second, in most studies, DU measurements are usually performed during in a supine position, whereas most exercise tests are performed in upright position. This means that the subject has to change positions for the measurement and real-time assessment of the splanchnic blood flow is not feasible. Finally, superimposed intestinal gas, respiratory movements (despite the use of breath-hold techniques) and aorta movement may prevent measurement of the vessel, especially in the CA with its retrogastric position.

Celiac artery blood flow reflects the largest part of the arterial flow to the splanchnic organs, but its short main trunk often hinders quick and precise measurements, especially during exercise [32,50]. The superior mesenteric artery allows the simplest and most accurate measurements compared to CA and portal vein measurement. However, Peters et al. showed that the even reproducibility of duplex ultrasound for measurement of the SMA in exercising volunteers was poor with an intra-individual variability of up to 30% [50].

Theoretically, the portal vein is the best vessel to estimate the total splanchnic blood flow as it receives blood from both the superior mesenteric artery and celiac artery. Flow measurement in the portal vein can be technically challenging because the diameter and flow pattern of the portal vein varies with respiration [51]. Rehrer et al performed DU of the portal vein in 8 healthy volunteers during high intensity exercise. They concluded that this was technically feasible. Moreover, the results were qualitatively comparable to other measurement techniques [49].

Magnetic Resonance Imaging (MRI) of splanchnic vessels

Phase-contrast MRI has been established as a non-invasive technique for characterization of blood flow in large vessels. It is a relatively new technique to measure physiological changes in splanchnic blood flow as well. Changes in the phase shifts of the flowing protons are used to create an image. The phase shift is proportional to the flowing protons' velocity, and this permits quantitative assessment of flow velocities and other flow parameters [52]. It has been shown that MRI-angiography enables imaging and measurement of CA, SMA and portal vein blood flow, even without contrast enhancement [53-55]. Tsukuda et al. performed a study in 29 volunteers to measure alterations in pre- and postprandial portal venous flow. The technique used for this study required that the subject could hold their breath for 30 seconds [56]. This makes this technique less usable for splanchnic blood flow measurement during exercise. Yzet and colleagues used phase contrast MRI which avoids the need for breath holding. However, contrast-enhanced MR-angiography takes an acquisition time of 1.5-2 minutes per vessel and a long total acquisition time [54,55]. To our knowledge, MR-angiography has not yet been used to measure exercise-induced changes in splanchnic blood flow. Recently, a study has been performed to assess changes in aortic and pulmonary artery blood flow during exercise using special designed cycle ergometer [57]. Possibly these technical improvements may also be used to measure changes in splanchnic blood flow during exercise using MR-angiography.

Tonometry

Tonometry has been successfully used for over 15 years in the diagnostic work-up for chronic gastrointestinal ischemia [58,59]. The principle of air tonometry is based on the presence of hypercapnia in the lumen of the GI-tract during ischemia. This increased pCO_2 stems from 1) buffering of protons produced during anaerobic glycolysis and 2) diminished CO_2 clearance by reduced blood flow [59]. Luminal CO_2 can be measured by air tonometry using a balloon-tipped catheter, placed in the stomach or jejunum. The balloon catheter is connected to a capnograph which measures pCO_2 every ten minutes. Intraluminal CO_2 diffuses into the balloon and after a 10 minute dwell time, the air is aspirated and measured ex-vivo with an infrared sensor. It has been shown that an increased luminal-blood pCO_2 gradient indicates gastrointestinal ischemia) and data by Larson show that tonometry may accurately detect a >50% decrease in SBF [35,58]. Tonometry can be used very well to detect ischemia during physical exercise. In healthy volunteers, it has been shown that during short-lived maximum intensity exercise, GI-ischemia could be demonstrated in 60% of subjects. We have successfully used exercise tonometry in the diagnostic work-up for athletes with exercise induced GI-symptoms. We have shown that gastrointestinal ischemia is highly prevalent among subjects with exercise-induced complaints, and that the presence of complaints could be related to a relatively high splanchnic vasoconstrictive response [60].

Visible light spectroscopy

Recently, visible light spectroscopy was introduced. This measurement technique allows direct measurement of mucosal tissue oxygen saturation during upper endoscopy [61]. In clinical studies, its accuracy in diagnosing ischemia was comparable to air tonometry [62]. Unfortunately, this technique provides a single measurement only and lacks the dynamic changes in pCO_2 as can be obtained by air tonometry. Moreover, the need of upper endoscopy to measure the oxygen saturation makes it intrinsically unfit for the use during physical exercise.

Serological markers

Small bowel intestinal ischemia may result in leakage of intracellular components from ischemically damaged cells into the circulation, such as intestinal fatty acid binding protein (I-FABP). Furthermore, due to decreased gut-barrier function, bacterial products, including lipopolysaccharides (LPS), may leak into the systemic bloodstream, a process referred to as bacterial translocation [63]. The potential value of several serological markers to detect early mucosal ischemic damage, such as I-FABP, D-lactate, and LPS, have been investigated [64,65]. I-FABP seems to have the most potential and may be used as an early serological marker to diagnose ischemia of the gastrointestinal tract [66]. It has been shown that I-FABP increased significantly after 30 minutes of iatrogenic ischemia of the jejunum but may decrease within 1 hour after reperfusion. I-FABP levels even increased during short periods of postprandial ischemia as measured with tonometry [67]. Van Noord et al could not detect increase in I-FABP after meals in GI ischemia patients and questioned its value [68]. These authors confirmed previous findings of an increased baseline iFABP in GI- ischemia patients. [67].

Although, serological markers for intestinal ischemia are promising for early detection of GI-ischemia, their potential has not been evaluated for detection of GI-ischemia during physical exercise.

Endoscopy

Endoscopic features of GI-ischemia in stomach and small bowel may be erosions, ulcerations and rarely gastroparesis but endoscopy may be completely normal as well. Histological features of gastrointestinal ischemia are capillary congestion, extravasation, haemorrhage and denudation of villi. Recently it was shown that histology of stomach and duodenum is of little aid in the diagnosis of chronic upper gastrointestinal ischemia [69]. Few studies report on the findings of upper endoscopy in athletes with gastrointestinal complaints. Gaudin et al performed upper endoscopy before and after running in seven subjects, of whom six suffered from abdominal cramps and diarrhoea during running. After running, all subjects had histological features of ischemia [70]. Choi et al. performed gastroscopy in 16 long distance runners of which five had anemia. 11 of the 16 runners had mucosal erosions [71]. In contrast to gastric and small bowel ischemia, endoscopy is very important for the diagnosis of colonic ischemia. The endoscopic appearance consists of superficial ulceration, edema and patchy areas of bleached or cyanotic mucosa [72]. Using colonoscopy, proximal, distal, or pancolitis due to ischemia have been demonstrated in athletes after exercise sometimes, which rarely may even result in massive rectal bleeding [73-76].

Aims and outline of the thesis

This thesis deals with three different aspects of gastrointestinal (GI) ischemia.
The first part of the thesis focuses on **the role of GI-ischemia in the pathophysiology of exercise induced gastrointestinal symptoms.** Abdominal complaints, like belching, cramps, urge to defecate and diarrhea are symptoms frequently encountered by athletes, both during exercise as well in the recovery phase. These symptoms may be mild but may even lead to hospitalization. The role of GI-ischemia as underlying mechanism for these exercise-induced complaints will be highlighted and explored.
In **chapter 2** the pathophysiology and the management of the most prevalent exercise-induced gastrointestinal symptoms is described. The various underlying mechanisms, including motility, secretion and absorption will be discussed. The hypothesis that GI-ischemia may be one of the crucial factors in the development of symptoms will be discussed in detail.
In **chapter 3** the results of an internet based epidemiological study among participants of the 2006 Enschede Marathon are presented. The 'Enschede Marathon' is a popular running event with distances ranging from 5 to 42 kilometers with over 7000 participants. The study was designed to assess the prevalence of the most common GI-symptoms and relevant risk factor for development of complaints during and the first 24 hours after the race using an internet based questionnaire.
In **chapter 4 and 5,** we report our experience with patients specifically referred to the Medical Spectrum Twente for evaluation of exercise-induced gastrointestinal symptoms.
In **chapter 4**, we describe the diagnostic work-up and management of three patients with exercise-induced GI-ischemia. We show that the spectrum of symptoms may have a wide variation and management of this patient category is highly individualized.
In **chapter 5,** we describe our experience with prolonged exercise tonometry in the evaluation of exercise induced GI-complaints. Prolonged exercise tonometry is a 30 minutes, incremental exercise test aimed to assess 1) GI-ischemia during submaximal exercise, 2) the occurrence and severity of GI-ischemia during maximum intensity exercise and 3) to assess the relation between GI-ischemia and the development of GI-symptoms during exercise tonometry. In this case series we aimed to establish whether prolonged exercise tonometry was of additional value in the evaluation and management of this patient group.

The second part of this thesis focuses on **the methods of CO2 measurement in the gastrointestinal tract.** In the Netherlands, The Medical Spectrum Twente is a referral hospital for patients suspected of gastrointestinal ischemia. In Enschede, both exercise tonometry and 24 hours tonometry are used as functional test to detect GI-ischemia. Tonometry has been successfully used for many years to detect gastrointestinal ischemia. It is based on the principle that mucosal GI-ischemia is associated with a rise in luminal pCO_2 due to buffering of protons produced during anaerobic glycolysis and decreased CO_2 clearance due to the reduced splanchnic blood flow.

In **chapter 6**, we evaluated measurement characteristics of the current tonometry device (Tonocap®) during an in vitro study. The Tonocap® allows CO_2 measurement with a ten minutes interval. This long measurement interval is a major drawback during the ten minutes exercise test and the effect of changes in intraluminal pCO_2 during on the measurement outcome during this measurement interval is currently not known. In this study we aimed to learn how changes in amplitude, length and timing of a CO_2 peak would affect the measurement characteristics of the Tonocap®.
In **Chapter 7**, we compared a new CO_2 sensor with the Tonocap®. In 2005, a hydrogel-based PCO_2 sensor was developed by the Mesa+ group of the Universiteit Twente (S Herber, project leader prof P Bergveld and prof A van de Berg). This sensor was constructed for future use in the diagnostic work-up for GI-ischemia. Herber has shown previously that continuous CO_2 measurement was feasible in a laboratory environment. He also made recommendations how to improve the stability and accuracy of the sensor. The sensor prototype was mounted to a catheter and thoroughly tested in vitro and during exercise tonometry in three healthy volunteers.

In the last part of the thesis, **the clinical presentation and atherosclerotic risk profile of patients with chronic gastrointestinal ischemia** was studied.
In **chapter 8,** we conducted a study to evaluate if medical history could be used to distinguish ischemic from non-ischemic patients. The current diagnostic work-up consists of an extensive anamnesis by both a gastroenterologist and vascular surgeon, imaging of the splanchnic vessels and functional tests to actually detect GI-ischemia. This is labour-intensive, invasive and expensive. Currently, 40% of the referred patients are ultimately diagnosed with chronic GI-ischemia (chronic splanchnic syndrome or CSS). It will become increasingly necessary to increase the yield of our diagnostic work-up by making a better selection of patients who should undergo the diagnostic work-up (high-risk patients) and which patients should not (low-risk patients). The aim of this study was to assess risk factors for CSS in the medical history of patients with splanchnic artery stenosis and whether these risk factors can be used to identify patients with high and low risk of CSS.
In **chapter 9,** the distribution of cardiovascular risk factors in patients with CSS due to atherosclerosis of the splanchnic vessels was studied. In the scarce literature, the atherosclerotic risk profile of patients with gastrointestinal ischemia seems to differ from other atherosclerotic vascular disorders with a reported female preponderance. We prospectively analysed atherosclerotic risk factors in consecutive patients with gastrointestinal ischemia and compared this profile to atherosclerosis in other vascular beds.

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Chapter

The pathophysiology and management of gastrointestinal symptoms during physical exercise and the role of splanchnic blood flow

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Abstract

Background:

The prevalence of exercise induced gastrointestinal (GI) symptoms has been reported up to 70%. The pathophysiology is largely unknown.

Aim:

To review the physiological and pathophysiological changes of the GI-tract during physical exercise and the management of the most common gastrointestinal symptoms.

Methods:

Search of the literature published in English and Dutch using the Pubmed database to review the literature that focused on the relation between splanchnic blood flow (SBF), development of ischemia, post-ischemic endotoxinemia and motility

Results:

During physical exercise, the increased activity of the sympathetic nervous system (SNS) redistributes blood flow from the splanchnic organs to the working muscles. With prolonged duration and/or intensity the SBF may be decreased by 80% or more. The reduction in SBF during exercise can be counteracted by ingestion of food/fluid. Most studies point in the direction of increased SNS-activity as central driving force for reduction in SBF. A severely reduced SBF may frequently cause GI ischemia. GI-ischemia combined with reduced vagal activity probably triggers changes in GI-motility and GI absorption derangements. GI-symptoms during physical exercise may be prevented by lowering the exercise intensity, preventing dehydration and avoid the ingestion of hypertonic fluids.

Conclusions:

Literature on the pathophysiology of exercise induced GI-symptoms is scarce. Increased sympathetic nervous system activity and decreased splanchnic blood flow during physical exercise seems to be the key factor in the pathogenesis of exercise induced GI-symptoms and this should be the target for symptom reduction.

Introduction

Physical activity has both positive and negative effects on general health and the gastrointestinal (GI) tract. A positive effect on reduced incidence of colorectal carcinoma and complicated diverticulitis has been reported [1,2]. On the down side, strenuous exercise may cause GI-symptoms in up to 70% and may even be the reason to stop with sport participation [3,4]. The purpose of this paper is to review the physiological and pathophysiological changes of the GI-tract during exercise, which are outlined in table 1.

We will specifically focus on the role of splanchnic blood flow reduction in the pathogenesis of exercise-induced GI-symptoms. Furthermore we give advices for the management of the most common gastrointestinal symptoms.

Table 1. Physiological and pathophysiological changes of the gastrointestinal tract during physical exercise

	Physiological changes during physical exercise	Pathophysiological changes during physical exercise
Splanchnic blood flow (SBF)	- Decrease in SBF up to 80% of baseline. * Aggravated by younger age, exercise intensity, and exercise duration, dehydration, high environmental temperature * Counteracted by ingestion of food/fluid	GI-ischemia if >50% decrease in SBF: 1) Mucosal damage; nutrient malabsorption, GI- bleeding, impaired gut-barrier function and increased GI-permeability 2) Dysmotility? 3) Reperfusion damage: mucosal damage, bacterial translocation
GI-motility, primary or secondary to GI-ischemia	1) Decreased oesophageal peristaltic activity and lower oesophageal sphincter tone 2) Disruption of antroduodenal motility 3) Small bowel and colon: no consistent effect.	- Decreased oesophageal clearance & delayed gastric emptying leading to belching, reflux, nausea and vomiting. - Diarrhea?
GI-secretion and absorption	- GI-secretion probably unaffected. - Water absorption unimpaired, - Limited carbohydrate absorption	- Osmotic diarrhea during carbohydrate overload or hypertonic fluids.

Physiology of splanchnic blood flow during exercise

In rest, the splanchnic organs receive 20% of the cardiac output but only consume 10-20% of the available oxygen [5]. To a certain extent, blood may be safely redistributed from the splanchnic organs to the working muscles and skin [6]. The splanchnic vascular bed may therefore act as a blood giver to the circulation during exercise.

Sympathetic nervous system (SNS) activity is massively increased in response to exercise [6]. This causes increased splanchnic vascular resistance which may decrease splanchnic blood flow (SBF), despite the massive rise in cardiac output associated with physical exercise [5,7,8]. In fact, SBF can decrease by 80% during maximum intensity exercise [5,9].

The importance of the SNS activity was demonstrated in a study in healthy subjects and subjects with spinal cord injury at two levels (high or low). The effects of exercise with an arm-crank test at 50% of maximum oxygen uptake (further referred to as $\%VO_2$ max) on the portal vein flow, and femoral artery were measured. In normal subjects and low level spinal cord lesions a 30% reduction in portal vein flow was observed, but in high spinal cord injury (sympathetic denervation) the portal vein flow was unchanged. The opposite effect was observed in the femoral artery blood flow; an increase in blood flow was only seen with sympathetic control [10]. A similar effect was seen in patients with sympathetic failure, diagnosed as pure autonomic failure and multiple system atrophy, where the superior mesenteric artery (SMA) blood flow was unchanged as well [11].

The effect of exercise on the GI blood flow is dependent on various factors including exercise duration, environmental temperature, age, prandial state and trained status.

The effect of exercise duration on SBF was studied by Rehrer et al in which volunteers exercised at 70% of VO_2 max for 60 minutes. A gradual reduction in portal vein flow from 20% after 10 minutes to 80% after one hour was observed (figure 1) [9]. A 30 min exercise test aimed at submaximal levels of approximately 70% of VO_2 max was associated with 43% and 56% reduction of splanchnic blood flow measured with SMA flow and indocyanin green, respectively [12,13].

The reduction in SBF during exercise is more pronounced in high temperatures [14-16]. Kenney et al. compared the effects of exercise at 60% VO_2 max in 22°C and 36°C in young and older individuals. Exercising in 36°C resulted in an additional 17% decrease in SBF compared to 22°C at the same relative exercise intensity. This decrease in SBF was accompanied by an increase in plasma norepinephrin levels in both old and young subjects, but young individuals had higher norepinephrin (NE) levels compared to older people during the same relative exercise intensity. This was associated with a more pronounced decrease in SBF at the same relative exercise intensity, suggesting that the splanchnic bed of young and elderly are still equal sensitive to NE [14,15].

The influence of trained status and exercise intensity on the decrease in SBF is complex. In trained subjects the exercise-induced decrease in SBF is lower compared to untrained individuals at the same absolute exercise intensity [14]. However, when focus-

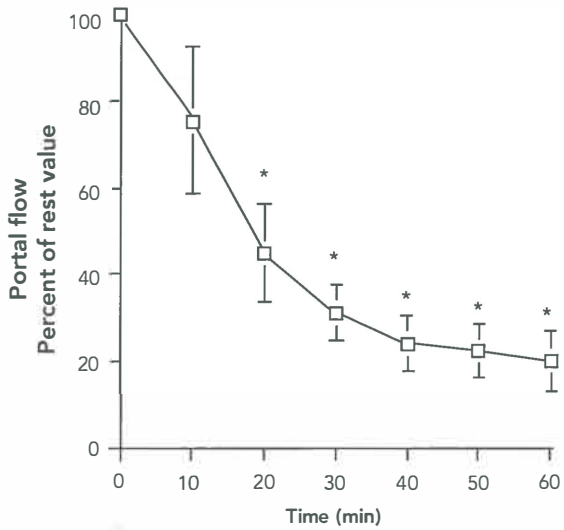

Figure 1. Portal vein flow at rest and during 60 min of cycling exercise at 70% VO_2 max in 8 healthy volunteers.
Data expressed as percentage resting value. * Significant compared to resting value.
Figure used with permission from Rehrer et al [9].

ing on relative exercise intensity (defined as the percentage of an individual's maximal oxygen uptake) no differences in response of SBF to exercise between trained and untrained individuals were found [17].

The modulating effect of a meal on decrease of SBF with exercise was nicely demonstrated in a study by Qamar et al [13]. In healthy volunteers the changes in SMA blood flow were assessed using duplex ultrasound in fasting state and a) after a 30 minutes exercise test, b) after a test meal (390 kcal) and c) the exercise test after ingestion of the test meal. The exercise test reduced the SMA blood flow by 43% whereas SMA blood flow was increased by 60% after ingestion of the test meal. When this exercise test was combined with the meal, the SMA blood flow was actually increased by 40%. This strongly suggests the effects of exercise-induced splanchnic blood flow reduction can be counteracted by ingestion of food/fluid. These findings have been confirmed by Eriksen et al [18].

Limited data are available if other regulating factors are important in exercise induced changes of SBF. Endothelin-1, a natural peptide exhibits potent vasoconstrictor activity. The potential effect of Endothelin-1 as splanchnic vasoconstrictor was shown by Ahlborg et al. who demonstrated that infusion of Endothelin-1 during an exercise test exaggerated the exercise induced decrease in SBF [19]. In a study in well-trained and untrained volunteers with 30 minutes exercise at 60% VO_2 max, post-exercise Endothelin-1 levels were elevated in the untrained healthy volunteers but were decreased in trained athletes [20]. Because many studies showed that the decrease in SBF is

related to relative exercise level, irrespective of trained status, it is therefore less likely that endothelin-1 plays a crucial role as regulator of post-exercise SBF decrease.
It has been shown that vasopressin levels increase significantly during exercise, an effect that was further enhanced during dehydration. Because infusion of vasopressin resulted in reduced splanchnic blood flow in septic and cardiac surgery patients, a causal relation seems plausible [21-23]. Still, whether the increased levels of vasopressin during exercise actually caused reduction of the splanchnic blood flow is currently unknown [24]. The effect of angiotensin on SBF during exercise seems to be very limited [25].
Although neuroendocrine hormones (like gastrin, motilin and Vasoactive Intestinal Peptide) have been shown to reduce SBF in animal models, the levels to accomplish these effects were higher than the levels observed in humans during exercise [24, 25].
It seems unlikely that these hormones play an important role in exercise-induced hypoperfusion of the GI-tract, although the number of reported studies and subjects are very small.
In summary, from the available studies can be appreciated that the decrease in SBF during exercise is closely related to the exercise intensity and this is regulated by SNS activity. The exercise induced decrease in SBF can been counteracted by ingestion of food/fluid.

Pathophysiology of changes in splanchnic blood flow during physical exercise

The question is whether the exercise induced decrease in SBF can result in 1) gastrointestinal ischemia and 2) functional disorders of the GI-tract. Furthermore it is unknown if this decrease can be held responsible for the development exercise-induced GI-complaints.

Splanchnic blood flow and GI-ischemia

The relation between relative exercise intensity and SBF is remarkably similar among studies [5,7-9,18,19,25,26]. After 30 minutes of exercise at 60-70% of VO_2max, reduction in SBF between 30-60% can be expected, while longer duration at this level, or higher intensity levels the decrease in SBF was up to 80% (table 2). However, no human or exercise studies have been performed to correlate the decrease in SBF with the development of GI-ischemia. In dogs and pigs, development of GI-ischemia was observed when SBF fell below a critical minimum of about 40-50% of normal SBF [27-29].
The frequent occurrence of exercise-induced GI-ischemia has been confirmed in several human studies. Nielsen et al showed that rowing at maximal levels for 30 minutes caused severe gastric ischemia in all six athletes [30]. We have shown that 30 minutes cycling in healthy volunteers, aimed at maximal level during the last 5-10 minutes caused gastric ischemia in 6 of 10 healthy volunteers [31]. Van Wijck et al also observed that GI-ischemia was present in all subjects who cycled for 60 minutes at 70% $V0_2$max [32]. In the

Table 2. Fasting splanchnic blood flow in response to exercise

Author (yr of publi-cation)	Method/ Vessel	Subjects	Exercise intensity (%VO_2 max), exercise mode	Duration	Outcome*	Remarks
Exercise <10 minutes						
Endo (2008)[125]	DU/SMA	8 women	40Watt cycling	4 min.	unchanged	
Exercise 10-30 minutes						
Rowell (1964) [5]	IGD/ PV	10 men	26-97 %, Treadmill	unknown	-47 to -87%	Heterogenous exercise intensity
Qamar (1987)[13]	DU/ SMA	8 men, 8 women	Intensity n.a., Treadmill uphill	15 min.	-43%	Measured immediately after exercise
Perko # (1998)[8]	DU/ CA and SMA	10 sex unknown	75% Cycling	15 min.	CA: -50% SMA: -32%	1 measurement failure in CA
Perko # (1998)[8]	IGD/ PV	8 sex unknown	75% Cycling	15 min.	-43%	
Bergeron (2001)[25]	IGD/ PV	8 men	70%, Cycling	30 min.	-45%	
Bergeron (2001)[25]	IGD/ PV	8 men	50%, Cycling	40 min.	0 %	
Peters (2001)[26]	DU/ SMA	12 men	70%, Cycling	60 min.	-50%	Poor individual reproducibility
Rehrer (2001)[9]	DU/ PV	8 men	70%, Cycling	60 min.	-80%	1 measurement failure, 3 measurements reaching 'no flow'
Exercise > 60 minutes						
Ahlborg (1995)[19]	IGD/ PV	6 men	40%, Cycling	120 min.	-52%	

* Compared to resting, fasting state. #Iidentical exercise protocol,
DU; Duplex-Ultrasound, IGD; Indocyanine Green Dye elimination technique, CA; Celiac Artery, SMA; Superior Mesenteric Artery, PV; Portal Vein, %VO_2max; percentage of maximal oxygen uptake,

latter study, Intestinal Fatty Acid Binding Protein (iFABP) was also measured as early serum marker for GI-ischemia [33]. They observed a rise in iFABP preceded by development of GI ischemia as measured with gastric tonometry (figure 2) [32].
Strenuous exercise was associated with increased endotoxinemia [34-36]. Endotoxemia in humans, defined as lipo-polysaccharides (LPS) concentrations >5 pg/ml, has been reported following prolonged exercise (e.g. ultra-distance marathon), but also after

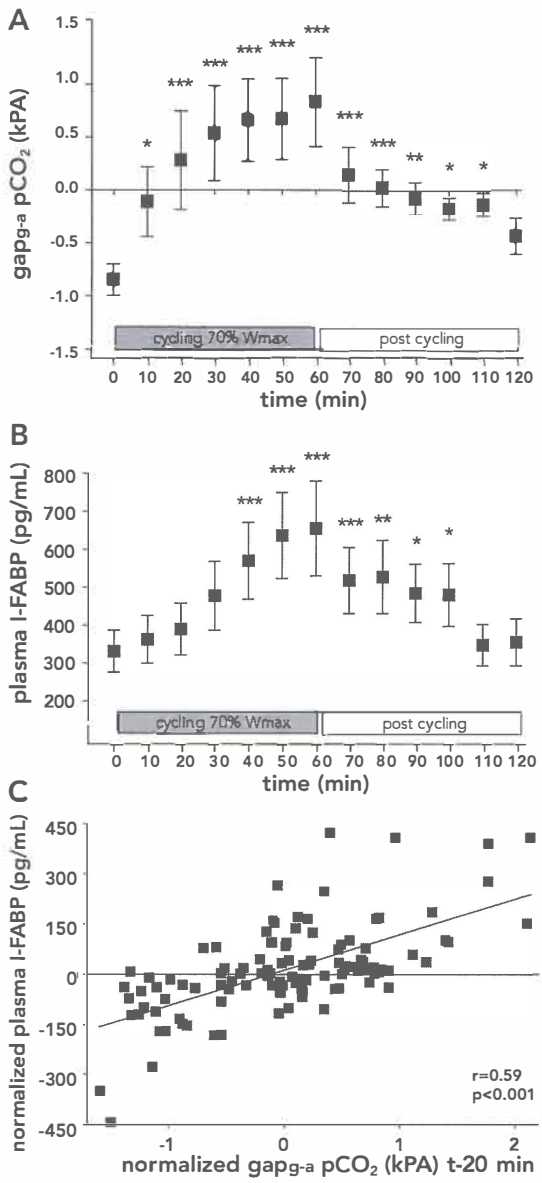

Figure 2. Physical exercise (60 min at 70% VO_2max) results in splanchnic hypoperfusion and epithelial damage.
A) Gastric tonometry shows decreased splanchnic perfusion during and after exercise (GAPg-a >0.8kPa reflects GI-ischemia)
B) Plasma I-FAB levels rise in response to exercise reflecting intestinal epithelial damage.
C) Significant correlation between I-FABP levels and splanchnic hypoperfusion (GAPg-a PCO2). Data are mean ± SEM. *p<0.01, ** p<0.001, ***p<0.0001. Used with permission from van Wijck *et al.* [32]

a short bout of exhaustional exercise [34,36-38]. Anti-LPS immunoglobulins are higher than normal in well-trained athletes, suggesting repeated leakage of small amounts of LPS during exercise [34]. These LPS data suggest increased intestinal permeability due to ischemia, but to our knowledge have focused on this causal relationship.

Splanchnic blood flow and GI-motility

It has been shown in several shock models using rats, dogs and mice that change in SBF influences the motility of the GI-tract. Changes in motility patterns could potentially affect the mucosal blood flow via mechanic compression of the microcirculation, although the latter effect seemed to be mild [39-44]. Most models include either severe shock (>50% decrease in systemic blood pressure) and/or prolonged duration of ischemia of up to 5 hours and their relevance to the pathophysiology of exercise induced symptoms in humans is highly unclear [39-43,45]. Few human studies have focused on the relation between SBF/GI-ischemia and motility disorders. Changes in motility may be present in both affected and non-affected surrounding bowel [41,43,45]. Eventually, motility normalized after reperfusion of an ischemic bowel although structural neuronal damage has been reported [46]. The available evidence from both animal and human studies supports the connection between decreased SBF and development of both dysmotility and GI-ischemia, with post-ischemic endotoxinemia. No studies are available that actually show a convincing relation between the development of GI-ischemia and real time development of GI-complaints. Otte et al showed that a 10 minutes exercise test to maximal intensity in healthy volunteers resulted in gastrointestinal ischemia, but did not result in the development of GI-symptoms [31]. We confirmed these observations in healthy, well-trained asymptomatic subjects [47]. Thus, although decreased GI blood flow is present in most people exercising at submaximal levels for 30 minutes or more, or at maximal levels for shorter times, the relation with development of GI-complaints has not been established so far.

Motility in the GI-tract during physical exercise

The effects of exercise on the esophagus and stomach have been studied in runners mainly. Decrements in esophageal peristaltic activity, decrease in lower esophageal sphincter tone and increased transient lower esophageal sphincter relaxation were observed. All factors may contribute to gastro-oesophageal reflux during exercise [48-51]. Exercise intensity, dehydration and hyperthermia may cause delayed gastric emptying by increased duodenal and decreased antral smooth muscle activity [50,52-55]. Furthermore it has been shown that gastric emptying rate may depend on the volume and energy content of the drink ingested during exercise as well [56]. Soffer et al showed that exercise may disrupt the normal antroduodenal motility. They showed an exercise intensity dependent interruption of the phase-3-like activity of the motor migrating

complex in 2/16 subjects exercising at 80% VO_2 max and 5 of 8 at 90% VO_2 max [54]. Finally, increased intra-abdominal pressure, e.g. during weightlifting, may expulse acidic fluids from the stomach into the esophagus [48].

The effects of exercise on the small bowel seem limited. Most studies demonstrated unchanged small bowel transit times with exercise, although one study found a moderate increase in small bowel transit time after mild exercise (15 minutes physical activity at 30% VO_2 max) in healthy, recreationally active, men and women [57]. In contrast, small bowel transit remained unchanged after 3 hours of exercise at 60% VO_2 max in 8 well trained, asymptomatic cyclists and in female long-distance runners with (n=6) and without (n=5) diarrhea [54]. No difference in small bowel transit time was found in rest and during 1 hour exercise in neither symptomatic nor asymptomatic runners [58]. Unfortunately, the lactulosis breath test, used to measure the oral cecal transit time, might unpredictably influence the measurement outcome as both the hypertonic meal and lactulose may accelerate oral cecal transit time [59]. In the earlier mentioned study by Rao no difference in colonic transit time between rest and exercise or symptomatic and asymptomatic subjects was found [58].

Only one study reports on the immediate effects of colon motility during exercise. During short bouts of incremental exercise a decrease in colonic motility was observed in 11 untrained subjects using a solid state measurement probe. Colonic motility was quickly restored or increased immediate post-exercise [60]. Two studies reported on colonic transit time with conflicting results. A reduced colonic transit time, and easier defecation, was found in sedentary, constipated patients after a twelve weeks period of daily 30 minutes brisk walking [61]. In a study in non-constipated healthy but sedentary volunteers a nine week training schedule no changes in colonic transit time and defecation was found, despite a marked increase in physical fitness [62].

Gastrointestinal absorption and gut permeability during physical exercise

The influence of exercise on gastrointestinal absorption depends on exercise intensity, nutritional status and the absorbed substances. Water absorption seems to be largely unaffected during normal physical exercise [63,64]. The maximum absorptive capacity of the bowel for carbohydrate is estimated at 70-90g/hour and seems to be maintained during strenuous exercise [65].

Several studies reported a reduced mucosal integrity of the bowel wall after exercise [66,67]. Lambert et al showed that the gastric and small bowel permeability damage was aggravated by the use of Non-Steroidal Anti-Inflammatory Drugs (NSAID) [68].

It was shown that water restriction during prolonged exercise worsened this intestinal permeability [69]. The results from the earlier mentioned study by van Wijck et al strongly suggests that this increased intestinal permeability is related to mucosal damage secondary to GI-ischemia [32].

Clinical presentation and management of exercise-induced gastrointestinal symptoms

Epidemiology of exercise induced GI-symptoms

A summary of epidemiological studies reporting the incidence of exercise induced GI-symptoms is presented in table 3. The overall incidence in athletes varies from 45-81% depending on the definitions of 'symptomatic'. The incidence and type of GI symptoms depend on many factors like type of sport, exercise intensity, (pre) competition food and fluid intake, age and sex [4,70,71]. The prevalence of GI symptoms in the resting state may be an important factor as well [4]. GI-symptoms in rest may be the result of exercise induced GI-symptoms, but may be pre-existent and (severely) increase during exercise [72,73]. Upper GI-symptoms include regurgitation, chest pain, heartburn, belching, nausea and vomiting. Lower GI symptoms include abdominal pain, flatulence, urge to defecate, diarrhea and rectal bleeding [4,70,74,75]. Lower GI-symptoms tend to occur more often in runners than upper GI-symptoms and in women [4]. In a large cohort of participants of the 2006 Enschede Marathon, the overall incidence of GI-symptoms was 19% in female compared to 8% in male runners [71].

Table 3. The incidence of exercise induced GI-symptoms

Author	Type sport	Level of sport	Number of athletes addressed (response %)	Overall incidence of GI-symptoms[$]	Incidence of upper GI-symptoms[*]	Incidence of lower GI-symptoms[#]
Keeffe[126] 1984	Running	Marathon	1700 (41%)	n.a	23%	66%
Worobetz[93] 1985	Multi-sport	Ultra-distance	119 (59%)	81%	58%	61%
Riddoch[127] 1988	Running	marathon	1750 (27%)	83%	36%	88%
Peters[4] 1999	Running	Marathon	177 (93%)	n.a.	36%	71%
	Cycling	Elite	191 (84%)	n.a.	67%	64%
	Triathlon	Elite	201 (71%)	n.a	53%	62
Peters[128] 1999	Long distance walking	40-50k/ day	480 (32%)	21%	8%	11%
Ter Steege [71] 2008	Running	Recreative	2076 (60%)	45%	28%	17%

[$]= all reported symptoms [*]= nausea, heartburn, vomiting [#]= cramps, urge to defecate, diarrhea
n.a.: not available.

Upper gastrointestinal symptoms

Upper GI symptoms are reported up to 40% in runners but may rise to 70% in cyclists [4]. The incidence of reflux/heartburn is usually the highest of the upper GI-symptoms and is estimated between 15-20% in runners [4]. Furthermore, reflux symptoms may be affected by prandial state, and type of sport [48,49]. Soffer et al studied reflux in 8 trained cyclists exercising at 60, 70 and 90% VO_2 max. Reflux episodes increased significantly at 90% VO_2 max but did not result in more severe GI-symptoms [76].

The exercise induced increase in intra-gastric pressure and disturbance in LES-function may cause GI-symptoms like heartburn, chest pain, belching and dyspepsia [48,50]. The intragastric pressure may rise due to contraction of abdominal musculature and by ingestion of fluid and food whereas carbohydrate containing beverage may induce transient lower esophageal sphincter relaxation. Aerophagia that often accompanies tachypnea during exercise may aggravate upper GI-symptoms [74,77]. Furthermore, hyperosmolar carbohydrate sport drinks delayed gastric emptying time in some well-designed studies in athletes [78-81]. Carrio et al studied the gastric emptying time during exercise and basal state in marathon runners. Athletes emptied their stomach significantly faster than controls in both rest and during exercise suggesting an effect of training [82]. Indeed, athletes not accustomed to fluid/food ingestion, had a twofold the risk in developing GI-symptoms compared to athletes who were accustomed to fluid/food ingestion during exercise [71]. As delayed gastric emptying during exercise may result in nausea and vomiting and side stitch.

Side stitch or Exercise Induced Transient Abdominal Pain (ETAP)

Side-ache, stitch and sub costal pain (commonly referred to as exercise induced transient abdominal pain or ETAP) are common during exercise [73]. Substantial research on ETAP has been performed by Morton and colleagues.

ETAP was reported in 18% of the competitors in a recreational run whereas 4% reported severe abdominal pain [71]. This observed incidence is comparable to a study in 848 runners in whom 27% experienced ETAP during a 14 km [83]. Morton et al also showed that the incidence of ETAP is influenced by the type of sport. In 965 sporting participants, ETAP was most prevalent in activities that involved repetitive torso movements, bouncing or longitudinal rotation [84]. The incidence of ETAP was higher in young subjects and after recent ingestion of fluid and food [78,85,86].

The aetiology of ETAP remains to be fully elucidated. Proposed pathophysiological mechanisms include diaphragmatic ischemia and stretch on visceral ligaments.[87-89]. It has recently been shown that electromyographic activity of the abdominal muscle wall was not elevated during exercise in athletes suffering from ETAP compared to asymptomatic subjects. This suggests that ETAP is not the result of muscle cramping either [90]. Morton et al propose that ETAP is a form of peritonitis which may develop in two ways. First, extensive diaphragmatic excursion during exercise would result in decreased serous peritoneal fluid. Second, peritoneal fluid could be further reduced by ingestion of hypertonic fluid. This might result in irritation of the peritoneum due to friction of the visceral and parietal folds. Distension of the stomach and gut by food ingestion or torso movements could exacerbate the friction of the peritoneum [91].

Lower GI-symptoms

Lower GI symptoms include abdominal pain, flatulence, cramping and urge to defecate, diarrhea and rectal bleeding. The exact incidence varies upon the type of sport and exercise intensity. Our research group found an incidence of 30% of severe lower GI-symptoms during a recreational run. However, this may increase up to 50% in cyclists and 70% in competitive long-distance runners [73,92,93].

The pathogenesis of lower GI-symptoms is probably multifactorial. For example, diarrhea during exercise may be provoked by incomplete bowel movement before starting exercise and mental stress. Furthermore, it has been suggested that increased GI-permeability, due to GI-ischemia or NSAIDs, might also induce diarrhea [94,95]. Still little evidence is available.The potential influence of GI-ischemia was nicely illustrated by a case report by Desmond. An elite runner suffered from abdominal pain and diarrhea after exercise. Compression of the celiac artery by the median arcuate ligament was diagnosed. After surgical division of the constricting ligament, complete symptom relief was achieved [96].

GI-bleeding and anemia

Occult gastrointestinal blood loss and iron deficiency in athletes has a reported prevalence of 20% [97-102]. Microscopic and macroscopic gastrointestinal blood loss may be caused by e.g. haemorrhoids, colonic polyps and possibly by ischemic mucosal damage [92,103,104]. Other potential pathogenic mechanisms of runner's iron deficiency and anaemia are expansion of plasma volume, traumatic haemolysis, haematuria and iron loss in sweat [105-107]. Acceleration/deceleration forces during running might result in hemorrhagic gastritis, hematuria and mechanic trauma to the colon, 'cecal slap syndrome', causing gastrointestinal blood loss [70,92,104,108].

The use of NSAIDs has been associated with a higher prevalence of occult blood loss and a higher amount of GI blood loss [109]. NSAIDs may result in additional ischemic damage, either by blocking the synthesis of the vasodilating substance prostaglandin of by inducing mitochondrial damage [110].

Massive and life threatening GI-blood loss due to ischemic colitis has been described in athletes [111]. Proximal, distal, or pancolitis due to ischemia, and even small bowel infarction after exercise have been reported, sometimes requiring major surgery [112-114]. It is conceivable that massive rectal bleeding and severe colonic ischemia may only occur in extreme conditions like high exercise intensity in hot environment and severe dehydration in which massive splanchnic vasoconstriction is present. Probably, several warning signs (like cramping pain, diarrhea and nausea) must be ignored before transmural ischemia develops [113].

GI-symptoms after physical exercise

Fever, shivering, nausea, vomiting and diarrhea after physical exercise have been reported up to 40% in endurance athletes [4]. In recreational runners, 11% reported GI-symptoms after a race, most often nausea (5%), shivering (5%) and diarrhea (5%). It has been shown that athletes with symptoms during exercise have a fourfold risk on development of symptoms after physical exercise [71]. The literature available on GI-

symptoms after physical exercise is very scarce. In animal studies, it has been shown that severe, reversible GI-ischemia could result in long-lasting dysmotility but this has not been studied in humans [44]. Furthermore, due to ischemia/reperfusion damage, endotoxemia and increased serum lipopolysasccharide levels have been shown. In one study by Ashton et al, 8 of 10 volunteers had chills and nausea after exercise until exhaustion, and all had endotoxemia [35]. Heat stroke and collapse during exertion may be caused by endotoxemia as well [115].

Management of GI-symptoms during physical exercise

General principles

There is very little evidence for treatment or prevention of exercise-induced complaints. Most are based on experience, or deduced from pathophysiological considerations, and are level V mostly. If an athlete presents with GI-symptoms during exercise, it should be ascertained that the symptoms are a sign of an underlying GI-disease. The widely given recommendations to reduce exercise induced GI-symptoms include reduction of exercise intensity, prevention of dehydration, and the use of isotonic fluids act at the level of SBF maintenance. Similarly, lowering the exercise intensity and prevention of dehydration may also help to maintain the splanchnic blood flow above the critical ischemical level [16]. Avoidance of NSAIDs or COX- inhibitors use makes sense as discussed previously. It should be noted that up to 25% of the athletes uses these drugs on a regular basis [116,117].

It is important for athletes to train to ingest food and fluids before exercise as it was shown to reduce the incidence of GI-symptoms besides its importance in maintaining the energy stores [71,82,118]. We showed that use of fluid and food in unaccustomed athletes resulted in a 2-fold risk on the development GI-symptoms [71].

Reflux and regurgitation

The avoidance of heavy meals before exercise and hypertonic fluids during exercise reduces problems of gastric fullness and regurgitation [78,119].

Reflux can be treated by H2-blockers and proton pump inhibitors, with proven effect on frequency and duration of reflux time and pH in esophagus during exercise [120,121]. From a physiological point of view, a proton pump inhibitor may be of additional help for reduction of ischemia as it lowers the basal metabolism of the stomach thereby reducing the oxygen demand [122]. However, this has not been proved in humans.

Lower GI symptoms

The literature on the prevention of lower GI-symptoms is even rarer than for upper GI symptoms. In literature, common sense' advices are often provided such as to defecate prior to exercise to prevent the urge for defecation during exercise [73]. Furthermore,

athletes should drink small amounts of hypotonic carbohydrate fluids to prevent the risk for osmotic diarrhea [65].

Side-stitch

For prevention of side-stitch or exercise-induced transient abdominal pain (ETAP), several empirically based advices have been reported: 1) wait 2-3 hours before exercising after a meal or drink, 2) take small amounts of drink during exercise and refrain from hypertonic fluids in order to reduce tugging of the gut on ligaments connecting the gut to the diaphragm. Only one clinical trial to prevent ETAP has been performed by Plunket et al. In a group of 10 athletes known with ETAP, tightening the abdominal muscles and breathing at a higher functional residual capacity alleviated side stitch within seconds [85].

Post-exercise complaints

Very little evidence is available how to prevent systemic and gastrointestinal symptoms after exercise. Ashton et al showed in a small study that a high dose of the antioxidant ascorbic acid could abolish the exercise induced increase in plasma LPS. Furthermore, the chills and nausea, experienced by the subjects after exercise, could be prevented in eight of the ten studied subjects by the ingestion of ascorbic acid [35].

Persistent gastrointestinal complaints

In athletes with persistent symptoms despite these advices, duplex ultrasound of the celiac artery and superior mesenteric artery might be performed to rule out obstructive splanchnic vessel disease. If present, a functional test like tonometry or visual light spectroscopy may be used to rule out the presence of GI-ischemia in daily life, which may be a reason for treatment of the stenosis [123,124].
Although the presented studies strongly suggest a pivotal role for reduced splanchnic blood flow and ischemia in the pathophysiology of exercise-induced GI complaints, many links are still missing. The relation between changes in blood flow or development of ischemia, and motility patterns are lacking. Similarly, more studies are needed to link the presence of GI-complaints on markers for ischemia, or motility disorders. These studies could guide therapeutic or prevention studies focused on reduction of exercise-induced GI-complaints.

In conclusion, from the limited available literature it emerges that exercise leads to activation of the sympathetic nervous system, which triggers a reduction in splanchnic blood flow. With prolonged or maximal exercise levels this reduced blood flow often results in GI-ischemia. Although it seems likely that exercise-induced dysmotility and complaints are at least partially caused by ischemia, no firm evidence is available. The literature on management of exercise induced GI-symptoms is even more marginal, and advice is mainly based on authority based evidence. Interestingly, many of these advices that were empirically based are aimed at maintaining the splanchnic blood flow, again suggesting a crucial role for GI-ischemia in exercise-induced GI complaints.

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Chapter 3

The prevalence of gastrointestinal complaints in runners competing in a long-distance run: an internet-based observational study in 1281 subjects

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Abstract

Objective:

To assess the prevalence, risk factors and timing of gastrointestinal (GI) complaints in a large group of runners competing in a long-distance run. GI symptoms indicating GI ischemia were of specific interest.

Methods:

A questionnaire was sent by e-mail to 2076 athletes who had competed in a recreational run and 1281 (62% response rate) were returned. Reported GI complaints were related to variables such as age, gender, distance, fluid and food ingestion and running experience. For statistical analyses, x^2 tests and logistic regression analyses were used.

Results:

The run was completed by 98% of the runners. Three athletes dropped out because of GI complaints, 45% had at least one GI complaint during running, while 11% of the runners suffered from serious GI complaints during the run, the last mentioned being significantly related to runners who were not familiar with fluid ingestion, those of younger age, female gender and those who did not complete the run. Of the runners, 2.7% had complaints during the first 24 h after the run. This was significantly related to female gender and GI complaints during the run.

Conclusions:

The prevalence of GI complaints during and after running was low compared with that reported in other studies, which is partly due to the definition of "symptomatic" used in our study. The risk factors associated with becoming symptomatic were identical to those in other studies. The relationship between complaints during the run and the type of complaints afterwards suggests a role of GI ischemia in the pathophysiology of running-induced GI symptoms.

Introduction

It is well known that physical exercise has a profound and beneficial effect on the gastrointestinal (GI) tract, but it can also result in GI complaints during normal (resting) daily life [1-4]. These complaints can limit the ability to take part in exercise and can result in physical activities being stopped [5,6]. There is a paucity of current data on the prevalence of exercise-induced GI symptoms. Among elite endurance athletes, the prevalence has risen to 70%, while in the group of recreational athletes, i.e. the vast majority of runners world-wide, Rehrer et al. found a prevalence of between 25 and 50% [4,6].
The pathophysiology of exercise-induced GI symptoms has not yet been fully elucidated. Exercise-induced GI symptoms are often attributed to altered motility, mechanical factors and altered secretion of neuroendocrine hormones [7]. GI ischemia is increasingly acknowledged as a potential cause of exercise-induced GI symptoms [8]. During maximal exercise, splanchnic blood flow may be reduced by up to 80% at the expense of the working muscles and the skin [9]. We have previously shown that exercise-induced GI ischemia can develop in otherwise healthy subjects during strenuous exercise [10]. When GI ischemia becomes symptomatic during exercise, it results in symptoms such as nausea, vomiting, abdominal pain and (bloody) diarrhea [8]. Post-exercise symptoms, such as collapse, shivering, nausea and vomiting may be related to reperfusion damage and endotoxaemia, a late result of GI ischemia [11,12].
The aim of this study was to focus on the prevalence, timing and risk factors of GI complaints in a large group of runners competing in a longdistance run. We were specifically interested in the GI symptoms indicating GI ischemia.

Materials and methods

The "Enschede Marathon" is an official run with distances of 5, 10, 21 and 42 kilometres. Within 48 h after the end of the event, an online questionnaire was sent to all runners for whom e-mail addresses were available. After 2 weeks, a reminder was sent. The questionnaire was designed to assess GI complaints during and after running. The questionnaire was divided into three parts. The first part covered data on age, gender and training status. The second part focused on the running day. The finish time was elicited or, if applicable, the main reason for giving up the run. Subjects were asked to indicate the type of fluid and food, the amount, and whether they were used to fluid or food ingestion during running. The presence of GI symptoms (belching, nausea, vomiting, abdominal cramps, side stitch, urge to defecate, flatulence and diarrhea) and systemic symptoms (shivering) and their influence or impact on the activity were assessed. The third part of the questionnaire covered GI and systemic symptoms (nausea, vomiting, diarrhea, bloody stools and shivering) within 24 h after completion of the run. The severity of the symptoms was categorized as "hardly any complaints", "moderate complaints", "severe complaints" and "very severe complaints".

Statistics

Statistics Data were analysed with SPSS software (version 14.0; SPSS Inc., Chicago, Ill., USA). We analysed the relation between the variables of interest and the prevalence of GI complaints, both during and after the run. For this analysis, GI complaints were defined as absent when "no" or "hardly any" complaints were reported. Complaints were considered as present when "moderate", "severe" or "very severe" complaints were reported.

Differences between subjects with and without GI complaints were tested for men and women combined, using the χ^2 test for categorical variables and analysis of variance for continuous variables. The variables included gender, age, running experience, distance, completion of the run, use of a heart-rate monitor, fluid and food ingestion. Correction for multiple testing was done according to the Bonferroni procedure with Holm's correction. A multivariate logistic regression analysis was carried out to establish the relative importance of factors related to GI complaints during and after the run. Differences with a p-value <0.05 were accepted as statistically significant.

Results

Response

In 2006, a total of 7166 athletes took part in this running event; 3645 (51%) athletes ran 5 km, 1017 (14%) 10 km, 1978 (27%) 21 km and 526 ran (7%) 42 km. The dropout rate was 2%, 1.5%, 1.5% and 6%, respectively. E-mail addresses for 2475 runners were available, but of these, 399 athletes had not given the organization permission to use their e-mail addresses for whatever purpose. Consequently, the questionnaires were sent to 2076 athletes. These were returned by 1281 athletes (response rate 62%). We excluded competitors running 5 km as we received only 27 questionnaires out of this large group of 3645 competitors. The group of responders (1281) was comparable with the total potential group of subjects for whom an e-mail address was available (2475) in terms of age, gender and dropout percentage (data not shown).

Baseline characteristics

The baseline characteristics of the 1254 remaining athletes (study group) are presented in Table 1. The median finishing time for 10, 21 and 42 km was 57 (range: 38-115), 114 (80-215) and 225 (162-310) min, respectively. Twenty-six athletes did not complete their run (dropout percentage 2%). Reasons for dropping out of the race were exhaustion (n=3), GI complaints (n=3), injuries (n=14) or other, unspecified, reasons (n=6). The dropout percentage among marathon runners was significantly higher than that in the 10- and 21 km groups. The marathon runners were significantly older, predominantly males, and were more experienced runners.

Table 1. Baseline characteristics of the study group.

	All runners (n=1254)	10km (n=261)	21km (n=766)	42km (n=227)
Completion of the run (%)	98	99 §	98 *	94%
Sex (%) male/female	70/30	53/47 # §	71/29 *	89/11
Age (%)		# §	*	
< 25 yr	10	16	9	7
25-45 yr	47	55	48	34
>45 yr	43	29	43	59
Running experience (%)				
0-5 yr / >5yr	50 / 50	73 / 27# §	50 / 50*	24 / 76
Use of heart rate monitor (%)	23	13 # §	25*	30
Fluid Ingestion (%)	88	78# §	98	99
Amount of fluid (%)		# §	*	
<500	59	76	75	18
500-1000ml	20	2	20	42
>1000ml	9	0	3	39
Food ingestion (%)	29	4# §	25*	77

= significantly different from 21 km group
§ = significantly different from 42km group
* = significantly different from 42km group

Fluid and food ingestion

Fluids, usually water (79%) or sports drinks (39%), were ingested by 88% of the athletes. Sixty-five percent of the athletes were used to taking fluids during running. Twenty-nine percent ingested some kind of food during running, usually fruit (71%), dextrose tablets (23%) or sports gels (20%). Seventy seven percent were accustomed to food ingestion during training for this run. Marathon runners ingested significantly more fluids and ate food more often than the athletes running 10 or 21 km.

GI complaints during the run

The total prevalence of symptoms during the run was 45.2%. The frequency of the specific complaints in the study group is presented in Figure 1. Eleven percent of the athletes reported having at least one serious GI complaint. Severe side stitch was reported significantly more often in the 10 km group compared with the 42 km group (4.9% versus 1.7%, p=0.01) and was reported significantly more frequently in women than in men (8.2% versus 1.8%, P<0.001). The relation between the

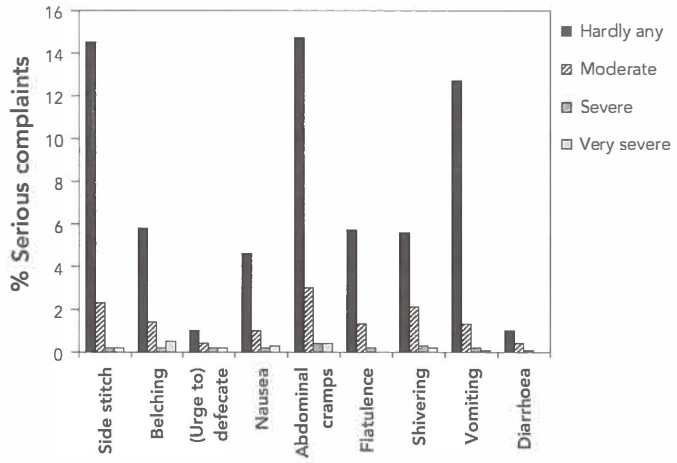

Figure 1. The prevalence of complaints during the run

investigated variables and the occurrence of GI complaints during the run is shown in Table 2. The significant variables in the study group (n=1254) were used in the multivariate analysis. Female gender, younger age and non-completion of the run were independent significant risk factors for having serious GI complaints during the run.

GI complaints after the run

Eleven percent of the athletes suffered from at least one complaint after the run (Figure 2), while 2.7% experienced serious complaints, usually nausea or diarrhea; only 4 athletes reported bloody stools. Two of these athletes had diarrhea and an urge to defecate during the run, followed by bloody diarrhea one day later, strongly suggesting ischemic colitis. Presence of GI complaints during the run resulted in the highest frequency of complaints after the run (OR 3.8, 95% CI 1.8-8.1, $p<0.001$). Female runners had a 3-fold increased risk of having post-exercise complaints compared with men (OR 3.0, 95% CI 1.5-6.3, $p<0.01$). Furthermore, running 42 km compared with 10 km showed a trend towards being a risk factor for GI complaints after the run as well (OR 3.2, 95% CI 0.9-11.8, $p=0.07$).

Fluid and food ingestion and GI complaints

Food or fluid ingestion was not associated with the occurrence of GI complaints during or after the run (Table 2). However, among runners who ingested fluids or food, respectively, 35% and 23%, were unaccustomed to doing so, and did this only during this run. In these subjects GI complaints were more common compared with in those who were used to fluid ingestion (15.5% versus 8.5%, $p<0.01$) and food ingestion (13.6% versus 9.7%, $p<0.01$).

Table 2. The incidence of GI complaints related to different variables during the run.

	All runners (n=1254)	10km (n=261)	21km (n=766)	42km (n=227)
	% Complaints			
Completion of the run				
No / Yes	27%/ 11%*	0%/ 10%	29% / 11%*	39% / 7%#
Sex				
Male / Female	8%/ 19%#	7% / 13%	8%/ 22%#	6% / 31%#
Age				
< 25 yr	16%	22%	13%	25%
25-45 yr	13%	7%	15%	12%
>45 yr	7%	9%	7%	5%
Running experience				
0-5 yr / >5yr	13%/ 9%*	11% / 7%	14% / 9%	11% / 8%
Heart rate monitor?				
No / Yes	12% / 7%*	11% / 6%N	13% / 7%*	10% / 7%
Fluid Ingestion?				
No / Yes	11%/ 11%	10% / 10%N	18% / 11%	0%/ 9%N
Food ingestion?				
No / Yes	11%/ 12%	10% / 22%N	11% / 11%	8% / 9%

* = p<0.005
# = p< 0.001
N = p-value cannot be calculated

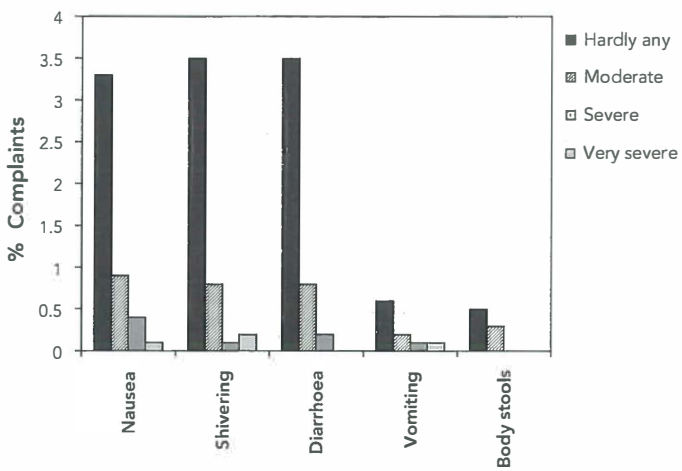

Figure 2. The prevalence of complaints after the run.

Discussion

To the best of our knowledge, this is the largest study on the prevalence of GI complaints during and after running. The main complaints during the run were belching, side stitch and an urge to defecate in almost half of the runners. Serious GI complaints were reported in 11% of runners and were usually seen in women, in those of younger age and in those with less running experience. In 3% of athletes, serious complaints developed the day after the run, mainly severe nausea and (bloody) diarrhea. The latter was strongly related to GI complaints during exercise.

The use of an internet-based questionnaire has several advantages. First, the high response rate of 62% is probably due to the low-threshold, user friendly questionnaire, which took only 5 min to complete. Second, more than 50% of the questionnaires were returned within 4 days after the run. This greatly reduced the recall bias, a serious confounder in retrospective epidemiological studies. Third, analysis was easy and fast because all results could be put directly into the database; the questionnaire guided the responders and thereby prevented incorrect answers. Finally, there was no need to interpret pencil errors or strike-outs. Unfortunately, the response rate for the 5 km run was very low because most of these athletes were last-minute competitors whose e-mail addresses were not known.

Our study group comprised athletes of varying levels, from barely trained recreational runners to very experienced runners, and at three different distances. In this heterogeneous group the total prevalence of GI complaints was 45%, which is in line with the reported prevalence of 50% and 70% in the literature [4,6]. Our study group differed from these studies because Peters et al. and Rehrer et al. only included well-trained athletes performing in long-distance runs [4,6]. Although the incidence of GI complaints was quite high, at 45%, only 11% could be considered as serious complaints. Because many other studies did not differentiate between the severity in levels of complaints, the reported incidences should be interpreted with caution. In many cases even a single occurrence or short duration of a certain GI symptom could render a runner symptomatic, even though it might not bother the athlete at all.

Side stitch was the most commonly reported GI complaint during the run, with a prevalence of 4%. This seems lower than reported by Morton et al., however, who reported on the prevalence of "a side stitch at least once during the last year", with a yearly incidence of 61% [13]. Overall, female gender, younger age and non-completion of the run were independent and significant variables associated with increased prevalence of GI complaints.

The higher prevalence of GI complaints in women is concordant with the findings of previous studies on this subject [4,14]. So far, no clear explanation has been given for this difference. Possibly, there is a similarity with the well-known higher incidence of irritable bowel syndrome in women. Gender, menses and hormones are believed to play a part in the gender-related differences in intestinal motor and sensory pathways and function [15] . Moreover, gastrointestinal ischemia has a strong female predominance (66% female) for reasons that are not fully understood [16].

It is unclear why runners who did not complete the run had a higher incidence

of GI complaints. Surprisingly, a minority reported to have stopped because of GI complaints. It may therefore be that these complaints merely accompanied the state of exhaustion in these athletes. The reduced incidence of complaints associated with a higher age has been reported previously [13,14,17]. This could be explained by lower norepinephrine levels, and consequently less splanchnic vasoconstriction, compared with in younger individuals at the same exercise intensity [18,19]. Alternatively, it could be a result of selection bias, because symptomatic athletes are more likely to quit long-distance running. To our surprise, we found no difference in GI symptoms between the three distances. This fact seemed to be in contradiction to a hypothesis stating that running induced GI symptoms are caused mainly by mechanical factors [7]. If that were the case, the longer distances would have to result in prolonged mechanical damage, and thus increased GI symptoms. In this study no relation was found between food and fluid ingestion and GI complaints during running. This seems to be a surprising finding at first glance because it has been shown repeatedly that insufficient fluid intake can provoke GI complaints. Once this process of exercise-induced dehydration has begun, drinking only worsens the situation [20,21]. Interestingly, our study showed no effect of fluid and food ingestion except in cases where the athletes were not used to following this practice. In other words, in those who never ate or drank during training, the ingestion of fluid and food increased the risk of developing GI complaints. It may be that these individuals started taking drinks too late during the run. An alternative explanation could be that drinking during a run should be part of the athlete's training, as well as running itself. GI complaints developed in the first 24 h after the race in 11% of the athletes. This is a lower incidence than the previously reported rates of 40-60% [4]. The main difference with this study is the classification of complaints, and our main focus on more severe complaints, which interfered with daily activities. In 3% of runners these complaints were severe, and included nausea, vomiting and diarrhea, with impaired recovery from the run. In four athletes (0.3%) bloody diarrhea occurred, probably caused by ischemic colitis, as reported previously [22,23]. These GI complaints during the aftermath of the run were closely related to complaints during exercise (OR 3.8). In our opinion, the most likely explanation is that GI ischemia during the run leads to reperfusion damage afterwards. This phenomenon of "leaky mucosa" and subsequent endotoxaemia has been shown to cause GI complaints and bowel dysfunction [11,24]. In conclusion, during the Enschede Marathon, serious GI complaints occurred in 1 out of 9 runners. Risk factors included female gender, young age, and fluid and food ingestion in individuals not trained in this practice. Severe complaints in the 24 h following the run were reported by 3% of the athletes and were associated with GI complaints during the run.

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Chapter 4

Gastrointestinal ischemia as a cause of exercise induced gastrointestinal complaints; a case series

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Abstract

* Gastrointestinal (GI) symptoms are reported by up to 70% of the endurance athletes. Although exercise leads to decreased gastro-intestinal blood flow, GI-ischemia is rarely reported as a cause. Mucosal ischemia may result in nausea, abdominal cramps and bloody diarrhea. After exercise, reperfusion damage and endotoxemia may cause systemic symptoms as well.

* In three subjects, two women aged 46 and 25 and a man aged 45 with a heterogeneous presentation of exercise induced GI-symptoms, GI-ischemia was demonstrated using gastric exercise tonometry. Air tonometry is mandatory for the diagnosis and follow-up.

*In one subject, an isolated celiac artery stenosis was found, after treatment she was asymptomatic and gastric air tonometry improved. Two other subjects had non-occlusive ischemia associated with high exercise intensity. Reduction of the exercise intensity resulted in disappearance of their complaints.

Introduction

Up to 70% of endurance athletes suffer from gastrointestinal (GI) complaints during and after physical exercise, including nausea, belching, vomiting, abdominal cramps, urge to defecate and diarrhea [1,2]. The severity of GI-complaints may vary from 'mild but disturbing' to 'severe' urging cessation of physical exercise or even hospitalization [3,4]. In literature, exercise induced GI-complaints are attributed to altered GI-motility, mechanical damage to mucosa, altered secretion of neuro-endocrine hormones and GI-ischemia [5,6].

Exercise induced GI-ischemia is caused by redistribution of blood flow from the splanchnic organs to working muscles and skin. Mucosal ischemia causes a luminal rise in pCO_2 and in stomach and jejunum. This can be reliably measured by air tonometry [7]. During tonometry, a balloon tipped catheter is placed nasogastrically and connected to a special designed capnograph (figure 1). Exercise tonometry is a reliable method of measurement in the diagnostic work-up for GI-ischemia [8,9]. GI-ischemia is diagnosed if the gradient between luminal pCO_2 and arterial pCO_2 is >0.8kPa (luminal-arterial gradient) [9]. Furthermore, we use duplex ultrasound to assess the blood flow of the celiac artery and superior mesenteric artery during inspiration and expiration, using validated criteria [10]. If the result of exercise tonometry and/or duplex ultrasound is abnormal, digital subtraction angiography of the abdominal aorta and splanchnic arteries is performed. The results of the diagnostic work up are discussed in a multidisciplinary team consisting of a gastroenterologist, vascular surgeon and radiologist.

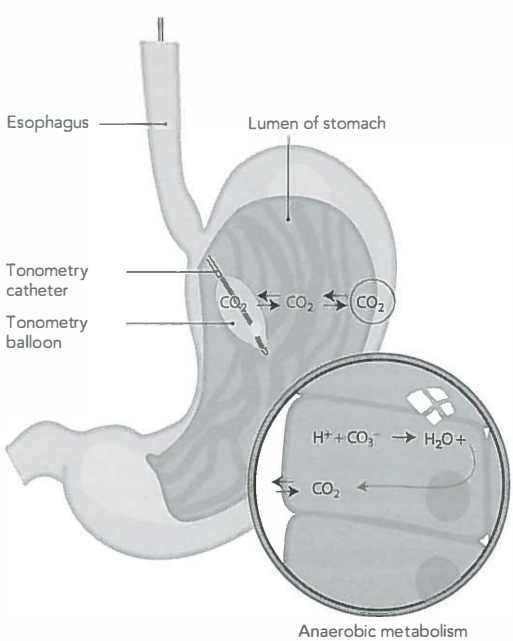

Figure 1. The principle of tonometry: CO_2 is produced in the gastric mucosa by anaerobic metabolism and diffuses from the lumen of the stomach into the tonometry balloon. During anaerobic metabolism, more lactate (acid) is produced which results in more CO_2 after buffering with bicarbonate.

In the last decade, more than 800 patients have undergone this diagnostic work-up for suspected GI-ischemia in our centre. Most referred patients suffered from symptoms attributed to GI-ischemia in daily life. Occasionally, a patient with isolated exercise induced GI-complaints was referred. In this case series, we discuss the clinical presentation, diagnostic work-up and possible treatment of exercise induced GI-ischemia.

Case presentation

Patient A was a 46-years old female recreational runner, referred because of nausea, abdominal pain and involuntary weight loss. For years, she had only had complaints when running. A few months before she was referred to us, she developed abdominal pain which started 10 minutes after a meal. Due to a fear of eating, she lost 5 kilograms in six months. Medical history revealed hypertension, mild gastro-esophageal reflux and a duodenal ulcer. She did not smoke and used an ACE-inhibitor and a thiazide diuretic. On physical examination, an abdominal bruit was observed with increased intensity on expiration. Conventional ultrasound of the abdomen and blood tests were unremarkable.

Because of her complaints of postprandial abdominal pain and weight loss due to her fear of eating, we decided to perform the diagnostic work-up for gastrointestinal ischemia. The results of exercise tonometry showed gastrointestinal ischemia (figure 2). Duplex ultrasound showed a subtotal occlusion of both celiac artery and superior mesenteric artery. Angiography showed an isolated celiac artery stenosis suspected to be caused by the arcuate ligament of the diaphragm. We concluded that this patient

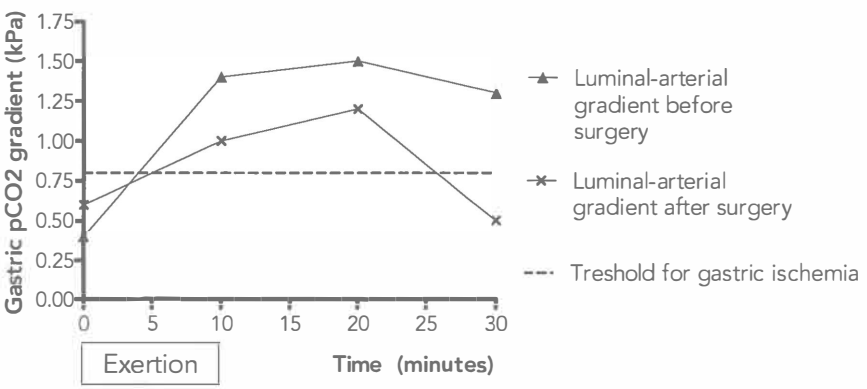

Figure 2. Results of exercise tonometry in patient A, before (▲) and after (x) surgical relieve of the arcuate ligament. If the gastric luminal-arterial gradient rises above the dotted line (threshold for gastric ischemia), exercise tonometry suggest ischemia.

suffered from gastrointestinal ischemia and a laparoscopic release of the arcuate ligament was performed. Now, three years later, the patient is still free of symptoms. Exercise tonometry improved and duplex ultrasound normalized.

Patient B was a 25-year old female professional athlete. She was referred to our centre because of suspected exercise induced GI-ischemia. She suffered from abdominal cramps, flatulence and diarrhea during physical exercise. The severity of complaints depended on the duration and intensity of exertion. After a race, she had complaints of nausea and bloody diarrhea and due to these symptoms she did not reach the top in her sport. In daily life, she was free of symptoms.
We performed the diagnostic work-up for GI-ischemia and we decided to extend the exercise tonometry to 60 minutes submaximal exercise. After 30 minutes, the familiar abdominal cramps reoccurred, accompanied by a rise in gastric pCO_2 and luminal-arterial pCO_2 gradient. After resting for 30 minutes, the pain disappeared and the gradient normalized. Duplex ultrasound showed a maximum 70% stenosis of celiac artery during expiration. We concluded that she suffered from exercise induced GI-ischemia due to a variable celiac artery stenosis and exercise mediated circulatory redistribution. We advised her to A) keep eating and drinking during exercise and B) use a proton pump inhibitor. This advice did not have the desired effect and she decided to adjust her goals.

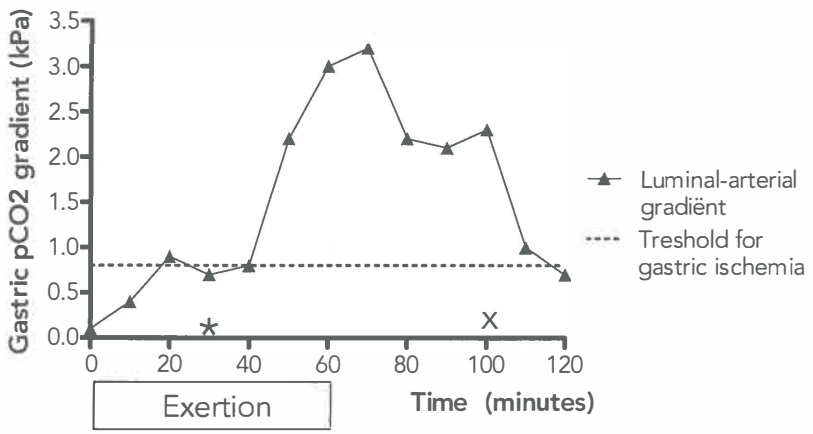

Figure 3. Results of exercise tonometry in patient B, *: Start of abdominal complaints, **x**: Relieve of abdominale complaints. The dotted line is the threshold for gastric ischemia

Patient C was a 40-year old male who was referred to us for second opinion because of periodic attacks of severe nausea, vomiting and abdominal pain. These attacks usually started early in the morning and were accompanied by profuse perspiration, fever, shivers and collapse. The abdominal pain could last as long as a week during which time food and fluid ingestion was difficult. He was repeatedly admitted to the local hospital because of dehydration. His weight loss was 6 kilos in one year. The time between two attacks was approximately six weeks during which he was free of symptoms. In the referring centre, no diagnosis could be made despite extensive diagnostic work-up. Upper endoscopy revealed reflux-esophagitis probably secondary to repeated vomiting.

When the patient was referred to our centre, we asked him to keep a diary to assess the relation between his complaints, eating pattern and daily activities. From this diary, it appeared that every episode was preceded by a high-intensity running training. During running, he was free of symptoms. The result of exercise tonometry was abnormal. Duplex ultrasound of the splanchnic arteries showed a 70% stenosis in the celiac artery in maximal expiration. Our hypothesis was that this patient had gastrointestinal ischemia during running which resulted in symptomatic reperfusion damage and endotoxemia. He was advised to reduce the intensity of his training. Since then, he uses a heart rate monitor during running and he is free of symptoms.

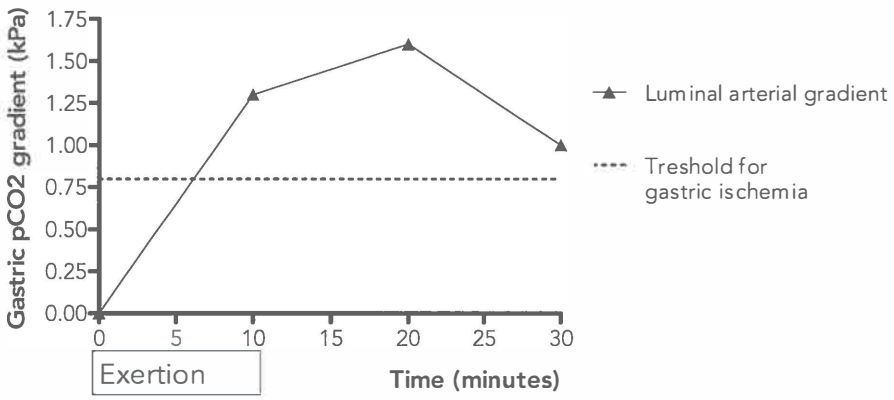

Figure 4. Results of exercise tonometry in patient C. The dotted line is the treshold for gastric ischemia.

Discussion

These three patients illustrate that abdominal complaints during physical exercise may be caused by GI-ischemia. In all patients, it was of clinical importance to diagnose GI-ischemia. In the case of patient A, the exercise induced complaints progressed to complaints in daily life. She underwent surgery and was free of complaints thereafter. With patient B, establishing the diagnosis 'exercise induced GI-ischemia' meant that she had to adjust her goals in order to reach the top in her sport. Patient C had been admitted many times without finding a cause for his complaints. After adjusting the exercise-intensity of his running training, he was free of symptoms.

Pathogenesis of exercise induced GI-ischemia

Physical exertion decreases splanchnic blood flow up to 70%. It is estimated that a 50% reduction of splanchnic blood flow may result in GI-ischemia [11,12]. In our patients, GI-ischemia developed by a combination of a subtle splanchnic artery stenosis and redistribution of blood flow from the splanchnic organs to working muscles and the skin. It has been shown by our group that healthy volunteers do not develop GI-ischemia during sub-maximal exercise whereas ten minutes of maximal exercise may already result in GI-ischemia [13]. GI-ischemia may result in mucosal damage and gastrointestinal dysfunction.

In the recovery phase following ischemia, reperfusion damage may develop. This is then caused by inflow of oxygen rich blood in previously ischemic tissue which results in development of reactive oxygen species. This may further damage the surrounding, non-ischemic tissue. This process may lead to loss of gut barrier function, endotoxemia and a systemic inflammatory response [14,15]. We speculate that this process caused the complaints in patient C.

Diagnostic work-up

Careful medical history taking is of great importance if exercise induced GI-ischemia is suspected. One should focus on the relation between the exercise intensity, length of physical exercise and the start of complaints. The presence of other factors resulting in further decrease in splanchnic blood flow, like heat and dehydration, should be assessed. During physical examination, an abdominal bruit may be heard but the absence does not rule out splanchnic artery stenosis [16]. Duplex ultrasound examination of the splanchnic artery is very helpful, if performed by an experienced examiner. Exercise tonometry is indispensable in diagnosing mucosal ischemia. An increase in luminal-arterial gradient after ten minutes of submaximal exercise is highly suggestive for GI-ischemia [9].

Treatment

The treatment of exercise induced GI-ischemia is aimed at restoring the balance between oxygen demand and supply in the GI-tract. For patient A, surgical release of the arcuate ligament of the diaphragm was the treatment chosen. Our research group has shown that exercise tonometry is helpful in detection of both multi-vessel chronic

GI-ischemia and ischemia due to isolated celiac artery stenosis which may result in patients being successfully treated [17]. It is more difficult to treat patients with (high suspicion on) GI-ischemia when no significant splanchnic artery stenosis has been found, like in patient B and C. In those patients, treatment should be aimed at maintaining the splanchnic blood flow above the critical ischemic level which may be achieved by reduction of exercise intensity. This was highly effective in patient C. Prevention of dehydration is of high importance as dehydration results in decreased effective circulating volume en leads to a further reduction of splanchnic blood flow [18]. It is recommended to use slight hypotonic or isotonic beverages to avoid hyponatriemia [19]. It is possible that carbohydrates may prevent exercise induced GI-ischemia [20]. Finally, it has been shown that proton pump inhibitors may reduce gastric oxygen demand by decreased acid production [21]. This advice was tried by patient B but did not sufficiently reduce her symptoms.

In conclusion, as illustrated by the three cases, gastrointestinal complaints during and after physical exercise may be caused by gastrointestinal ischemia. This diagnosis may be established by careful medical history taking and exercise tonometry. Any advice on treatment should be individualized.

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Chapter

Abdominal symptoms during physical exercise and the role of gastrointestinal ischemia; a study in 12 symptomatic athletes

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Abstract

Background:

Gastrointestinal (GI) symptoms during exercise may be caused by GI ischemia. The authors report our experience with the diagnostic protocol and management of athletes with symptomatic exercise induced GI ischemia. The value of prolonged exercise tonometry in the diagnostic protocol of these patients was evaluated.

Methods:

Patients referred for GI symptoms during physical exercise underwent a standardized diagnostic protocol, including prolonged exercise tonometry. Indicators of GI ischemia, as measured by tonometry, were related to the presence of symptoms during the exercise test (S+ and S− tests) and exercise intensity.

Results:

12 athletes were specifically referred for GI symptoms during exercise (five males and seven females; median age 29 years (range 15–46 years)). Type of sport was cycling (n=6), long-distance running (n=4) and triathlon (n=2). Median duration of symptoms was 32 months (range 7–240 months). Splanchnic artery stenosis was found in one athlete. GI ischemia was found in six athletes during submaximal exercise. All athletes had gastric and jejunal ischemia during maximum intensity exercise. No significant difference was found in gastric and jejunal pCO_2 or gradients between S+ and S− tests during any phase of the exercise protocol. In S+ tests, but not in S− tests, a significant correlation between lactate and gastric gradient was found. In S+ tests, the regression coefficients of gradients were higher than
those in S− tests. Treatment advices aimed at limiting GI ischemia were successful in reducing complaints in the majority of the athletes.

Conclusion:

GI ischemia was present in all athletes during maximum intensity exercise and in 50% during submaximal exercise. Athletes with GI symptoms had higher gastric gradients per mmol/l increase in lactate, suggesting an increased susceptibility for the development of ischemia during exercise. Treatment advices aimed at limiting GI ischemia helped the majority of the referred athletes to reduce their complaints. Our results suggest an important role for GI ischemia in the pathophysiology of their complaints.

Introduction

Up to 70% of the endurance athletes experience gastrointestinal (GI) symptoms during exercise [1]. Frequently reported GI symptoms include nausea, belching, urge to defecate and abdominal cramps. During the recovery phase, symptoms may consist of nausea, vomiting, bloody diarrhea and even collapse.[1-3]. The severity of the symptoms varies from 'mild but disturbing' to 'severe' and may even lead to hospitalization and emergency surgery [4,5].

These exercise-induced GI symptoms are attributed to GI motility disorders, mechanical factors and altered secretion of neuroendocrine hormones. GI ischemia is also increasingly acknowledged as an important factor, although the direct relationship between GI symptoms and GI ischemia during physical exercise has never been examined. During exercise, splanchnic blood flow is redistributed to the working muscles and skin, mainly at the expense of GI perfusion [6]. During high intensity exercise, splanchnic blood fl ow may be reduced up to 70%, and it has been estimated that GI ischemia might be induced from a 50% reduction of splanchnic blood flow [6-9]. The mechanism of exercise-induced GI ischemia is comparable to non-obstructive mesenteric ischemia, a condition where GI ischemia develops in the absence of major splanchnic artery stenosis. Non-obstructive mesenteric ischemia is the end stage of normal adaptive mechanism in which redistribution of blood flow at the expense of the GI tract occurs during conditions of reduced effective circulating volume [10]. Since 1996, patients referred to our hospital for suspected GI ischemia undergo a standardized diagnostic protocol. This includes a thorough history taking, duplex ultrasound scanning of the splanchnic arteries and digital subtraction angiography of the splanchnic arteries on indication. Exercise tonometry, a 10-min exercise test at submaximal exercise intensity, is used as a functional test to assess GI ischemia [9,11]. The principles and technique of tonometry have been described in detail before[12]. During this normal exercise tonometry, GI ischemia is observed only in patients with ischemia cause by vascular stenosis or splanchnic vasospasm [11]. A study in 10 healthy volunteers showed that none of the subjects developed gastric ischemia during submaximal exercise but that almost all had GI ischemia during maximum intensity exercise [9]. In our daily practice, we use an exercise protocol of 30-min incremental exercise (prolonged exercise tonometry) to evaluate the role of GI ischemia in athletes referred to us for analysis of exercise-induced symptoms. This protocol is designed to (1) assess the presence of GI ischemia during submaximal exercise and (2) provoke the GI symptoms during maximum intensity exercise while measuring luminal pCO_2. In this study, we report our experience with the diagnostic protocol and management of athletes suspected of symptomatic exercise-induced GI ischemia. Furthermore, the value of prolonged exercise tonometry was evaluated.

Materials and methods

All patients specifically referred for evaluation of exercise-induced GI complaints between 1999 and 2010 were included in this study.

Prolonged exercise tonometry

Preparation for exercise tonometry using both gastric and jejuna catheters was performed as described in detail before [12]. Exercise was performed on a bicycle ergometer (Lode, Groningen, the Netherlands). For acid suppression, intravenous esomeprazole infusion was used with a bolus of 80 mg and infusion of 8 mg/h. The protocol for prolonged exercise tonometry consisted of three phases.

Phase 1. Normal exercise tonometry: From 0 to 10 min, workload was gradually increased and aimed at reaching submaximal exercise intensity, defined as lactate between 3 and 5.5 mmol/l. Lactate measurement was performed every 2 min using a rapid lactate measurement kit (Accusport, Boehringer, Mannheim, Germany).

Phase 2. Submaximal intensity: From 10 to 20 min, the workload was kept at the submaximal intensity level by adjusting workload based on lactate, which was measured every 3 min.

Phase 3. Maximal intensity: From 20 to 30 min, the workload was further increased in steps of 10% of the submaximal workload every 3 min until exhaustion. Lactate was measured every 3 min.

During the exercise test, the following study parameters were recorded: heart rate, workload (in Watt) and lactate levels. Arterial, gastric and jejunal pCO_2 were measured every 10 min; gastric–arterial pCO_2 gradient (hereafter called as gastric gradient) and jejunal–arterial pCO_2 gradient (hereafter called as jejunal gradient) were also calculated. If an athlete developed symptoms during the exercise test, the test was considered symptomatic (S+). If an athlete did not experience any symptoms, the test was considered asymptomatic (S-).

Definition for gastric and jejunal ischemia

The validated criteria for ischemia during exercise tonometry in phase 1 were (1) serum lactate <8 mmol/l; (2) increased luminal pCO_2 compared with baseline luminal pCO_2; and (3) gastric gradient >0.8 kPa or jejunal gradient >1.4 kPa.12 Ischemia during phase 2 and 3 was defined as (1) increased luminal pCO_2 compared with baseline luminal pCO_2; and (2) gastric gradient >0.8 kPa or jejunal gradient >1.4 kPa.

Imaging of the splanchnic arteries

Transabdominal duplex ultrasound scanning of the celiac artery and superior mesenteric artery was performed using a standardized protocol, after 6 h fasting. Duplex ultrasound probes for 3.5 to 5.0 MHz with steerable linear array or convex sector probes were used. The definition for normal or stenotic artery origins was based on criteria published by Moneta et al [13]. Splanchnic artery stenosis >70% was considered significant. Digital subtraction angiography of the splanchnic arteries was performed as described previously, but only if exercise tonometry was abnormal during phase 1 or major stenosis was suspected on duplex ultrasound [14].

Diagnosis, treatment advice and follow-up

The results of diagnostic protocol were discussed with our multidisciplinary team for GI ischemia, arrived at a consensus on whether the GI symptoms could be ascribed to GI ischemia and a treatment advice was formulated. All athletes were contacted for follow-up. Effect of treatment advice on the severity of GI symptoms and on exercise level and intensity was assessed during an interview over the phone.

Statistics

Data were expressed as mean and SD or median and range when appropriate. Testing for normality was performed using the Shapiro-Wilk test. Differences in study parameters between the different phases of exercise tonometry were tested using a paired t test. Differences between S+ and S. tests were compared using a χ^2 test or Fisher exact test, as appropriate, for nominal variables, or using Student t test or Wilcoxon ranksum test, as appropriate, for continuous data. The relationship between lactate and study parameters was analysed by linear regression analysis. Multiple linear regression analysis was performed to assess the relationship between lactate and study parameters in athletes with and without symptoms during exercise tonometry and interaction term was assessed. A p value <0.05 was considered significant.

Results

Patient characteristics

Between January 1999 and January 2010, 1005 patients were referred for suspected GI ischemia. Twelve (1.1% of all referrals) patients were specifically referred for evaluation of exercise-induced GI symptoms (hereafter called as athletes). An overview of the athletes' characteristics is presented in table 1. Most frequently reported upper GI symptoms were nausea (55%), gastro-esophageal reflux (30%) and vomiting (18%). Abdominal cramp was the most frequently reported lower GI symptom (75%) followed by urge to defecate (25%). Bloody diarrhea after exercise was reported by two athletes (16%). Systemic symptoms after exercise, compatible with reperfusion damage, were reported by three athletes (25%). The median duration of symptoms was 32 months (range 7–240 months). Median time of development of symptoms was after 60 min of starting the exercise (range 10–240 min). In athlete 12, GI complaints started 4 h after physical exercise. Reported provocative factors for development of GI symptoms were increasing exercise intensity (n=12) and ingestion of hypertonic fluids/sport gels (n=3). In athlete 5, the exercise-related symptoms were preceded by gastroenteritis period; in athlete 9, the exercise-related symptoms were by a surgically treated perforated appendicitis. Median age of the 12 athletes was 29 years (range 15–46 years; five females). The type of sport was cycling in six, long distance running in four and triathlon in two athletes. The level of sport was 'recreational' in five, 'competitive' in four and 'professional' in three athletes. Four athletes had previous abdominal surgery (inguinal hernia in athletes 2 and 4; appendicitis in athletes 9 and

Table 1. Patient characteristics, results of exercise tonometry, duplex ultrasound and ultimate diagnosis

Pt	Sex/ age	Sport /level	Main GI-symptom	Anatomical substrate?	GET Phase 1		GET Phase 2		GET Phase 3		Complaints during GET	Diagnosis
					G	J	G	J	G	J		
1	F 40	Running Recreative	Abd. Cramps/ 10min	No stenosis	-	+	+	+	+	+	No	NOMI
2	M 36	Running Recreative	Abd Cramps/ 10min	Unknown*	+	+	+	+	+	+	Yes	NOMI
3	F 19	Cycling Professional	Abd Cramps/ maximum intensity	No stenosis	+	+	-	+	+	+	No	NOMI
4	M 19	Cycling Recreative	Upper abdominal pain/ maximum intensity	70-99% celiac artery stenosis during expiration	-	-	-	+	+	+	Yes	NOMI+Reflux#
5	M 28	Cycling Professional	Abd Cramps/ maximum intensity	No stenosis (after release)	-	-	+	+	+	+	Yes	NOMI + postinfectious irritable bowel syndrome
6	M 21	Cycling Competitive	Abd Cramps/ maximum intensity	No stenosis	-	-	-	-	+	+	Yes	NOMI
7	F 29	Running Recreative	pain right lower quadrant/ 10 min	50-70% celiac artery stenosis	+	-	+	+	+	+-	Yes	NOMI
8	M 15	Cycling Competitive	Pain and flatulence/ maximum intensity exercise	No stenosis	-	+	-	-	+	+	No	NOMI
9	M 28	Triathlon Competitive	Epigastric pain/ 90 minutes	50-70% celiac artery stenosis	-	-	+	+	+	+	Yes	NOMI, adhesions after peritonitis
10	F 50	Running Recreative	Epigastric pain/ 20 minutes	No stenosis	-	-	-	-	+	+	Yes	NOMI
11	F 35	Triathlon Competitive	Cramps+urge to defecate/ 60 min.	50-70% celiac artery stenosis	-						Yes	NOMI
12	M46	Running Recreative	Vomiting/ from 4 hours after exercising	50-70% celiac artery stenosis	+	-					No	Reperfusion damage by NOMI

G=gastric tonometry J=Jejunal tonometry, +: ischemia, -: no ischemia
NOMI= non-obstructive mesenteric ischemia
*No complaints during normal daily life, no angiography performed
Two separate complaints. 1) Pain in rest improving with intravenous proton pump inhibitor. 2) Pain with peak exercise

10). One athlete reported the use of non-steroidal anti-inflammatory drugs. None of the athletes reported the use of doping. In athlete 4, a respiration dependent compression of the celiac artery by the arcuate ligament was found. In all other athletes, no significant splanchnic artery stenosis was present. In athlete 2, duplex ultrasound was not feasible because of excessive intestinal gas. Athlete 2 was free of symptoms except during heavy training and therefore angiography was not performed.

Prolonged exercise tonometry

Two athletes did not perform the exercise protocol as previously described because of the following reasons: only 10 min submaximal exercise, n=1; no buildup to maximum intensity exercise, n=1. Data of 10 athletes were available for analysis. Study parameters during the exercise test are presented in table 2. Heart rate and lactate increased significantly during the exercise test. Frequently, the workload in phase 2 had to be slightly reduced compared with phase 1 to prevent lactate >8 mmol/l in phase 2. Capillary pCO_2 decreased significantly during maximum intensity exercise as a result of hyperventilation (phase 3). During phase 3, gastric pCO_2, gastric–arterial gradient and jejunal–arterial gradient were significantly increased compared with phase 1 and 2. There was no significant difference in jejunal pCO_2 between phase 3 and phases 1 and 2. During phase 1, six athletes had GI ischemia: two had both gastric and jejunal ischemia, two had gastric ischemia and two had jejunal ischemia. During maximum intensity exercise (phase 3), all athletes had gastric and jejunal ischemia. Seven athletes had GI symptoms during the 30-min exercise tonometry, and the test was considered symptomatic (S+). Mean time between start of the exercise test and onset of complaints was 20 min (SD 6.6 min). No significant difference was found in gastric and jejunal pCO_2 or gastric and jejunal gradients between S+ and S− tests during any phase of exercise tonometry (table 3). In S+ tests, significantly higher lactate levels (mean 9.8 mmol/l, SD 1) during phase 3 were found compared with

Table 2. Study parameters of different phases in exercise tonometry. (n=10)

	Rest	Phase 1	Phase 2	Phase 3
Heart rate (beats/min)	62 (7)	152 (14)**	157 (15)**§	177 (16)**$^{\#\#}$
Lactate (mmol/l)	0.9 (0.9)	4.4 (1.6)*	4.7 (1.8)*	9 (1.7)**$^{\#\#}$
Watt		193 (74)	179 (82)§	234 (80)$^{\#}$
$paCO_2$ (kPa)	5.4 (0.4)	5.2 (0.5)	5.1 (0.8)	4.2 (0.4)**$^{\#\#}$
$pgCO_2$ (kPa)	5.4 (0.6)	5.7 (0.6)*	6.0 (0.7)*	6.4 (0.9)*$^{\#}$
g-aCO_2 (kPa)	-0.1 (0.5)	0.5 (0.7)*	0.9 (0.8)*	2.3 (0.9)*$^{\#}$
$pjCO_2$ (kPa)	6.2 (0.5)	6.6 (0.6)*	6.7 (0.7)*	6.8 (0.6)*
j-aCO_2 (kPa)	0.7 (0.6)	1.4 (0.5)**	1.6 (0.5)*	2.7 (0.4)**$^{\#\#}$

g:gastric a: arterial j: jejunal

*p<0.05 for value vs. baseline value, **<0.001 for value vs. baseline value.

§ p<0.05 for value comparing phase 1 and 2

$^{\#}$ p<0.05 for value comparing phase 1/2 to 3 $^{\#\#}$ p<0.001 for value comparing phase 1/2 to 3

Table 3. Study parameters of athletes during exercise tonometry in mean (SD)

	GI-symptoms during exercise test (n=7)	No GI-symptoms during exercise test (n=3)	p-value
Phase 1			
Gastric pCO_2	5.7 (0.5)	5.7 (0.9)	0.94
Gastric gradient	0.5 (0.7)	0.5 (0.9)	0.96
Jejunal pCO_2	6.5 (0.7)	6.8 (0.4)	0.45
Jejunal gradient	1.3 (0.6)	1.6 (0.4)	0.36
Lactate	4.6 (1.6)	3.8 (1.4)	0.44
Phase 2			
Gastric pCO_2	6.0 (0.7)	5.8 (1.0)	0.66
Gastric gradient	1.1 (0.7)	0.5 (1.1)	0.30
Jejunal pCO_2	6.6 (0.7)	6.9 (0.6)	0.49
Jejunal gradient	1.6 (0.6)	1.6 (0.2)	0.93
Lactate	5.3 (1.8)	3.2 (0.7)	0.09
Phase 3			
Gastric pCO_2	6.6 (0.9)	6.0 (1.1)	0.36
Gastric gradient	2.5 (0.8)	1.7 (0.9)	0.17
Jejunal pCO_2	6.8 (0.7)	6.9 (0.6)	0.94
Jejunal gradient	2.7 (0.4)	2.5 (0.5)	0.51
Lactate	9.8 (1.0) *	7.3 (1.9)	0.03

*$p<0.05$

S– tests (mean 7.3 mmol, SD 1.9) (p=0.03). To correct for this difference in exercise intensity, gastric and jejunal gradients were related to lactate level (as marker for exercise intensity). In S+ tests, a significant correlation between lactate and both gastric (0.29, 95% CI 0.22 to 0.36, p<0.001) and jejunal gradient (0.22, 95% CI 0.16 to 0.28, p<0.001) was found. In S– tests, there was a significant correlation between lactate and jejunal gradient (0.19, 95% CI 0.06 to 0.32, p=0.001) but not for gastric gradient 0.11 (95% CI 0.16 to 0.39, p=0.38) (see figures 1 and 2). No significant difference in the relationship between lactate and study parameters within the S+ and S– tests was found (interaction term >0.05).

Management and follow-up

All athletes were treated conservatively with the general advices given as described earlier. Of the 12 athletes, nine were successfully contacted for follow-up; median follow-up time was 15 months (range 7–72 months). Two athletes (athletes 4 and 5; table 1) could not be contacted. In athlete 10, follow-up time was too short. Six of the nine athletes reported significant improvement by following the treatment advices. In one athlete (athlete 9; table 1), symptoms had worsened. In two athletes (athletes 3 and 11), symptoms were unchanged. Three athletes (athletes 9, 11 and 12) reported a significant reduction in level of sport, whereas level of sport was unchanged or increased in the other six athletes. Athlete 3 tried vasodilating therapy, although we discouraged, and had hypotensive collapses. Athlete 4 was free of symptoms in daily life, although compression of the celiac artery by the arcuate ligament was assessed. Surgical relieve of the arcuate ligament was not recommended in this patient.

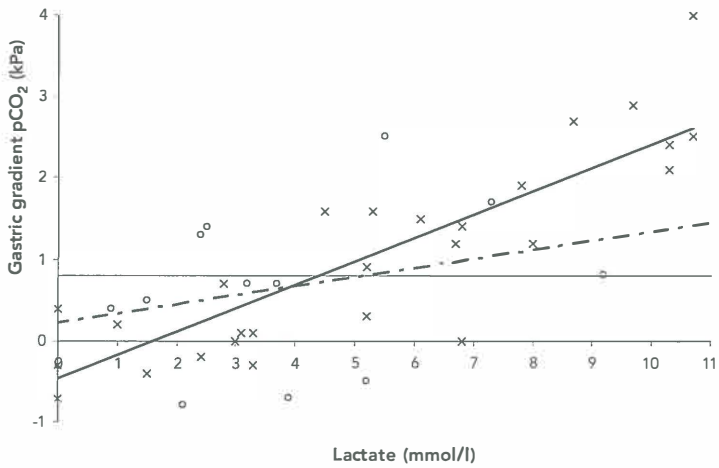

Figure 1. Relation between lactate and gastric gradient during exercise tonometry in S+ tests (crosses and continuous thick line) and S- tests (circles and dotted line). Regression coefficient in S+ tests was 0.29 (95% c.i 0.22- 0.36, p<0.001), regression coefficient for S- tests was 0.11 (95% c.i -0.16- 0.39, p=0.38). The thin continuous line (0.8kPa) represents the threshold for gastric ischemia.

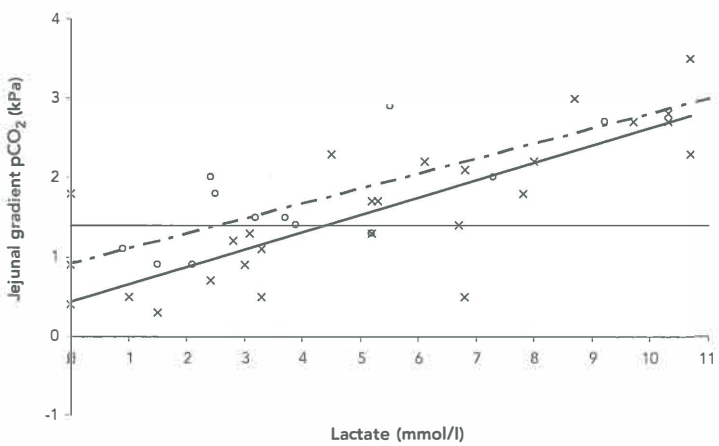

Figure 2. Relation between lactate and jejunal gradient during exercise tonometry in S+ tests (crosses and continuous thick line) and S- tests (circles, dotted line). Regression coefficient for S+ tests was 0.22 (95% c.i. 0.16- 0.28, p<0.001), regression coefficient for S- tests was 0.19 (95% c.i. 0.06- 0.32, p=0.001). The thin continuous line (1.4kPa) represents the threshold for jejunal ischemia.

Discussion

In this study, GI ischemia was present in all subjects during maximal exercise and in 50% during submaximal exercise. No significant stenoses in the splanchnic arteries were found.
There was no significant difference in severity of GI ischemia between athletes with or without symptoms during prolonged exercise tonometry. Treatment advices, aimed at reducing GI ischemia during exercise, helped the athletes to reduce their complaints with satisfactory level of sport.

In our study, six of 12 athletes had an abnormal standard exercise tonometry. This is uncommon in patients without major splanchnic artery stenosis [9]. As shown in table 1, the presence of GI ischemia was equally distributed between patients with minimal splanchnic artery narrowing and completely normal splanchnic arteries. Therefore, the high percentage of positive standard exercise tonometry cannot be solely attributed to the mild arterial stenosis and may indicate a higher than normal splanchnic vasoconstriction in response to a condition with low splanchnic blood flow in athletes with abdominal symptoms during exercise. During maximum intensity exercise, gastric and jejuna ischemia were observed in all athletes. The presence of GI ischemia during high-intensity exercise has been confirmed in several studies. Nielsen *et al* showed that in well-trained, asymptomatic rowers rowing for 30 min at high intensity, the pH of gastric mucosa (a surrogate marker for mucosal ischemia) approached values similar to those in patients with chronic splanchnic ischemia [15]. A study by Otte *et al* showed that in untrained healthy volunteers, 10 min of exercise until exhaustion resulted in GI ischemia in six of 10 subjects, with a mean gastric gradient of 1 kPa [9]. Finally, in a previous study by our group, three well-trained asymptomatic volunteers performed the same exercise protocol as used in this study. Their mean gastric gradient at maximum intensity exercise was 2.5 kPa, which is similar to the findings in the current study [16]. Although our results show that after correction for difference in exercise intensity, the gastric and jejunal gradients of athletes with complaints during the exercise test exhibited a stronger increase per mmol/l lactate than those of athletes without symptoms, this was not statistically significant. Furthermore, in healthy volunteers, the gastric regression coefficient was 0.27 (95% CI 0.11 to 0.42, p=0.003), which is not different from both the symptomatic and asymptomatic group.
Previously, it has been shown that GI ischemia may induce a wide range of symptoms, including impaired motility, pain and diarrhoea [17,18]. We have previously shown that GI ischemia occurs frequently during high-intensity exercise in asymptomatic subjects [15,16]. In the current study, GI ischemia was present in all subjects referred for exercise-induced GI symptoms, irrespective of whether or not their symptoms were provoked by our exercise test. These data may be explained in different ways.
First, the GI tract of athletes with exercise-induced complaints could be more susceptible to the effects of ischemia. A similar phenomenon has been demonstrated in patients with irritable bowel syndrome and gastro-esophageal reflux disease and is referred to as visceral hyperalgesia [19,20]. Alternatively, the repetitive ischemic stimuli

during exercise may overreach the adaptive capacity of the GI tract in athletes with exercise-induced GI symptoms. GI ischemia and reperfusion damage may result in impaired gut-barrier function with increased GI permeability as a result of intestinal cell damage, and there is also evidence that human GI tract can adapt to exercise by, for example, increased gastric emptying and improved gut-barrier function [21-23]. Data from our study may indirectly support the latter hypothesis. Several athletes have reduced their exercise intensity for a few months. After slowly resuming and increasing exercise intensity, the athletes were able to reach their original exercise level. It would be of interest to investigate whether the gut-barrier function in athletes with exercise-induced GI symptoms is indeed reduced. This could be achieved by measuring the levels of serologic markers indicating gut epithelial damage (such as intestinal fatty acid–binding protein and citrulline) [24,25].

The inability of exercise tonometry to distinguish between asymptomatic and symptomatic athletes may lead to the conclusion that this test is of little value in the management of this patient group. However, we believe that exercise tonometry was beneficial in several aspects. First, in our experience, the results of exercise tonometry were helpful to explain the link between GI symptoms induced by exercise and the presence of GI ischemia to the athletes. We observed that 'rigorous' advices such as attenuating the exercise intensity were more easy to understand and followed by the usually fanatic athletes, once GI ischemia during maximum intensity exercise has been shown. Second, in athletes with a significant splanchnic arterial stenosis, exercise tonometry may be used to guide in deciding whether revascularization would be beneficial [14,18]. In athlete 4, for example, the tonometry during submaximal exercise was normal. This was a strong argument against an operative procedure. This is important because we have shown that GI symptoms during exercise may be an important clue to the development of chronic GI ischemia in non-exercising conditions [26]. During follow-up, all athletes reported to be satisfied with the diagnostic protocol, explanations and treatment advices. We usually give several advices for the management of athletes with exercise-induced GI symptoms. First, other causes for the symptoms, such as rectal bleeding, should be ruled out.

Second, if symptomatic exercise-induced GI ischemia is suspected, duplex ultrasound should be performed to rule out a haemodynamically significant stenosis. If a significant stenosis is present, surgical treatment may be advised, especially if the athlete has ischemic complaints in daily life as well. If there are no complaints in daily life, surgical treatment should be thoroughly counseled with the athlete. If a hemodynamically significant splanchnic artery stenosis is absent, we advise the athletes to: (1) aim at a steady state heart rate of 5 to 10 beats per min below the heart rate during which their symptoms usually develop; (2) eat and drink small amounts immediately before and during physical exertion and to train this; (3) reduce the exercise intensity for several months and slowly resume the exercise intensity; and (4) avoid the use of non-steroidal anti-inflammatory drugs or cyclo-oxygenase-2 inhibitors because these drugs may result in additional ischemic damage, either by blocking the synthesis of the vasodilating substance prostaglandin or by inducing mitochondrial damage [24].

In conclusion, GI ischemia is common during maximum intensity exercise. The large

proportion of abnormal tonometry tests during submaximal exercise in the study group, in the absence of major splanchnic artery stenosis and a slightly larger increase in pCO_2 gradient relative to lactate increase in symptomatic subjects during the exercise test, point to the increased susceptibility for the development of ischemia during exercise. Our diagnostic approach and treatment advices helped the majority of the referred athletes to understand the causes of their complaints.

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Chapter

In vitro characterization of air tonometry

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Abstract

Background:

In air tonometry the pCO_2 in the gastrointestinal lumen is measured every 10 minutes to detect ischemia. The aim of this study was to establish the influence on the pCO_2 measurement of 1) the timing, length and amplitude of a CO_2 peak within measurement cycle and 2) covering of the tonometry balloon with water.

Methods:

In a 30ml equilibration chamber a baseline pCO_2 of 5.1 kPa was accomplished. Three experiments were performed using CO_2 peaks of 10.1 and 15.3kPa. In experiment 1 a series of measurements with increasing peak length at the end of the dwell time was performed. In experiment 2 and 3, a series of measurements with peak length of two minutes (exp 2) and 4 minutes (exp 3) was performed at various time points of the dwell time. All experiments were performed under three circumstances: with the balloon in air, the ballon half covered in water, and finally fully covered with water. The measured tonometerPCO_2 ($TpCO_2$) is expressed as % of the peak value.

Results:

No difference in $\%TpCO_2$ between 10.1kPa and 15.2kPa peaks was found.
Experiment 1. With increasing peak length from 2 to 10 minutes, the $\%TpCO_2$ rose from 32% to 98% (balloon uncovered), 25% to 85% (balloon partially covered) and 8-65% (balloon fully covered).
Experiment 2 and 3. A peak during the early phases of the dwell time caused the lowest rise in $\%TpCO_2$. Maximum $\%TpCO_2$ was achieved during a very late pCO_2 peak when balloon was not or partially covered. With a covered balloon, the maximum $\%TpCO_2$ was reached after a peak in the middle of a measurement cycle.

Conclusion:

Changes in pCO_2 during the last minutes of the dwell time have the largest influence on the measurement results. Covering the tonometry balloon with water leads to significant slower build-up of measured pCO_2, and can be explained by buffering of CO_2 in the fluid surrounding the balloon.

Introduction

During gastrointestinal ischemia, lack of oxygen leads to anaerobic metabolism which results in production of lactic acid and other protons. These excess protons are buffered by tissue bicarbonate and CO_2 forms. In numerous animal studies it was shown that an increased tissue pCO_2 is a highly accurate indicator of ischemia [1]. Because mucosal CO_2 equilibrates with luminal CO_2 within minutes, intraluminal pCO_2 reflects mucosal values. Luminal CO_2 can be measured by air tonometry using a balloon-tipped catheter, placed in the stomach or jejunum. In the early years of tonometry the pCO_2 was measured by infusion and aspiration of saline, using a blood gas analyser [2]. Over the years, the measurement interval of tonometry has been shortened by replacing saline as tonometer fluid for air, recycling of the sampled air and using a correction factor for incomplete equilibration [3,4]. The development of semi-continuous air tonometry proved to be more accurate with shorter response times [5,6]. The currently used measurement device for air tonometry is the Tonocap ® (Datex-Engstrom, Finland). The Tonocap® consists of a capnograph and balloon tipped catheter, allowing for semi-automated pCO_2 measurement every ten minutes. Intraluminal CO_2 diffuses in the balloon and after a standard 10 minutes dwell time, the air is aspirated and pCO_2 is measured.

Most studies in tonometry have been performed in critical care medicine. For use in these patients this 10-minute measurement interval proved sufficient as the clinical situation usually develops over hours, rather than minutes [1,4,7]. In critically ill patients an abnormal tonometry result was sensitive but not specific as predictor of a poor clinical outcome [7].

However, when tonometry is used for detection of chronic gastrointestinal ischemia a 10-minute exercise test is used as provocative manoeuvre for development of during submaximal exercise. The combination of splanchnic artery stenosis and exercise induced splanchnic vasoconstriction proved to be accurate in GI-ischemia detection. Furthermore it may help in the clinical decision making [8-10]. The standard 10-minute measurement interval of the Tonocap is long in view of the exercise test which has the same length. Essentially, each test only results in one measurement point. Previously, a study using a device with very rapid response demonstrated that pCO_2 increases within minutes after the onset of ischemia [11]. Apart from this long measurement interval, we also do not know the influence on timing and amplitude of a CO_2 peak during the 10 minutes exercise test on the ultimate measurement value of the Tonocap. This may be of clinical importance as the ischemic response to a certain exercise level is highly individual and difficult to predict. It is not feasible to construct an exercise protocol in such a way that the timing and amplitude of a CO_2 peak occurs at a fixed time within the ten minutes of exercise. Another unknown factor is at which extent the diffusion of CO_2 into the balloon is influenced by covering of the tonometry balloon of gastric content. A better knowledge of these factors might improve the current accuracy of 86% for detection of GI-ischemia during exercise [8].

The aim of this study was to establish the influence of the timing, length and amplitude of a CO_2 peak within the dwell time of the Tonocap on the measurement

outcome. Furthermore we investigated whether covering the balloon with water had effect on the measurement characteristics of the Tonocap.

Materials and method

Equilibration chamber

A balloon tipped catheter (TRIP® tonometer, Tonometrics Division, Instrumentarium Corp, Finland) was placed in a 30ml Perspex chamber containing distilled water to maintain relative high humidity. A gas mixing setup was used, consisting of two mass flow controllers (El-Flow, Bronkhorst Nederland B.V, The Netherlands) which accurately mixed 100% N_2 and premixed gas of 50% CO_2 /50% N_2 (Hoek Loos B.V, Amsterdam, The Netherlands). The total error in the mixing process was calculated at <2%. The gas mixture flowed through the equilibration chamber with 50 ml/min. The chamber was sealed airtight (Parafilm "M", America National Can, USA) with the exception of a ventilation hole, to avoid overpressure. It was estimated that it would take approximately one minute before a new steady state CO_2 concentration was reached in the chamber after setting a different gas mixture.

Air tonometry

The balloon tipped catheter was connected to an air tonometry device (TC-200 Tonocap®, Tonometrics Division, Finland). The Tonocap® automatically fills the tonometer catheter with 5ml of room air, which is then kept in the catheter balloon for ten minutes (dwell time). A sample is automatically drawn from the catheter and the concentration of CO_2 is measured externally using an infrared sensor. This measurement process takes approximately 30 seconds. The aspirated air is then recycled to the catheter balloon for the next measurement cycle.

Experiments

All experiments were performed with the tonometry-balloon in air, half covered with water and fully covered with water by filling the chamber with 5ml, 10ml or 20ml distilled water respectively.

Experiment 1: increasing length of CO_2 peak: The time frame of this experiment is presented in figure 1. The baseline pCO_2 was kept at 5.1 kPa. A series of measurements with increasing peak length at the end of the dwell time was performed at two CO_2 levels: 10.1 kPA and 15.2 kPa. The measurement started at t=0. A 2 minutes (min) peak was created from 8-10min, a 4-min peak from 26-30 min, an 8 min peak from 62 to 70 min, and a 10 min peak from 80-90 min.

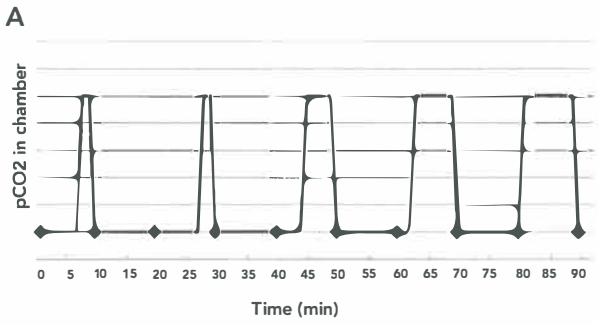
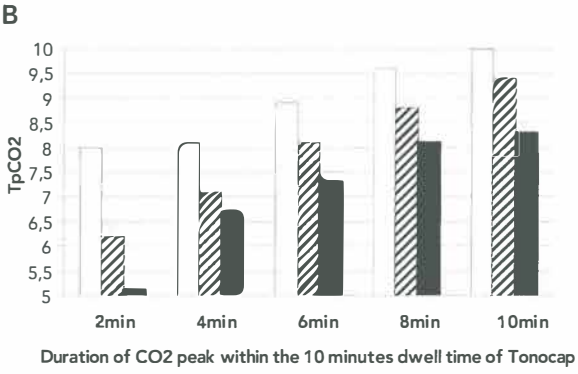
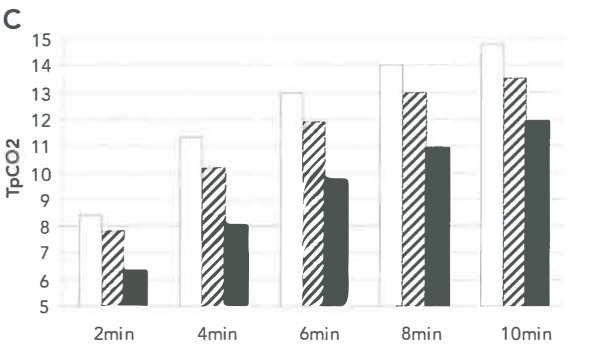


Figure 1. Measurement protocol and results with progressive length of CO_2 peak.
A. measurement protocol. Continuous line: schematic value of pCO_2 in chamber. Diamonds: measurement of Tonocap.

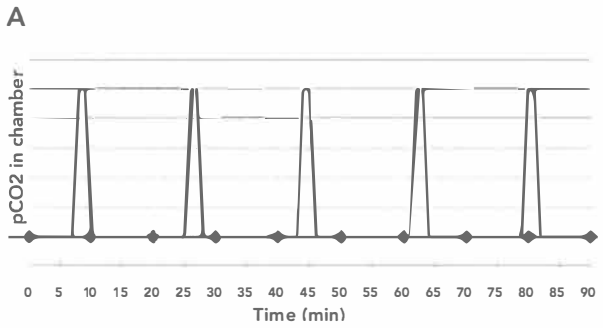


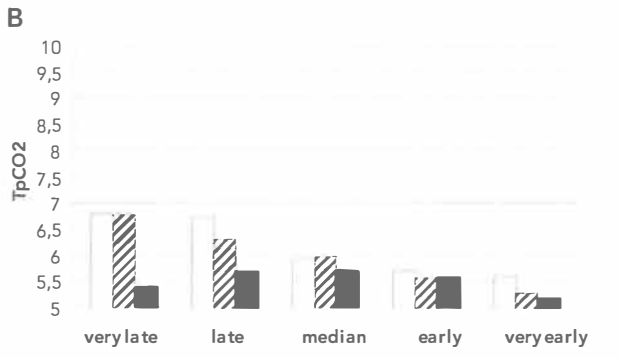
B. Measurement results with CO_2 peak of 10.1 kPa. White bar: balloon in air, striped bar: balloon partially covered, black bar: balloon fully covered. Baseline pCO_2 is 5.1kPa. Maximum measurable $TpCO_2$ is 10.1kPa.



C. Measurement results with CO_2 peak of 15.2 kPa, White bar: balloon in air, striped bar: balloon partially covered, black bar: balloon fully covered. Baseline pCO_2 is 5.1kPa. Maximum measurable $TpCO_2$ is 15.2kpA.

Experiment 2: A two minutes CO_2 peak at various moments of the measurement cycle: The time frame of this experiment is presented in figure 2. The baseline pCO_2 was kept at 5.1 kPa. A series of measurements with peak length of two minutes was performed at various time points of the dwell time, again at two CO_2 levels: 10.1 kPA and 15.2 kPa. The measurement started at t=0. A two min peak was created from 8-10min (very late peak), 26-28min (late peak), 44-46min (median peak), 62-64min (early peak) and 80-82min (very early peak).





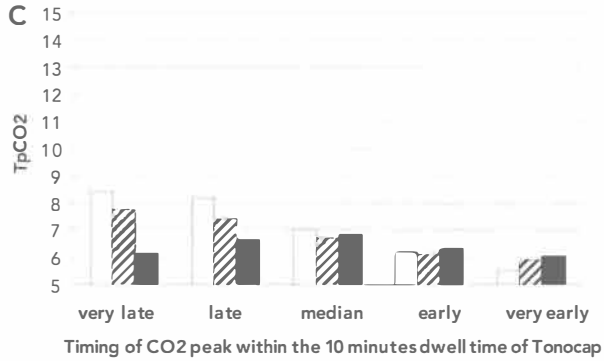


Figure 2. Measurement protocol and results with two minutes CO_2 peak
A. Measurement protocol. Continuous line: schematic value of pCO_2 in chamber. Diamonds: measurement of Tonocap.

B and C. Two-minute pCO_2 peaks at different time points of the measurement cycle.

B. Measurement results with CO_2 peak of 10.1 kPa. White bar: balloon in air, striped bar: balloon partially covered, black bar: balloon fully covered. Baseline pCO_2 is 5.1kPa. Maximum measurable $TpCO_2$ is 10.1kPa.

C. Measurement results with CO_2 peak of 15.2 kPa. White bar: balloon in air, striped bar: balloon partially covered, black bar: balloon fully covered. Baseline pCO_2 is 5.1kPa. Maximum measurable $TpCO_2$ is 15.2kPa.

Experiment 3: A four minutes CO_2 peak at various moments of the measurement cycle: The time frame of this experiment is presented in figure 3. The baseline pCO_2 was kept at 5.1 kPa. A series of measurements with peak length of four minutes was performed at two CO_2 levels: 10.1 kPA and 15.2 kPa. The measurement started at t=0. A four minutes peak was created from 6-10min (late peak), 24-28min (median peak), 42-44min (early peak) and 60-64min (very early peak).

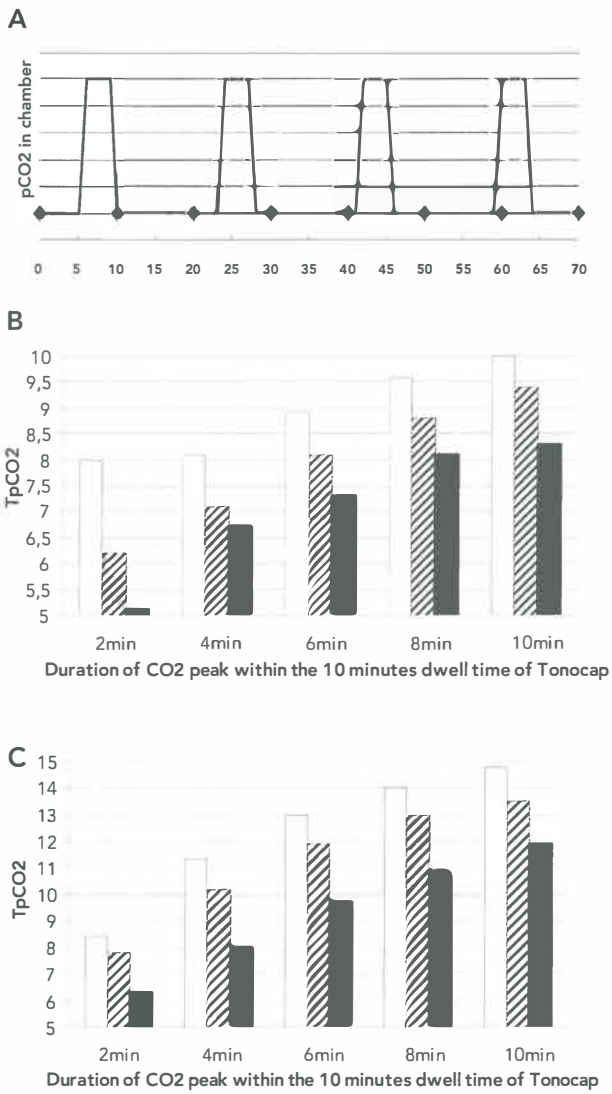


Figure 3 Measurement protocol and results with four minutes CO_2 peak

A. Measurement protocol. Continuous line: schematic value of pCO_2 in chamber. Diamonds: measurement of Tonocap.

B and C. Four-minute pCO_2 peaks at different time points of the measurement cycle

B. Measurement results with CO_2 peak of 10.1 kPa. White bar: balloon in air, striped bar: balloon partially covered, black bar: balloon fully covered. Baseline pCO_2 is 5.1kPa. Maximum measurable $TpCO_2$ is 10.1kPa.

C. Measurement results with CO_2 peak of 15.2 kPa. White bar: balloon in air, striped bar: balloon partially covered, black bar: balloon fully covered. Baseline pCO_2 is 5.1kPa. Maximum measurable $TpCO_2$ is 15.2kPA.

6

Statistical analysis

Data are presented as Tonocap pCO_2 ($TpCO_2$), defined as the first measurement value of the Tonocap after the applied CO_2 peak and $\%TpCO_2$ (expressed in %), defined as the percentage of the maximum theoretical rise in $TpCO_2$ (5kPa during 10.1kPa peaks, and 10.1kPa during 15.2kPa peaks). The dwell time of the Tonocap was defined as the available time for CO_2 diffusion into the tonometry balloon and was 10 minutes in this study.

Results

During all experiments, the 15.2kPa CO_2 peak applied resulted in a higher$TpCO_2$ compared to the 10.1kPa CO_2 peak, independent of the timing of the CO_2 peak or the covering of the balloon. The $\%TpCO_2$ was identical between 10.1kPa and 15.2kPa peaks, independent of the timing, and length of the CO_2 peak or the covering of the balloon.

Experiment 1: increasing length of CO_2 peak

The results of experiment 1 are presented in figure 1B and C. With increasing peak length from 2 to 10 minutes, the $\%TpCO_2$ rose from 32% to 98% (balloon uncovered). With a fully covered balloon, $\%TpCO_2$ was 8% during a 2-minute peak, 30% after 4 minutes and reached 65% after a 10 minutes peak. The partial covered balloon showed $\%TpCO_2$ from 25% (2 minutes peaks) to 85% (10 minutes peak).

Experiment 2: A two minutes CO_2 peak at various moments of the measurement cycle

The results of experiment 2 are presented in figure 2B and C. A peak during the (very) early phases of measurement caused a <10% rise in $\%TpCO_2$ both with 10.1 and 15.2 kPa peaks, independent of covering of the balloon. With very late and late peaks, $\%TpCO_2$ was 32 and 34% with the balloon in air. These values were 22 and 24%, respectively, when the balloon was partial covered. With a fully covered balloon, the maximum $\%TpCO_2$ was achieved during the median peak (14%).

Experiment 3: A four minutes CO_2 peak at various moments of the measurement cycle

The results of experiment 3 are presented in figure 3B and C. With the balloon in air, the $\%TpCO_2$ rose from 15% (very early peak) to 65% (late peak) whereas these percentages were 18% to 48% when the balloon was partially covered. With the balloon fully covered, these percentages were 23% and 31% whereas the maximum $\%TpCO_2$ of 43% was reached during the median peak.

Discussion

From this study can be appreciated that timing, length and amplitude of a CO_2 peak in relation to the measurement cycle of the Tonocap had profound impact on the measurement results. The pCO_2 during the last minutes of the dwell time had the largest influence on the measurement result. Fluid covering the tonometry balloon served as damper and buffer for changes in pCO_2 and therefore influenced the measurement outcome. These measurement characteristics are inherently related to the tonometry technique and represent the limitations of this measurement technique.

As shown in experiment 1, a 10 minutes CO_2 peak was almost completely detected by the Tonocap if the balloon was not covered with fluid. This quick response to a CO_2

change has been confirmed in another study from our group and is probably the result of the small volume of the equilibration chamber (30ml) combined with a high flow of CO_2 (50ml/min). The quick change in chamber pCO_2 enables a long time for CO_2 diffusion at the optimal CO_2 gradient into the tonometry balloon. Moreover, doubling of the amplitude of a CO_2 peak resulted in doubling of the rise in $TpCO_2$ so the speed of CO_2 diffusion into the balloon was no limiting factor. As might be expected, the earlier the CO_2 peak started, the higher was the $TpCO_2$.
The later a CO_2 peak was timed within the dwell time, the higher was the $TpCO_2$, except when the balloon was fully covered by water. Thus, the timing of a short lived CO_2 peak (exp 2 and 3) and a long lasting CO_2 peak (exp 1) have both large influences on the $TpCO_2$.
Covering the tonometry balloon with water resulted in a less pronounced $TpCO_2$ compared to the situation in when the balloon was totally surrounded by air, except when an early CO_2 peak was applied. Due to buffering of CO_2 in water, an early CO_2 peak lasted longer in water than in air and resulted in a larger $TpCO_2$ compared to a balloon surrounded by air. This buffering effect is well illustrated in figure 2C, 3B and 3C. In fact the diffusion of CO_2 into the balloon, in presence of water (or in human conditions, the gastric contents) is a two-stage process: first, diffusion of CO_2 into the fluid and second, from the fluid into the tonometer balloon. This is of clinical importance as, in vivo, it is estimated that there is 50-60ml fluid and mucus in the stomach during fasting state [12]. Although, this will probably result in total covering of the balloon, it has been shown that the main part of tonometer CO_2 stems from buffered CO_2 in this gastric content [13].
Despite the profound influence of timing, amplitude, length of a CO_2 peak and covering of the balloon on the measurement characteristics of air tonometry, the accuracy of GET for detecting ischemia is still 86%. This may be explained in several ways. First, after inducing GI-ischemia during GET, tonometry value remains high for at least 10 minutes during recovery time [14]. Once GI-ischemia (i.e. rise in pCO_2) has developed, luminal pCO_2 remains high for a period >10 minutes (as was simulated in experiment 1). This implicates that the pattern of short-lived CO_2 peaks, as performed in experiment 2 and 3, is unlikely to occur during gastric exercise tonometry. Although the individual exercise tolerance is highly variable, we do not experience many difficulties to achieve the right exercise intensity in daily practice. Second, should a CO_2 peak be induced during the last two minutes of the exercise, the first measurement during recovery will notify the CO_2 peak.

In conclusion, this in vitro study shows that changes in pCO_2 during the last minutes of the dwell time have the largest influence on the measurement results. The effect of covering of the tonometry balloon on the measurement characteristics is the result of buffering of CO_2 in the fluid surrounding the balloon. Although air tonometry has been shown to have a high accuracy in detecting gastrointestinal ischemia in daily practice, its measurement characteristics still warrant new methods for continuous luminal CO_2 measurement.

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Chapter

In vitro and in vivo assessment of a prototype hydrogel-based carbon dioxide sensor; comparison with air tonometry

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Abstract

Background:

Gastrointestinal ischemia is always accompanied by an increased luminal CO_2. Currently, air tonometry is used to measure luminal CO_2. To improve the response time a new sensor was developed, enabling continuous CO_2 measurement. It consists of a pH-sensitive hydrogel which swells and shrinks in response to pH changes related to luminal CO_2, which is measured by the pressure sensor. We evaluated the potential clinical value of the sensor during an in vitro and in vivo study.

Material/methods:

The response time to immediate and stepwise change in pCO_2 was determined between 5 and 15 kPa, as well as temperature sensitivity between 25 and 40 °C at two pCO_2 levels. The sensor was compared to air tonometry (Tonocap®) in three healthy volunteers using a stepwise incremental exercise test, followed by a period of hyperventilation and an artificial CO_2 peak.

Results:

The in vitro response time to CO_2 increase and decrease was mean 5.9 and 6.6 min. The bias, precision and reproducibility were +5%, 3% and 2%, resp. Increase of 1 °C at constant pCO_2 decreased sensor signal by 8%. In vivo tests: The relation with the Tonocap® was poor during the exercise test. The response time of the sensor was 3 min during hyperventilation and the CO_2 peak.

Conclusion:

The hydrogel carbon dioxide sensor enabled fast and accurate pCO_2 measurement in a controlled environment but is very temperature dependent. The current prototype hydrogel sensor is still too unstable for clinical use, and should therefore be improved.

Introduction

Detection of an increased pCO_2 as measure of gastrointestinal (GI) ischemia is based on the association between ischemia and luminal hypercapnia. This CO_2 stems from buffering of protons produced during anaerobic glycolysis and diminished CO_2 clearance by reduced blood flow [1]. The mucosal CO_2 equilibrates with luminal CO_2. The latter can be measured by air tonometry using a balloontipped catheter, placed in the stomach. Gastric acid suppression is used to avoid increases in CO_2 from buffering of gastric acid by duodenal bicarbonate [2,3]. The current standard for luminal pCO_2 measurement is the Tonocap® (Datex-Engstrom, Finland). The Tonocap® consists of a capnograph and balloon tipped catheter, allowing for semi-automated pCO_2 measurement every ten minutes. Intraluminal CO_2 diffuses into the balloon and after a 10 min dwell time, the air is aspirated and measured exvivo with an infrared sensor. It has been shown that an increased luminal-blood pCO_2 gradient indicates gastrointestinal ischemia [4].

Air tonometry has several limitations. First, the maximal measurement frequency is once every 10 min. Second, air tonometry may influence the environment because CO_2 is removed and O_2 delivered during measurement [5,6]. Finally, air tonometry is unsuitable for ambulant measurements. This led us to develop a new sensor. The hydrogel-based carbon-dioxide sensor consists of a pH-sensitive hydrogel in a bicarbonate solution mounted on a catheter-tip pressure sensor. It is covered by a gas permeable membrane (figure 1). The hydrogel will swell or shrink dependent on the CO_2. Because it is tightly mounted on the pressure sensor, this will be reflected by pressure changes [7].

This study was aimed to assess the performance of the hydrogel-based sensor and its potential clinical value.

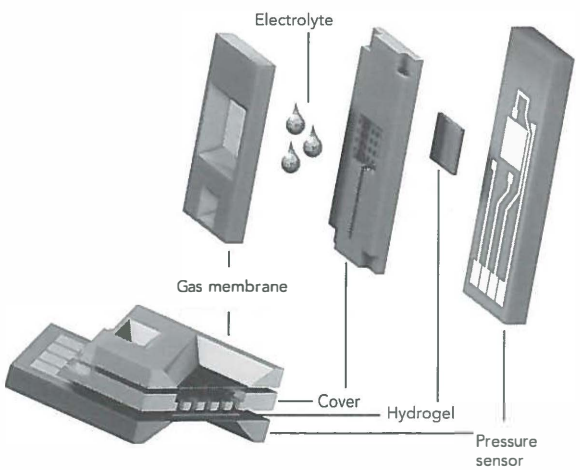

Figure 1. Exploded view of all parts and assembly drawing of the final hydrogel-based CO_2 sensor.

Materials and methods

Air tonometry

The balloon tipped catheter was connected to an air tonometry device (TC-200 Tonocap®, Tonometrics Division, Finland). The Tonocap® automatically fills the tonometer catheter with 5 ml of room air, which is then kept in the catheter balloon for ten minutes. A sample is automatically drawn from the catheter and the concentration of CO_2 is measured externally by an infrared sensor, which takes 30 seconds. The aspirated air is then recycled to the catheter balloon for the next measurement cycle. The Tonocap® was calibrated according to its standard procedure.

The hydrogel-based CO_2 sensor

The current prototype hydrogel-based CO_2 sensor was connected to a measurement device (Luna, Medical Measurement Systems B.V, the Netherlands). The Luna reads out the hydrogel-based sensor signal and transmits it every second wireless to a laptop. LabVIEW software (National Instruments, USA) was used to convert the hydrogel-based sensor data to pCO_2 on the basis of a calibration curve. All data were automatically logged every second.

In vitro test

A 30 ml Perspex chamber was filled with 5 ml distilled water to obtain high relative humidity. Both the hydrogel- based sensor and the balloon tipped catheter (TRIP tonometer, Tonometrics Division, Instrumentarium Corp, Finland) were placed in the chamber after calibration. The temperature was held at 37°C in a thermostat bath regulated by a temperature controller (MTCA series, Melcor Corporation, USA). A gas mixing setup was used, consisting of two mass flow controllers (El-Flow, Bronkhorst Nederland B.V, The Netherlands) which accurately mix 100% N2 and premixed gas of 50% CO_2/50% N2 (Hoek Loos B.V, Amsterdam, the Netherlands). The gas mixture continuously flowed through the equilibration chamber with 50 ml/min. The total error in the mixing process was calculated at <2%. The gas chamber was sealed airtight (Parafilm "M", America National Can, USA) with the exception of a ventilation hole, to avoid overpressure in the chamber due to the continuous gas flow. It was estimated that it would take approximately one minute before a new steady state CO_2 concentration is reached in the chamber after setting a different gas mixture (chamber equilibration time).

Experiment 1: A baseline pCO_2 of 5.1 kPa was accomplished. The pCO_2 was increased within 1 minute and maintained at 15.2 kPa for 40 min. Then the pCO_2 was reduced within 1 minute and maintained at 5.1 kPa for 40 min. This cycle was repeated 3 times.

Experiment 2: The chamber pCO_2 was set at 5.1 kPa. At t = 0, pCO_2 was increased to 15.2 kPa with steps of 1 kPa every minute. The p CO_2 concentration of 15.2 kPa was maintained for 20 min. Then pCO_2 was decreased with steps of 1 kPa per min to 5.1 kPa again. This pCO_2 was again maintained for 20 min.

Experiment 3: The chamber pCO_2 was kept at 5.1 kPa in the first and 10.2 kPa in the second experiment. At each pCO_2 level, the temperature was increased in 3 °C steps from 25 to 40 °C in steps of 3 °C every 15 min.

In vivo study

Subjects

Three healthy, trained male volunteers, taking no medication, were included in this study. Trained status was defined as >4 hours endurance training per week. Exclusion criteria were; any medication, prolonged QT-syndrome, diabetes mellitus, epilepsy, deformity to throat/nose/ear. 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 constitution after approval from the Institutional Ethics Committee.

Preparation

An electrocardiogram was performed to exclude the prolonged QT-syndrome. The subjects were fasted for food ten hours, and fluid two hours before the start of the study. They were not allowed to drink or eat during study time. After calibration of the pH measurement catheter (pHersaflex, Medical Measurements Systems, Enschede, the Netherlands), it was placed transnasally approximately 10 cm below the gastro-esophageal junction in two subjects. This was identified by an abrupt pH decrease as the probe enters the stomach. The values were stored in a microcomputer system for pH analysis (UPS 2020 Orion, Medical Measurement Systems, Enschede, the Netherlands). The gastric tonometer was placed at the same distance from the nose as the pH electrode and connected to the air tonometry device. The pCO_2 was measured every ten minutes. The hydrogel-based sensor was placed nasogastrically at the same distance. An intravenous catheter was placed and Esomeprazole infusion was given by a priming dose of 80 mg, followed by 8 mg/hour to inhibit gastric acid secretion to prevent CO_2 production by buffering of gastric acid.

Protocol

The exercise test was started as soon as the gastric pH was >4 for 30 minutes. A 12-lead electrocardiogram was recorded during the exercise protocol. (Schiller, Switzerland) In subject 3, body temperature was measured at t = 0 min, t = 20 min and t = 30 min (Thermoscan, Braun, Kronberg, Germany). Exercise was performed on a bicycle ergo meter (Lode, Groningen, The Netherlands). From t = 0 min to t = 10 min, the workload was increased every two minutes to reach sub maximal intensity. This was defined as capillary lactate between 3.5–5 mmol/l. Lactate was measured every two minutes from t = 0 min to t = 10 min (Accusport, Boehringer, Mannheim, Germany). From t = 10 min to t = 20 min, exercise intensity was maintained at sub maximal level, which was controlled by lactate measurements every three minutes. From t = 20 min to t = 30 min, the workload was increased with 10% of the sub maximal workload every three minutes until exhaustion. Lactate was measured every three minutes. The subjects recovered from t = 40 min to t = 75 min. At t =

75 min, subjects were asked to hyperventilate for 5 minutes to rapidly decrease the arterial CO_2. At t = 110 min, an artificial CO_2 peak was induced by oral ingestion of 1 g $NaHCO_3$ and administering 200 ml apple juice through the catheter. At t = 140 min, the study was finished. Arteriolized capillary blood samples were drawn for determination of capillary pCO_2 at t = 0 min, t = 20 min, t = 30 min and t = 75 min (blood-gas analyzer; Radiometer ABL520, Copenhagen, Denmark).

Statistical analysis

In vitro test

Data are expressed as mean (standard deviation). The error of pCO_2 measurement, calculated from experiment 1, was defined as the percentage difference between the applied pCO_2 and measured values of the sensor and Tonocap® after a change in bath pCO_2. The precision is the standard deviation of the error, and standard deviation divided by means was calculated as a measure of reproducibility. The 90% response time of the sensor was established as follows. First, the 90% value between the baseline (b) and ultimate (u) value was calculated following the formula

$$90\%\ value = (u-b)*0.9 + b \quad (1)$$

Second, the corresponding times to this 90% value (=90%vt) and the baseline value (=Bvt) was derived from the data sheet containing the sensor response. Finally, the 90% response time was calculated following the formula

$$90\%\ response\ time = 90\%vt - Bvt - 1\ minute\ (chamber\ equilibration\ time). \quad (2)$$

The response time of upward and downward pCO_2 changes were compared with an unpaired t-test. To assess the drift of the sensor, the three steady state values of the sensor at each pCO_2 were compared using the one-way ANOVA. $P<0.05$ was considered significant.

In vivo test

The peak pCO_2 at sub-maximal and maximal intensity exercise was determined. The pCO_2 response on hyperventilation and following the artificial CO_2 peak was assessed. The sensors were individually compared to the Tonocap® and the differences between the sensors were assessed. Luminal-capillary CO_2 gradient was calculated at t=0min, t=20min and t=30min from the Tonocap® values. A CO_2 gradient ≤0.8kPa was considered as normal [4]. To examine the relation between the sensor and manometer values, a linear regression analysis was performed.

Results

In vitro test

Experiment 1

Bias, precision and reproducibility of air tonometry and the hydrogel-based sensor are presented in table 1. As shown in figure 2, the sensor exhibits an upward drift. The hydrogel-based sensor reading during the second and third period of at 15.2 kPa was 0.4% and 3% higher compared to the first period. At 5.1 kPa, this upward change was 1.9% and 2.8%, respectively. This drift was significant at both values of applied pCO_2 ($p< 0.001$). After changing the chamber pCO_2, the sensor signal started to change after 200 seconds. The response time for an increase in pCO_2 was slightly, but significant faster than for a decrease (353 (14) versus 394 (10) seconds, $p = 0.01$).

Experiment 2

The response of the hydrogel-based sensor and air tonometry to a gradual change in pCO_2 is presented in figure 3. There was no difference in response time between the hydrogel-based sensor and air tonometry. It accurately showed the trend in changes of pCO_2, with a delay of approximately 210 seconds.

Experiment 3

The effect of temperature on the hydrogel-based sensor response is shown in figure 4. At 25°C, the real pCO_2 (i.e. 5.1 or 10.2 kPa) is overestimated over 300% by the hydrogel-based sensor in both experiments when comparing it to the hydrogel-based sensor values at calibration temperature (37 °C). On average, a 1°C increase in temperature caused a decrease of 8% in hydrogel sensor signal at 5.1 kPa, and 7% at 10.2kPa.

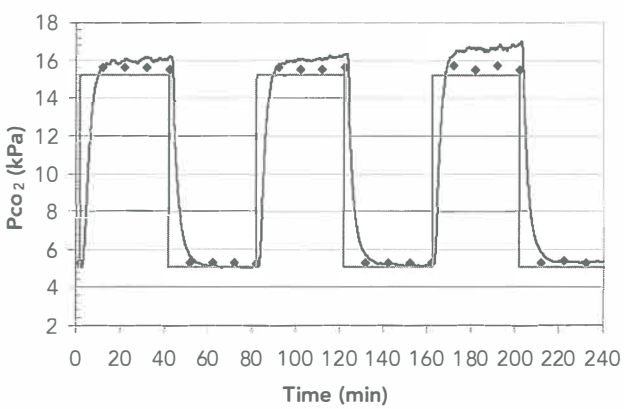

Figure 2. Bias, precision and drift of air tonometry and the hydrogel sensor.
pCO_2 was changed in three cycles from 5.1 to 15.2 kPa, maintained at 15.2 kPa for 40 minutes, changed to 5.1 kPa again and maintained at 5.1 kPa for 40 minutes (grey line). Black line represents the hydrogel sensor, black diamonds represent air tonometry.

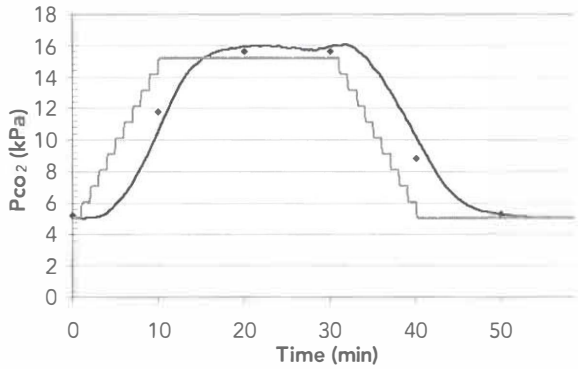

Figure 3. Response of air tonometry and the hydrogel sensor to a gradual change in pCO_2. pCO_2 was increased with 1 kPa/min to 15.2 kPa. After 20 min pCO_2 was decreased with 1 kPa/min to 5.1 kPa (grey line). Black line represents the hydrogel sensor, diamonds represent air tonometry.

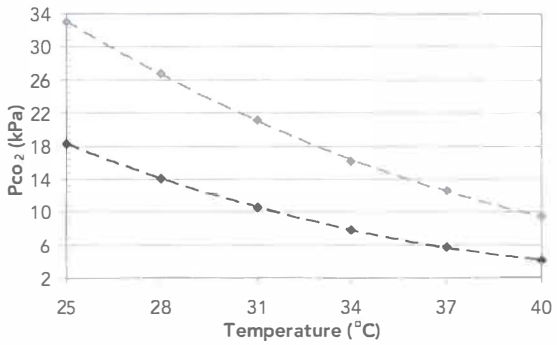

Figure 4. Effect of temperature change on the signal of the hydrogel sensor. Temperature was increased with steps of 3 °C from 25 °C to 40 °C with a constant pCO_2 of 5.1 kPa (black diamonds and dotted line) and 10.2 kPa (grey diamonds and dotted line).

In vivo test

Exercise

The main results of the exercise protocol are presented in figure 5A–C. All subjects exercised until exhaustion, maximum lactate levels were 10, 10 and 12 mmol/l, respectively. As represented in Figure 5A, all subjects had gastrointestinal ischemia at the moment of exercise at maximal intensity, represented by an increased luminal-capillary CO_2 gradient (values: 1.9, 3.5 and 2.3 kPa) as measured by air tonometry. Luminal pCO_2, measured by air tonometry, also increased from t = 20 to t = 30 (figure 5B). Figure 5C shows that only the hydrogel-based sensor in subject 2 correctly detected this rise in luminal pCO_2, from t = 20 to t = 30, during which GI ischemia developed.

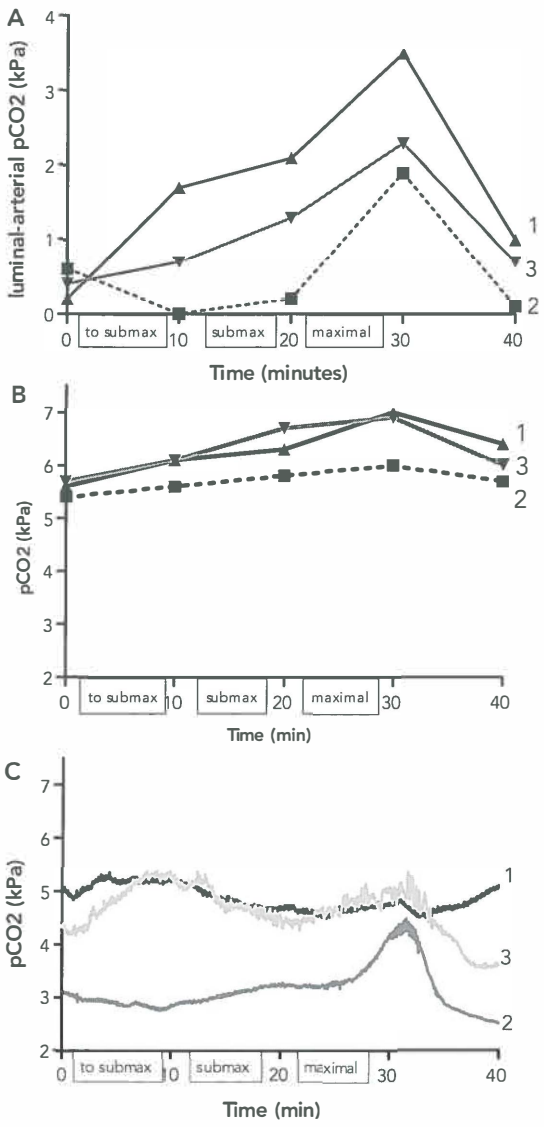

Figure 5.
A) Response of luminal-arterial pCO_2 gradient to the exercise protocol in 3 healthy volunteers.
B) Response of gastric pCO_2 as measured by air tonometry to the exercise protocol in 3 healthy volunteers.
C) Response of gastric pCO_2 as measured by the hydrogel-based sensor to the exercise protocol in 3 healthy volunteers.

Hyperventilation

Average capillary pCO_2 fell with 42% (from 5.4 kPa to 3.1 kPa). The mean tonometry value fell with 11%, the maximum average decrease of the hydrogel-based sensors in response to hyperventilation was 13%. The results of the response of the hydrogel-based sensors to the hyperventilation test are presented in figure 6. The hydrogel-based sensor signals of subject 1 and 3 started to fall at t = 78, three minutes after starting with hyperventilation. The hydrogel-based sensor signal of subject 2 started to fall at t = 81, six minutes after starting with hyperventilation.

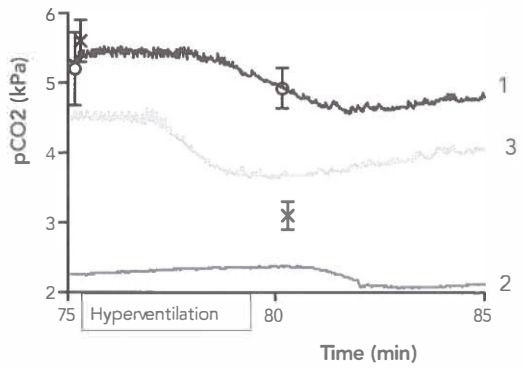

Figure 6. Response to hyperventilation.
Open circles represent mean capillary CO_2 , crosses represents mean outcome air tonometry value (crosses) and continuous lines represent the hydrogel based CO_2 sensors.

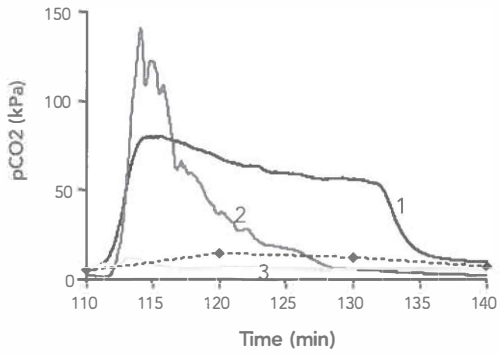

Figure 7. Response to an artificial CO_2 peak.
Diamonds represent air tonometry, continuous lines represent the hydrogel sensor. The CO_2 peak was accomplished at t=110 min.

Artificial CO_2 peak

The measurements results of the CO_2 peak are presented in figure 7. The tonometry value in the three volunteers all increased by 200%. The hydrogel-based sensor signal started to increase within 2 minutes after the CO_2 peak was induced. The increase from its baseline value differed from 1500% in subject 1, 5500% in subject 2 to 280% in subject 3.

Discussion

The prototype hydrogel-based CO_2 sensor was developed to overcome the drawbacks of air tonometry. In the current study it was shown that this prototype met some of the requirements: it enabled continuous measurement of CO_2 and fast detection of both sudden and gradual changes in pCO_2. However, the current state of stability of its measurement signal, in terms of hysteresis and temperature sensitivity, will have to be improved before clinical application is possible.

We have previously demonstrated the development of gastric ischemia within ten minutes of strenuous exercise [8]. However, the precise CO_2 dynamics during these tests are unknown. The current standard, air tonometry, is unable to monitor the trend of pCO_2 because of its ten minutes measurement interval. The ability of the new hydrogel-based sensor to measure pCO_2 continuously is major advantage over routine air tonometry. From the in vitro part of the study can be concluded that the hydrogel-based sensor is suitable for trend monitoring allowing detection of CO_2 changes within 3 minutes. The response time of the hydrogel-based sensor is considerably faster than currently published response times of air tonometry and other (semi) continuous CO_2 measurement devices [5,9,10]. A further improvement of the response-time could be achieved by decreasing the thickness of the hydrogel [7]. The very fast response of air tonometry in this study is probably related to the small volume of the equilibration chamber. In larger volumes, air tonometry proved to be slower, with response times of 18 minutes [11].

The bias, precision and reproducibility of air tonometry in this study are comparable to previous studies [11,12]. The bias, precision and reproducibility of the hydrogel-based sensor were promising for clinical use. In fact, the hydrogel-based sensor had a comparable accuracy as air tonometry. However, during the in vitro test, it already had an upward drift and during the in vivo tests, it proved to be insufficiently stable for clinical use. An example of instability (i.e. hysteresis) can be seen during the exercise test in subject 3 (figure 5C): the hydrogel-based sensor in subject 3 reached a stable signal from t = 35 min to t = 40 min. However, this differed about 1 kPa from its baseline value at t = 0 min whereas air tonometry showed a similar pCO_2 at t = 0 min and t = 40 min.

At first glance, these stability problems are quite disturbing. Interestingly, the calibration curves done after completion of the study, was identical to the one performed before the study. In addition, an earlier prototype of this hydrogel-based sensor, which was not yet mounted on a catheter, proved perfectly stable [7]. These observations indicate that the hydrogel-based sensor itself is stable, and the instability is due to imperfect, manual, assembly into the catheter. Manual assembly causes imperfections in the gluing/fixation of the hydrogel-based sensor parts, and, partly irreversibly, movement of the various parts. This is a well-established cause of varying characteristics, drift and hysteresis in most prototype sensors. For example, in the early phase of development of a pressure transducer for biomedical application by Ko et. al, similar problems were encountered [13]. These authors have shown that the major cause of baseline drift in the device was not related to the sensor design or processing but rather the

assembly and structure of the device. As expected, that problem was solved with automated machinated manufacturing techniques, and these in time and such devices are currently used worldwide in large quantities. Therefore, comparable construction and manufacturing techniques will likely eliminate or drastically decrease the drift problem in our hydrogel-based sensor. During the in vitro tests, the hydrogel-based sensor had large and irreversible temperature sensitivity.
During the in vivo tests, a 1 degree increase in body temperature was measured during the incremental exercise test. This probably decreased the hydrogel-based sensor signal by 8% and may therefore be one of the reasons that GI ischemia was insufficiently detected during maximum intensity exercise. Temperature sensitivity was expected as an intrinsic property of the hydrogel. However, in an earlier prototype, not mounted on the catheter, this effect was both reversible and predictable [7]. Again, incomplete fixation of the hydrogel-based sensor to the catheter is the most probable cause of the irreversible temperature sensitivity. Automated machinated assembly should make temperature sensitivity more predictable. Temperature correction will always be needed, however. This is a disadvantage compared to air tonometry which is not sensitive to temperature [14,15].

In conclusion, the prototype hydrogel-based CO_2 sensor allows for continuous measurement of pCO_2 in a clinically significant range. It enables fast and continuous luminal CO_2 measurement, picking up changes within 3 minutes. The current stability problems and irreversible temperature sensitivity are mainly related to the handmade assembly. To meet clinical demands more likely, a next version of the hydrogel sensor will have to be made by automated assembly.

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Chapter

Splanchnic artery stenosis and abdominal complaints: clinical history is of limited value in detection of gastrointestinal ischemia

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Submitted

Abstract

Background:

Splanchnic artery stenosis is common and mostly asymptomatic (chronic splanchnic disease, CSD) but may lead to gastrointestinal ischemia (chronic splanchnic syndrome, CSS). The aim of this study was to assess factors in the medical history of patients with splanchnic artery stenosis that predict the presence or absence of GI-ischemia.

Material and methods:

All patients referred for suspected CSS underwent a standardized work up including a medical history with questionnaire, duplex ultrasound, gastrointestinal tonometry, and angiography. Definitive diagnosis and treatment advice was made in a multidisciplinary team. In patients with splanchnic stenosis, those with established ischemia (CSS) were compared with non-ischemic patients (CSD).

Results:

270 Patients (102 M, 168 F, mean age 53) with splanchnic artery stenosis were analyzed of whom 109 (40%) had CSS and 161 no CSS. CSS-patients more often reported postprandial pain (87 % vs. 72%, p=0.007), weight loss (85% vs. 70%, p=0.006), adapted eating pattern (90% vs. 79%, p 0.005) and diarrhea (35% vs. 22%, p 0.023). If none of these risk factors were present, the probability of CSS was 13%, if all were present the probability was 60%. Adapted eating pattern (OR 3.1, 95% CI 1.08-8.88) and diarrhea (OR 2.6, 95% CI 1.31-5.30) were statistically significant in multivariate analysis.

Conclusion:

In patients with splanchnic artery stenosis the clinical history is of limited value for detection of CSS. A diagnostic test to detect ischemia is indispensable for proper selection of patients with splanchnic artery stenosis who might benefit from treatment.

Introduction

The classical presentation of patients with chronic gastrointestinal ischemia, also called chronic splanchnic syndrome (CSS) consists of postprandial abdominal pain, weight loss and an abdominal bruit. However, it has been shown that this classical triad is present in a minority [1-4]. In CSS, the postprandial pain typically starts 15-30 minutes after the meal, may last for 2-3 hours and may result in fear of eating. The reduced caloric intake for fear of eating causes the serious weight loss. Changes in bowel habits, usually diarrhea, may sometimes occur [1,4,5]. Nausea, dyspepsia with fullness, bloating and pain after mental stress or exercise has also been mentioned [6,7]. Data on the clinical presentation depend on retrospective studies reporting on case series of 20 to 144 patients [1,3]. To our knowledge no prospective studies in patients with splanchnic artery stenosis comparing the clinical history in those with and without ischemia have been published. Thus, the precise role of clinical features in diagnosing CSS is unknown.

The prevalence of asymptomatic splanchnic artery stenosis increases with age up to 30-50% in elderly subjects [8,9]. In the majority of subjects these stenosis remain asymptomatic (chronic splanchnic disease or CSD) while in some CSS develops. Splanchnic artery stenosis is caused by atherosclerosis in most cases. If ischemic complaints have developed in presence of extrinsic compression of the celiac artery by the arcuate ligament of the diaphragm, the Celiac Artery Compression Syndrome (CACS) is diagnosed. Among young women this is the most prevalent cause of CSS [10]. Still, most subjects with compression of the celiac artery remain asymptomatic.

We and others have demonstrated that measurement of an increased pCO_2 in the gastric and small bowel lumen is indicative of local ischemia [11,12]. This local pCO_2 stems from buffering of protons produced during anaerobic metabolism in the mucosal tissue, and is present in all studied ischemia models [12]. The pCO_2 can be measured with a nasogastric balloon-tipped catheter attached to modified capnograph, and allows for semi-continuous measurement. An abnormal tonometry test after exercise or test meals allowed for accurate selection of patients who may benefit treatment of vessels stenosis [3,13].

Because the number of 'incidentally found' splanchnic artery stenosis will increase as a result of increased use of high resolution CT scan and MRI, the risk of over diagnosis and overtreatment is quite conceivable. It would therefore be desirable to establish the sensitivity, specificity and positive and negative predictive value of the various parameters in the medical history that may specifically point to the presence or absence of clinical relevant ischemia. That would allow for better identification of patients in whom diagnostic work up, like tonometry, and treatment would be indicated and in whom it could be omitted. Our group, a nationwide referral centre for splanchnic vascular disorders, has ample experience with analysis and treatment of this complex group of patients [11,14].

During the last decade 40-50% of patients with splanchnic artery stenosis who were referred where diagnosed with CSS [11,15]. The aim of this study was to assess risk factors for CSS in the medical history of patients with splanchnic artery stenoses and if these risk factors can be used to identify patients with high and low risk of CSS.

Patients and methods

Patient selection and data collection

All patients referred for possible CSS undergo a standardized diagnostic work-up as previously reported [13]. All data are recorded in a database. For this study, we included data of all patients referred between 1 February 2006 and 31 May 2009. Exclusion criteria were: 1) incomplete diagnostic work-up (no tonometry and no imaging or patients who were not discussed in our Multi-DisciplinaryTeam (MDT) for splanchnic ischemia, 2) previous treatment for CSS, 3) Non-Obstructive Mesenteric Ischemia (NOMI) i.e. gastrointestinal ischemia in absence of splanchnic artery stenosis, 4) alternative diagnosis found during evaluation, 5) follow up less than three months after treatment or patients lost to follow up after treatment

Medical history and clinical features

All patients were asked to complete a questionnaire (see appendix). The questions were based on our initial studies and relevant literature [3,4,6,10,11]. The medical history notes of the two experienced main investigators (JKO and RHG) were also analyzed to maximize the potential of valuable factors. Both investigators have over 20 years of experience in the field of CSS. A clinical feature (e.g. weight loss) could be scored in both the questionnaire and medical history notes.

Duplex ultrasound

Duplex ultrasonography (DU) was performed after six hours of fasting. DU was performed using a standard protocol. The definition of normal and stenotic artery origins was based on the criteria published by Moneta et al [15].

Tonometry

The principles of air tonometry have been described before [2,11]. Exercise tonometry was performed before, during, and after 10 minutes of submaximal exercise. The criteria as published by Otte *et al.* were used to define a positive test result [11]. In the 24 hour-tonometry, standardized meals were given to patients to provoke ischemia [3]. The criteria published by Mensink *et al.* were used to define a positive test result [16,17].

Angiography

Digital subtraction angiography of the splanchnic arteries was performed if the result of tonometry and/or duplex ultrasound was abnormal. The origins of the splanchnic vessels were visualized during expiration and inspiration as described previously [3].

Diagnosis and follow-up

The results of the diagnostic work-up were discussed in the MDT consisting of a gastroenterologist, a vascular surgeon and an interventional radiologist and a consensus diagnosis was made. The initial diagnosis was based on 1) clinical presentation, 2) presence of splanchnic artery stenosis and 3) results of tonometry. The diagnosis

was classified as CSS, CSD or no CSD (alternative diagnosis). In this study, the CSS group consisted of 1) CSS due to atherosclerotic stenosis and 2) CSS due to eccentric celiac artery compression by the arcuate ligament with ischemia (CACS). Only patients with the diagnosis CSS were considered for treatment.

The final diagnosis was based on the outcome of follow-up, including the effects of treatment. In treated patients the diagnosis was sustained if symptoms were severely reduced or completely resolved after successful revascularization of the affected vessels. If an alternative explanation for the complaints was found, the diagnosis was adjusted. The final diagnosis was used for the analysis.

Treated patients were scheduled for follow-up. The first follow up appointment was 3 months after treatment, and thereafter every 6 months in the first two years for assessment of the medical history and a duplex ultrasound scan. Untreated patients were not seen on a regular basis in our centre but were further treated by the referring physician. From a previous study it was learned that this is a safe strategy [3]. Two patient groups were constructed based on their final diagnosis sustained on follow up (figure 1).

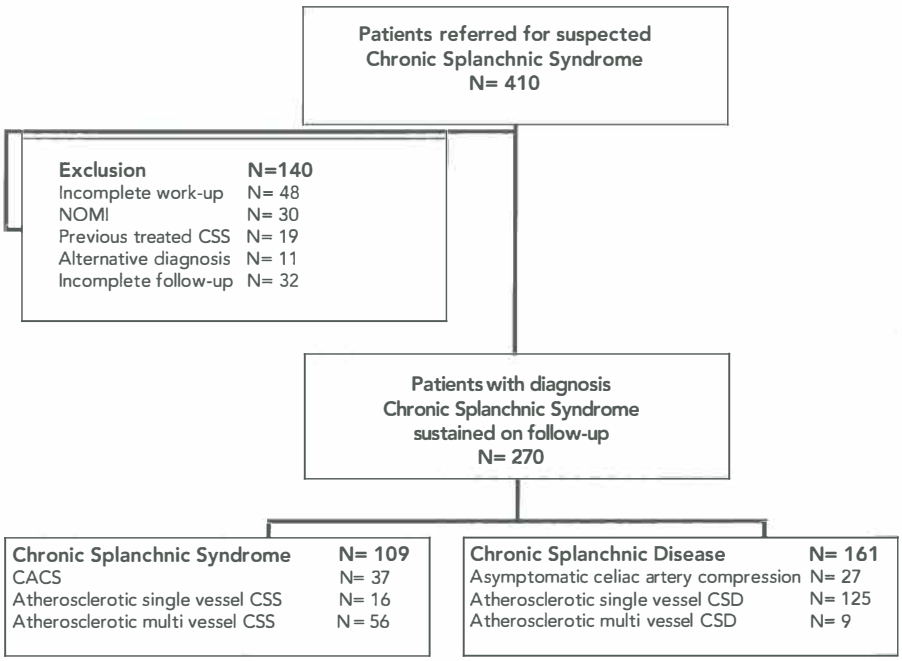

Figure 1. Flowchart of study protocol

CSS= Chronic splanchnic syndrome, NOMI= non-obstructive mesenteric ischemia, CACS=Celiac artery compression syndrome, CSD=Chronic splanchnic disease

Statistical analysis

Data were analyzed with the Statistical Package of Social Sciences (SPSS inc. Chicago, Illinois). Continuous data was expressed as mean (standard deviation) for normal variables and median (range) for non-normal variables. Nominal variables were expressed as the percentage of patients positive for this variable over the total number scored in the patient category.

Data between CSS and non-CSS patients were compared using a χ^2-test or Fisher's exact test, as appropriate, for nominal variables, or student-t-test or Wilcoxon's Rank Sum test, as appropriate, for continuous data. Relevant clinical features for the diagnosis of CSS were selected by a univariate analysis. Clinical features of CSS, significant at $P<0.15$ in univariate analysis and scored in ≥ 100 patients were eligible for multivariate logistic regression analysis. For these factors, sensitivity, specificity, positive predictive value, and negative predictive value was calculated. $P<0.05$ value was considered statistical significant. Non-significant variables were removed one by one from the full model, until the model significantly deteriorated, based on the -2 log likelihood. With these results a predictive model was constructed and interaction between variables was tested if necessary. These data were expressed as odds ratio with 95% confidence interval (95%CI).

Results

Patient characteristics

In the study period, 410 patients were referred for analysis of suspected CSS. The flow chart of the study is presented in figure 1. 270 patients with chronic abdominal symptoms and stenosis of at least one splanchnic artery were eligible for analysis. 109 patients had the final diagnosis CSS (72 with CSS and 37 with CACS) and 161 were diagnosed with CSD. Patient characteristics are outlined in table 1.

CSS, CACS and CSD

Overall clinical presentation of patients with CACS was comparable to patients with atherosclerotic CSS. For the CACS cohort the duration of complaints was longer (18 vs. 7 months p=0.03, weight loss was less common in the CACS patients (72% vs. 91%, p=0.01) and more patients with CACS experienced pain during stress (50% vs. 27%o=0.02). For further analysis, patients with CACS and atherosclerotic CSS were taken together and compared with CSD patients.

In patients with CSS, mean age was 54 (range 16-84) and 33% was male. In the CSD the mean age was 53 (range 15-84) and 41% was male (not significant). Results from univariate analysis between CSS and CSD patients are presented in table 2. The mean duration of symptoms was shorter in CSS vs. CSD (10.5 vs. 14.0 months, p= 0.02). Postprandial pain was significantly more often reported in CSS patients (87 vs. 72%, p=0.007). Time between end of the meal and onset of the pain was not statistically significant between the two groups. Diarrhea and weight loss were significantly more often reported in patients with CSS compared to CSD (diarrhea 35 vs. 22%, p=0.02,

Table 1. Characteristics of patients with final diagnosis CACS, CSS and CSD.

Patient characteristics Total group n= 270, 102 Male, median age 53 (range 15-84)	Atherosclerotic CSS (n=72)	CACS (n=37)	CSD (n=161)
Sex (Male: Female)	30 : 42*	6 : 31#	66 : 95
Median age in years (range)	65 (33-84)$*	34 (15-75)#	52 (16-84)
Mean Body Mass Index in kg/m² (SD)	22.5 (4.5)	21.8 (3.7)#	23.5 (4.6)
Diabetes	14%	0%#	11%
Hypertension	44%$$**	3%##	16%
Hypercholesterolemia	11%	6%	6%
Coronary artery disease	28%$*	0%#	14%
Peripheral artery disease	51%$$**	0%##	25%
Earlier episode of colonic ischemia	4%	3%	1%
Smoking	54%$	28%#	48%
Family members with atherosclerosis	74%$*	58%	57%
Median duration of follow up in months (range)	10 (1-37)	15 (2-39)	8 (1-43)
Median duration of symptoms in months (range)	7.0 (0.2-120)	18 (1-252)	14,0 (0,1-408)
Patients without follow up	6	0	122

CSS: chronic splanchnic syndrome, CACS: celiac artery compression syndrome, CSD: chronic splanchnic disease.
$ p<0.05 for atherosclerotic CSS vs. no CSS, $$ p<0.001 for atherosclerotic CSS vs. CSD;
* p<0.05 for atherosclerotic CSS vs. CACS, **p<0.001 for atherosclerotic CSS vs. CACS; #
p<0.05 for CACS vs. CSD; ## p<0.001 for CACS vs. CSD.

weight loss 85 vs. 70%, p=0.006). The results of the univariate analysis of the clinical features are presented in table 3. Their individual potential to distinguish CSS from CSD is low with the highest accuracy for diarrhea (61%) and the lowest accuracy for postprandial pain and change in eating habits (both 49%).

Risk stratification The main clinical features with p<0.15 in the univariate analysis and scored in >100 patients were used for multivariate logistic regression analysis.. Adapted eating pattern (OR 3.1, 95%, CI 1.08-8.88) and diarrhea (OR 2.6, 95%, CI 1.31-5.30) were statistically significant clinical features in multivariate analysis. A prediction model was constructed from four significant of the clinical features in univariate analysis. These included 'adapted eating pattern', 'weight loss', 'diarrhea' and 'postprandial pain'. This model could be tested in the 164 patients in whom the presence of absence of these factors was known (table 4). The probability for CSS in absence of the four criteria was 13% (number needed to treat 7.7). All four criteria

Table 2. Major features from medical history notes and questionnaire of CSS patients versus CSD patients; results from the univariate analysis.

Clinical Feature	Scored[Δ]	CSS (n=109)	CSD (n=161)	p-value
Postprandial pain	228	87 %	71%	0.007*
Median interval end of meal – onset of pain in minutes (range)	106	15 (5-120)	15 (5-360)	0.84
Median duration of pain in hours (range)	113	2.0 (0,3-96)	2.0 (2.0-72)	0.09*
Weight loss	262	85%	70%	0.006*
Median weight loss in kg/month (range)	194	1.8 (0.1-12)	1.9 (0.3-14.3)	0.85
Adapted eating pattern [$]	168	90%	79%	0.07*
Smaller portions	129	100%	90%	0.02
Pain after exercise	262	62%	67%	0.45
Pain with stress	257	35%	41%	0.34
Pain in relation with posture	211	64%	56%	0.23
Diarrhea	264	35%	22%	0.02*

Total group n=270. CSS: chronic splanchnic syndrome, CSD: chronic splanchnic disease. *used for multivariate analysis; [Δ]: number of patients in which the clinical feature was described. [$]smaller portions, change in meal composition

Table 3. Performance of significant clinical features to diagnose chronic splanchnic syndrome

Clinical feature	Sensitivity	Specificity	PPV	NPV	Accuracy
Postprandial pain	72%	35%	41%	66%	49%
Weight loss	80%	30%	44%	75%	52%
Change in eating habits	90%	21%	44%	75%	49%
diarrhea	34%	78%	49%	65%	61%

PPV=positive predictive value, NPV=negative predictive value.

Table 4. Probability of chronic splanchnic syndrome in the study population

Clinical features present in medical history	Probability of CSS	NNT (mean)
0	13%	7.7
1	14 – 29%	7.1 – 3.4 (5.3)
2	18 – 51%	5.5 – 2.0 (3.8)
3	37 – 51%	2.7 – 2.0 (2.4)
4	60%	1.7

The clinical features were 'adapted eating pattern', 'diarrhea', 'postprandial pain' and 'weight loss'. NNT: numbers needed to treat.

were absent in 7 patients of whom one had multivessel CSS. The probability for CSS in presence of all four criteria was 60% (number needed to treat 1.7). This was present in 6 patients in whom 4 actually had CSS. 151 Patients had two or three clinical features present in their medical history.

Discussion

The medical history of patients with splanchnic artery stenosis may help to predict the presence of chronic gastrointestinal ischemia (chronic splanchnic syndrome or CSS). In addition to the well-established ischemic complaints of pain after meals and weight loss we found diarrhea and the presence of an adapted eating pattern as significant clinical features of CSS. In our study population the likelihood for CSS rose from 13% when none of these four factors was present to 60% when all were present. Therefore, even in patients with the most suspicious clinical presentation of CSS, 40% of them where actually not suffering from their splanchnic artery stenosis (chronic splanchnic disease or CSD), and treatment would be not indicated.

Postprandial pain and the presence of weight loss were present in the majority of both CSS and CSD patients and did not help in differentiation between CSS and CSD. BMI and degree of weight loss was not statistically significant either. Probably this is all caused by selection bias because for most referring physicians, postprandial pain and weight loss trigger the suspicion of CSS. These are considered typical for GI ischemia [5]. The two complaints that were independent risk factors for the presence of CSS in this study, diarrhea and an adapted eating pattern, are less well established. Both factors have been described before in the clinical presentation of CSS as atypical features, but have not been appreciated as important factors [4].

The constructed model combining the two supposed classical risk factors (postprandial pain, weight loss) with adapted eating pattern and diarrhea had a modest per-

formance in risk assessment of CSS. Furthermore, the performance to safely exclude low-risk patients from diagnostic work up was poor. In the absence of all four complaints, there was still a 13% probability on the presence of CSS. If this patient group would not undergo the diagnostic work-up, this would lead to a minor reduction in workload, but at the expense of missing important pathology. The disappointing role of the medical history in ischemia detection is in line with a recent paper by Sana et al. who assessed the clinical features of CSS as well. Their strongest predictors were 'postprandial pain', 'weight loss per kg/month'. Their data support our conclusion that clinical features alone have a limited value to correctly diagnose CSS [18].

The risk stratification model, as described in table 4, may be used in daily clinical practice to estimate the risk for CSS if the severity of splanchnic artery stenosis is taken into consideration Especially in patients with single vessel involvement a low pre-test probability might justify a wait and see policy, as the prognosis on mortality is excellent and the risk on acute bowel infarction is absent. In multivessel disease, with a significant chance of bowel infarction and death, proper evaluation is indicated even in absence of ischemic complaints [19,20]. Further studies, in non-tertiary centres are needed to evaluate the utility of the constructed risk model.

As clinical history alone is insufficient to discriminate between CSS and CSD, other diagnostic tests are needed. Both air tonometry and visible light spectroscopy are methods to detect mucosal ischemia in the GI-tract. The technical principles of both techniques have been extensively described elsewhere [2,21]. Noord et al showed that both tests have almost similar accuracy [21]. For tonometry, Otte et al showed in a large patient cohort that sensitivity and specificity for detection of ischemia were 78% and 92% respectively [11] In a cohort with 28 patients ultimately diagnosed with CSS, 57% would have been missed with clinical history alone while the accuracy of tonometry was 80% [13].

This analysis was performed from a large data set to identify factors in the clinical history that would help to pre-select patients who would need further analysis, and hopefully eliminate individuals with a very low probability on CSS. The results of this study indicate that clinical history alone is clearly insufficient and a test that accurately demonstrates ischemia is needed.

This study has its methodological shortcomings. First, patients were included that were referred to our specialized working group. This has probably filtered out patients with less typical presentation for GI ischemia. Probably, most patients with splanchnic artery stenosis are asymptomatic in daily life [22,23]. Therefore, using the same four criteria in a non-tertiary centre will probably lead to even lower likelihoods for CSS. Second, the method of data collection has its drawbacks. In order to avoid missing data we included both the notes of two highly experienced clinicians, as well as a standard questionnaire. The medical notes from the former contained more factors known to be specific for CSS, and less non-specific issues. Both clinicians only reported remarkable items in the medical history notes, either positive or negative, with regard to CSS as diagnosis. Parameters from the medical history notes could only be scored as present or absent when specifically mentioned. If it was not mentioned it could not be ascertained with 100% certainty whether that item had been discussed

with the patient. Therefore, it was scored as 'missing'. This resulted in a reliable data-set, at the expense of loss of information. The data from the questionnaire were more complete on these less-typical complaints but may have been subject to interpretative problems.

In conclusion, in patients with splanchnic stenosis four parameters determine the likelihood of having gastrointestinal ischemia. These factors are postprandial pain, weight loss, adapted eating pattern and diarrhea. The likelihood rose from 13% to 60% when none or all were present. This is not sufficient to make a decision which patient to treat. An accurate function test to demonstrate ischemia is needed for an accurate diagnosis of chronic gastrointestinal ischemia.

Appendix

Questionnaire

- Postprandial pain
  - After a meal I experience
    1. No pain
    2. Pain, but it does not interfere with daily life
    3. Pain, with small impairment on daily life
    4. Pain, with severe impairment on daily life
    5. Pain, with total impairment on daily life
- Pain with exertion
  - After physical exercise I experience
    1. No pain
    2. Pain, but it does not interfere with daily life
    3. Pain, with small impairment on daily life
    4. Pain, with severe impairment on daily life
    5. Pain, with total impairment on daily life
- Pain with stress
  - During mental stress, I experience
    1. No pain
    2. Pain, but it does not interfere with daily life
    3. Pain, with small impairment on daily life
    4. Pain, with severe impairment on daily life
    5. Pain, with total impairment on daily life
- Relationship with posture
  - Do you experience more pain in a certain posture?
    Yes or no.
- Stools
  - How many times a day do you defecate? .....
    1. What is the consistency?
    2. Separate hard lumps, like nuts (hard to pass)
    3. Sausage-shaped, but lumpy
    4. Like peanut butter a sausage or snake, smooth and soft
    5. Watery, no solid pieces. Entirely liquid
- Weight loss
  - Did you lose weight recently?
    Yes or No
- Degree of weight loss (kg/month)
  - I lost.....kilograms of weight during the last.....weeks / months / years

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Chapter

The cardiovascular risk profile of atherosclerotic gastrointestinal ischemia is different from other vascular beds

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Abstract

Background:

The distribution of cardiovascular risk factors in patients with chronic gastrointestinal ischemia due to atherosclerosis of the splanchnic vessels (chronic splanchnic syndrome, CSS) is not well studied. The aim of this study was to determine the cardiovascular risk factor pattern in CSS patients.

Methods:

From April 2003 to September 2007, atherosclerotic risk factors in consecutive CSS patients were prospectively compared to the general atherosclerotic risk profile in Western Europe and worldwide risk profile of coronary heart disease, peripheral artery disease and cerebral vascular disease.

Results:

97 of 376 analyzed patients were diagnosed with CSS. Data of 90 patients were available for analysis (7 excluded because of incomplete data). Mean age was 63 years (range 28-86) with 74% of female sex. 59 % of the patients had atherosclerotic disease in other vascular beds. Smoking was reported in 57 %, increased bodyweight in 21%. Hypercholesterolemia was present in 53%, hypertension in 62%, Diabetes in 21%.

Conclusions:

The atherosclerotic risk profile in CSS patients differed from other atherosclerotic diseases with a female preponderance, lower incidence of obesity/increased bodyweight, diabetes, hypertension and hypercholesterolemia. Reduced caloric intake, related to the postprandial pain, may explain the observed differences.

Introduction

The prevalence of splanchnic artery stenosis is reported up to 50% in the Celiac artery (CA) and 30% in the superior and inferior mesenteric arteries (SMA, IMA) [1,2]. In subjects over the age of 65 a stenosis of the CA and/or SMA was found in 17.5 % [3]. This prevalence is comparable to that of atherosclerotic stenosis of the lower extremities (14.5%) and the coronary arteries (22%) [4].
The cardiovascular risk profile for coronary artery disease (CAD), peripheral arterial disease (PAD) and cerebral vascular disease CVD) are well studied and are characterized by a high prevalence of hypertension, hypercholesterolemia, diabetes, increased bodyweight and smoking, although the pattern of this risk profile differs between CAD, CVD and PAD [4-7].
The cardiovascular risk profile of symptomatic splanchnic artery stenosis (chronic splanchnic syndrome, CSS) is largely unknown. A female preponderance has been reported, which is in contrast to all other atherosclerotic vascular disorders [8].

The purpose of this study was to assess the cardiovascular risk factors in patients with CSS and compare them to the risk profile of atherosclerotic vascular disease in other arterial beds.

Methods

Since 1996, a multidisciplinary team for the diagnosis and treatment of gastrointestinal ischemia,was established in a large, non-academic teaching hospital in the Netherlands (Medical Spectrum Twente, Enschede). Consecutive patients referred between April 2003 and September 2007 for evaluation of suspected chronic gastrointestinal ischemia, were eligible for this study. All patients underwent a standardized work-up including assessment of clinical symptoms, medical history, physical examination, duplex ultrasound and/or digital subtraction angiography of the splanchnic vessels and gastrointestinal tonometry. All patients were discussed in multidisciplinary setting. The diagnosis 'chronic splanchnic syndrome' was made if all following criteria were met:

1. Complaints consistent with GI-ischemia
2. Significant stenosis (defined as > 70 %) stenosis of one or more abdominal arteries
3. Pathological gastrointestinal tonometry

The work-up has been described in detail before [9-11]. For this study, we used only the patients with CSS due to atherosclerosis. This study was approved by the medical ethical committee of our hospital.

Risk profile of cardiovascular disease

Structured questionnaires concerning lifestyle and diet were administered. Information about personal and family history of cardiovascular disease, and risk factors (hypertension, diabetes) was obtained from the medical charts, the questionnaire and medical history taking. The definitions from Bhatt et al were used to define Coronary Artery Disease (CAD), Cerebral Vascular Disease (CVD), and Peripheral Vascular Disease (PVD) [7].

The presence of hypertension was based on a previous diagnosis, medication use, or a systolic blood pressure of >140 mm Hg, diastolic blood pressure of >90 mm Hg on repeated measurements. Blood samples for serum cholesterol, triglyceride, glucose, homocystein, creatinin were drawn in fasting state. Hypercholesterolemia was defined as a total cholesterol level > 6.2mmol/l of LDL-cholesterol >2.5mmol/l, physician diagnosis, or medication use. Diabetes was defined as self-reported physician diagnosis, use of diabetes medication, fasting glucose of > 7.0mmol/l or non-fasting glucose > 11.1mmol/l. An elevated homocystein level was defined as >15umol/l. Overweight was defined as a BMI between 25 and 30kg/m^2, obesity as a BMI of >30kg/m^2. We compared our results with data from a large epidemiological study of patients with CAD, PAD and CVD worldwide [5 7].

Statistical analysis

Data were expressed as mean and standard deviation or median and range, when appropriate. Subgroup analysis for sex, vessel involvement (single- versus multi-vessel) and concomitant cardiovascular disease was performed. The group comparisons were performed using unpaired t test or Fisher's exact test when appropriate. Non-parametric data were tested using a Mann-Whitney test. To assess differences in risk factors between CSS and outpatients with atherothrombosis in Western Europe, a binomial test was performed. A p-value < 0.05 was considered significant.

Results

From the 376 patients evaluated for suspected chronic gastrointestinal ischemia, 97 patients were included in this study. Reasons for exclusion were: 1) no significant splanchnic artery stenosis or GI-ischemia present (n=137), 2) GI-ischemia in presence of normal splanchnic vessels (n=28), 3) non-atherosclerotic CSS (n=89), 4), CSD (n=25). In 7 patients, laboratory data were incomplete; therefore data of 90 CSS patients were available for analysis. The mean age of the study group was 63 years (range 28-86) years and 67 (74%) were female. Single- and multi-vessel CSS was diagnosed in respectively 28 and 62 patients. The baseline characteristics of the study population are presented in table 1.

Table 1. Baseline characteristics, concomitant disease and measurements in patients with chronic splanchnic syndrome (n=90)

Baseline characteristics	
Age (range)	63 (28-86)
Male sex (%)	26 %
Smoking (%)	58 %
Body mass index (kg/m²)	22 ± 4.5
Systolic art pressure (mm Hg)	136 ± 25
Diastolic art pressure (mm Hg)	74 ± 11
Hypertension* (%)	62 %
Hypercholesterolemia‡ (%)	53 %
Diabetes† (%)	21 %
Overweight (%)	17 %
Obesity (%)	4 %
Family history vascular disease (%)	68 %
Previous cardiovascular disease (%)	59 %
Coronary heart disease (%)	33 %
Peripheral vascular disease (%)	34 %
Cerebral vascular disease (%)	13 %
Medication use	
Antiplatelets or anticoagulation (%)	76 %
Lipid-lowering agents (%)	44 %
Laboratory measurements	
Glucose (mmol/l)	5.9 ± 2.3
Cholesterol (mmol/l)	4.3 ± 1.2
HDL-cholesterol (mmol/l)	1.3 ± 0.5
LDL-cholesterol (mmol/l)	2.4 ± 1.0
Triglycerides (mmol/l)	1.5 ± 0.7
Creatinine clearance (Cockroft) (ml/min)	67 ± 27
Fasting homocystein (µmol/l)	14.7 ± 6.3

Data are presented as percentage or mean (Standard deviation)
*Systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or use of blood pressure lowering agents
‡Cholesterol > 6.1 mmol/l or LDL-cholesterol > 2.5 mmol/l
†Patients taking glucose-lowering agents or fasting glucose > 7.0 mmol/l or non-fasting glucose > 11.1 mmol/l

Medical history

The medical history revealed hypercholesterolemia in 44 (49 %), hypertension in 52 (58 %) and diabetes in 15 (17 %) of the patients. A history of coronary, cerebral or peripheral artery disease was present in 30 (33 %), 12 (13%) and 31 (34 %) patients. Lipid-lowering agents were used by 38 of 44 (86%) previously diagnosed hypercholesterolemia patients, blood pressure lowering agents by 37 of 52 previously diagnosed hypertensive patients (71%). 14 (93%) of the diabetes mellitus patients reported the use of anti-diabetic medication.

Physical examination

The mean body mass index was 22.0 (SD 4.5) kg/m^2; overweight was found in 15 (17 %) patients, and obesity in four (4 %) patients. The mean blood pressure was 136 (SD 25) mm Hg systolic and 74 (SD 11) mm Hg diastolic. From the 56 patients (62%) with hypertension, this was newly diagnosed in four patients.

Laboratory results

The serum total cholesterol at referral was mean 4.3 (SD 1.2) mmol/l, HDL-cholesterol 1.3 (SD 0.5) mmol/l, LDL-cholesterol 2.4 (SD 1.0) mmol/l, triglyceride was 1.5 (SD 0.7) mmol/l. Fasting serum total cholesterol was elevated in 4 patients not previously diagnosed with hypercholesterolemia; therefore 48 (53%) patients had hypercholesterolemia. Serum glucose measurements did not reveal new cases of diabetes mellitus. An elevated fasting homocystein was found in 38 (43 %) patients.

Table 2. Distribution of atherosclerotic risk factors according to singe/multivessel disease in patients with CSS (n=90)

Baseline characteristics	Single vessel n=28	Multi vessel n=62	p-value
Age (mean)	61	63	p=0.53
Smoking (%)	57	58	p=0.94
Medication use			
Anticoagulation (%)	76	75	p=1.00
Lipid lowering agents (%)	48	43	p=0.80
Body mass index (kg/m^2)	21.9 ± 4.9	22.1 ± 4.4	p=0.84
Concomitant disease			
Family history vascular disease (%)	76	78	p=1.00
Previous cardiovascular disease (%)	50	63	p=0.25
Hypertension (%)	43	71	p=0.11
Hypercholesterolemia (%)	39	60	p=0.07
Diabetes (%)	29	18	p=0.24

Data are presented as percentage or mean (Standard deviation)

Subgroup analysis

No clinical significant differences in the prevalence of risk factors between male and female CSS patients were observed although fasting serum cholesterol in the female patients was slightly higher (3.8 ± 0.9 vs. 4.4 ± 1.3mmol/l, p=0.01). The baseline characteristics of CSS patients with single or multi-vessel distribution are presented in table 2. No significant differences in atherosclerotic risk factors between patients with single and multi-vessel disease were observed. There was no statistically significant difference in BMI between single vessel multi-vessel CSS (21.9 +/- 4.9 vs. 22.1 +/- 4.4, p=0.84). No clinical significant difference in the prevalence of risk factors between patients with (n=53) or without (n=37) concomitant atherosclerotic disease in other vascular beds was found except for increased BMI (28.3% in patients with CSS and concomitant atherosclerotic disease vs. 11% in CSS without concomitant atherosclerotic disease, p<0.05).

Comparison to symptomatic atherosclerosis in other vascular beds

The risk profile of CSS patients was compared to the risk profile of atherothrombotic patients in Western Europe (figure 1) [7]. In the CSS cohort, a strong female preponderance was observed and the prevalence of diabetes, BMI >25kg/m², diabetes mel-

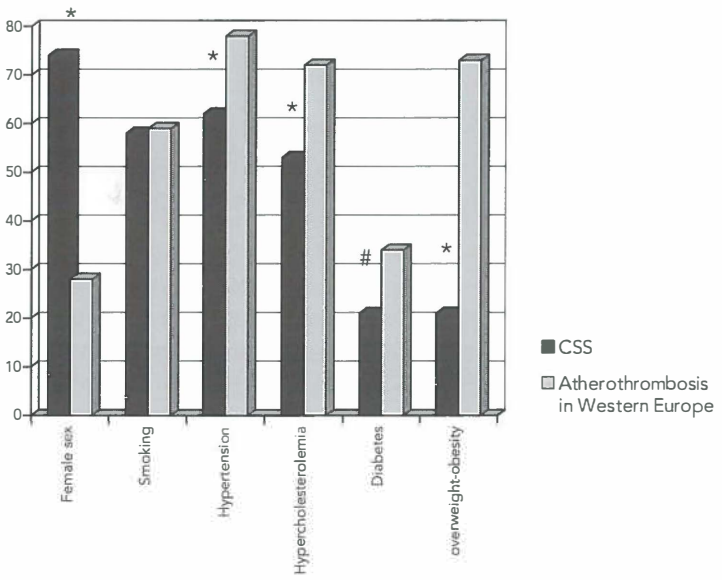

Figure 1. Atherosclerotic risk profile of patients diagnosed with chronic splanchnic syndrome compared with outpatients in Western Europe diagnosed with atherotrombosis. Definitions of cohort 'atherothrombotic risk profile in Western Europe' derived from Bhatt et al[7].
* p<0.0001 compared to outpatients with atherothrombosis in Western Europe
# p<0.005 compared to outpatients with atherothrombosis in Western Europe

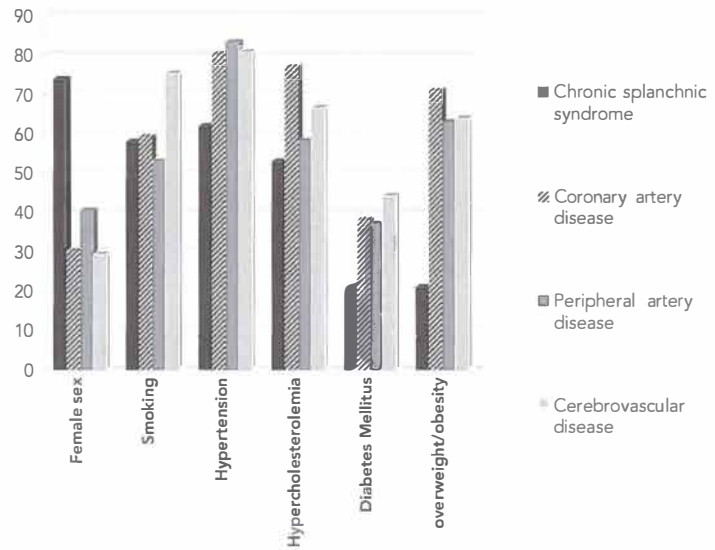

Figure 2. Atherosclerotic risk profile of chronic splanchnic syndrome in comparison to coronary artery disease, peripheral artery disease and cerebrovascular disease worldwide [7].

litus and hypercholesterolemia was significant lower compared to the general atherothrombotic risk profile in Western Europe.

In comparison to patients with coronary artery disease (CAD), peripheral arterial disease (PAD) and cerebral vascular disease (CVD) worldwide, the strong female preponderance and a lower prevalence of overweight/obesity and diabetes in CSS patients was found (figure 2) [5 7].

Discussion

This is one of the first studies to define the cardiovascular risk factor profile in patients with symptomatic chronic gastrointestinal ischemia. The risk profile of patients with CSS differed significantly from that observed in other vascular beds. The most striking differences were a strong female preponderance and a low prevalence of overweight and obesity.

In a recent large international study to the atherosclerotic risk factor profile in over 60.000 patients the risk profile for atherothrombosis in Western Europe was characterized by a high prevalence of hypertension, hypercholesterolemia, diabetes and overweight/obesity [7]. The risk profile of CSS in our study differed markedly from those in CVD, CAD and PAD worldwide and to the risk profile of atherothrombosis in Western Europe [5-7].

The low prevalence of overweight may be well explained by the reduced caloric intake in patients with CSS. The majority of these patients report postprandial pains, resulting in fear of eating and reduced caloric intake [10]. This seems a logical explanation for the observed difference in prevalence of obesity/obesity between CSS and atherosclerosis in other vascular beds. The 19% lower prevalence of hypercholesterolemia and 13% lower prevalence of diabetes mellitus in CSS patients may also be explained by the reduced caloric intake. Another effect of this reduced caloric intake could be that it has a direct beneficial effect on the atherosclerosis process, as has been recently reconfirmed [12,13]. Furthermore, as CSS patients attempt to maintain their caloric intake just at or below the pain threshold, all ingredients for optimal and prolonged collateral formation are present [14]. Probably, accelerated atherosclerosis after revascularization of the stenotic splanchnic vessels may occur.
The high proportion of female patients of 74% in CSS patients is in line with earlier observations in CSS patients and contrasts with studies in CAD, PAD and CVD with a strong male preponderance [7,15-19]. A similar pattern was seen in an autopsy study in 120 subjects, where female patients had a two times higher prevalence splanchnic artery stenosis compared to men. In this study, this difference could partly be explained by the fact that in the studied population, women were on average 16 years older than men [8]. We currently have no explanation for this gender difference.
In this study, the poor adherence to management of cardiovascular risk factors was similar to the literature [7]. Once again, as treatment of CSS results in restoration of normal caloric intake, this probably leads to development or even acceleration of atherosclerosis. Active treatment of the risk factors is therefore highly recommended.
Limitations of this study are the small size of our cohort, especially compared to the large studies in CVD, CAD and PAD. As CSS is still a rare disease and most vascular centres assessed a few patients suspected for CSS per year, studying a large cohort prospectively is challenging. Furthermore, the prevalence of some risk factors was based on a questionnaire and therefore ascertained some errors. Finally often slightly different definitions for the several risk factors are used in studies which may difficult a strict head-to-head comparison of the results.

In conclusion, CSS seems to be a disease of mainly the female gender. The atherosclerotic risk profile in CSS differs strikingly from other vascular beds, with a very low incidence of overweight and obesity, a low incidence of hypercholesterolemia and diabetes. These differences are probably related to adaptation of caloric intake to avoid postprandial pain.

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Chapter 10

Summary and conclusions

Summary and conclusions

This thesis deals with three entire different aspects of gastrointestinal (GI) ischemia. **Chapter 1** starts with an introduction and describes the aims and outlines of the thesis.

The first part of the thesis focuses on **the role of GI-ischemia in the pathophysiology of exercise induced gastrointestinal symptoms.**
In **chapter 2** the pathophysiology and the management of the most prevalent exercise-induced gastrointestinal symptoms are described. First, the effect of physical exercise on GI-motility, secretion and absorption is described. Both GI-ischemia and increased sympathetic nervous system activity might cause dysmotility in the GI-tract. Gastrointestinal secretion and absorption seem to be unaffected during normal physical exercise, but may be affected at extreme exercise levels.
The increase in sympathetic nervous system activity caused by physical exercise is probably an important factor in alteration of GI-physiology during exercise. Due to vasoconstriction of the splanchnic vessels, blood is redistributed from the splanchnic organs to the working muscle. This may cause GI-ischemia. GI-ischemia may lead to endotoxemia, microscopic or macroscopic gastrointestinal blood loss and diarrhoea. Exercise induced diarrhoea remains unknown is probably caused by a combination of altered motility and dysfunction of the mucosa by gastrointestinal ischemia. Upper GI-symptoms are probably caused by altered GI-motility resulting in symptoms like regurgitation, chest pain, and nausea/vomiting. Advices to prevent GI-symptoms consist of lowering the exercise intensity and preventing dehydration.
The prevalence of exercise induced GI-symptoms is the highest in competitive athletes. The prevalence in the largest group of athletes, the recreational athletes, has not been well studied.
In **chapter 3** the results of an internet based epidemiological study among participants of the 2006 'Enschede Marathon' are described. The 'Enschede Marathon' is an official run with distances of 5, 10, 21 and 42 kilometers with over 7000 competitors. The study was designed to assess the prevalence of the most common GI-symptoms during and the first 24 hours after the race and contained questions to assess risk factors for GI-complaints. The questionnaire was distributed among 2076 participants with a response rate of 68%. 45% had at least one GI-complaint during running, and 11% of the runners suffered from serious GI complaints during the run. The latter was significantly related to runners not familiar with fluid ingestion, younger age, female sex and non-completion of the run. 2.7% of the runners had complaints during the first 24 hours after the run. This was significantly related to female sex and GI complaints during the run. Prevalence of GI complaints during and after running is low compared to other studies, which is partly caused by the definition of 'symptomatic' we used in this study. The risk factors for GI-symptoms were to other studies. The relation between complaints during the run and the type of complaints afterwards suggests a role for GI ischemia in the pathophysiology of running induced GI symptoms.
Over the last 10 years, some athletes have been specifically referred to the Medi-

cal Spectrum Twente Enschede for the evaluation of exercise-induced gastrointestinal symptoms. In these patients, GI-ischemia was suspected to cause their symptoms.
In **chapter 4**, we describe the diagnostic work-up and management of three of these patients with exercise-induced GI-ischemia. We show that the spectrum of gastrointestinal and systemic symptoms caused by exercise induced GI-ischemia may have a wide variation. In three patients, GI-ischemia was demonstrated using gastric exercise tonometry. In our view, gastric tonometry is mandatory for the diagnosis and management of this complex patient group. In the first patient, an isolated celiac artery stenosis was found; after incision of the left crus of the diaphragm, she was asymptomatic and the results of gastric tonometry improved. The other two patients had non-occlusive ischemia associated with high exercise intensity. Reduction of the exercise intensity resulted in the complaints disappearing. This case series show that gastrointestinal complaints during and after physical exercise may be caused by gastrointestinal ischemia. This diagnosis may be established by careful medical history taking and exercise tonometry.
In **chapter 5** we describe our experience with prolonged exercise tonometry in the evaluation of exercise induced GI-complaints. Prolonged exercise tonometry is a 30 minutes, incremental exercise test aimed to assess a) GI-ischemia during submaximal exercise b) the development and severity of GI-ischemia during maximum intensity exercise and c) the relation between GI-ischemia and the development of GI-symptoms during exercise tonometry. In 10 years, 12 patients were studied. 50% had GI ischemia during submaximal exercise. During prolonged exercise tonometry, all athletes had gastric and jejunal ischemia during maximum intensity exercise. No difference could be found in severity of ischemia between patients with GI- symptoms during the exercise test and asymptomatic athletes. Athletes with symptoms tended to higher gastric gradients when exercise intensity was increased. Advices aimed at limiting GI ischemia were successful to reduce complaints in the majority. The high percentage of ischemia during submaximal exercise and the higher gastric gradients in response to exercise in symptomatic athletes, might suggest more susceptibility for the development of ischemia during exercise.

The second part of this thesis comprises two chapters studying **the methods of CO_2 measurement in the gastrointestinal tract.** Air tonometry has been successfully used for many years to detect a rise in luminal pCO_2. Such a rise is strongly associated with gastrointestinal ischemia. Luminal pCO_2 rises as a result from buffering of protons produced during anaerobic glycolysis and decreased CO_2 clearance due to decreased splanchnic blood flow. Exercise tonometry is a ten minutes exercise test at submaximal exercise intensity used to provoke the development of GI-ischemia during exercise. The combination of splanchnic artery stenosis and exercise induced splanchnic vasoconstriction has been shown to be accurate in GI-ischemia detection. However, for the use in exercise tonometry, the ten minutes measurement interval is unfavourable.
In **chapter 6**, the Tonocap®, the current measurement device used during exercise tonometry, was evaluated. The influence of the timing, length and amplitude of a CO_2

peak within the dwell time of the Tonocap® on the measurement outcome, as well as the influence of covering the balloon with water on the measurement characteristics of the Tonocap® was evaluated. The timing, length and amplitude of a CO_2 peak in relation to the measurement cycle of the Tonocap® had profound impact on the measurement results. Changes in pCO_2 during the last minutes of the dwell time had the largest influence on the measurement results. As was appreciated with the experiments with changing the applied amplitude, the speed of CO_2 diffusion into the tonometry balloon was no limiting factor. The effect of covering of the tonometry balloon on the measurement characteristics is the result of buffering of CO_2 in the fluid surrounding the balloon. Although air tonometry has been shown to have a high accuracy in detecting gastrointestinal ischemia in daily practice, its measurement characteristics still warrant new methods for continuous luminal CO_2 measurement.
In **chapter 7,** a hydrogel-based CO_2 sensor, specifically engineered for continuous CO_2 measurement in the GI-tract by Mesa+ group of the Universiteit Twente (S Herber, project leader prof P Bergveld and prof A van de Berg), was evaluated in vitro and during exercise tonometry. The hydrogel-based CO_2 sensor consists of a pH-sensitive hydrogel in a bicarbonate solution mounted on a catheter-tip pressure sensor. It is covered by a gas permeable membrane. The hydrogel will swell or shrink dependent on the CO_2. Because it is tightly mounted on the pressure sensor, this will be reflected by pressure changes.
During the in-vitro test, the new sensor was compared to air tonometry during instant and gradual increasing the pCO_2 in a small equilibration chamber. During the in vivo study, three healthy volunteers during a stepwise incremental exercise test, hyperventilation and an artificial CO_2-peak. The hydrogel carbon dioxide sensor enabled fast and accurate pCO_2 measurement in a controlled environment but proved to be very temperature dependent and was too unstable for clinical use. Many of these problems were related tot the handmade assembly and would be diminished with automated assembly.

In the last part of the thesis, **the clinical presentation and atherosclerotic risk profile of patients with chronic gastrointestinal ischemia** was studied.
In **chapter 8,** risk factors for chronic gastrointestinal ischemia (chronic splanchnic syndrome or CSS) in the medical history of patients with splanchnic artery stenosis were assessed and it was evaluated whether these risk factors could be used to identify patients with high and low risk of CSS. All relevant data from a questionnaire as well as medical notes were collected in a database and CSS patients were compared to no-CSS patients. The final diagnosis CSS diagnosis was based on the outcome of follow-up, including the effects of treatment and this was used for analysis. With the results a prediction model for the risk on CSS was constructed. 109/270 analyzed patients had CSS. CSS-patients more often reported postprandial pain, weight loss, an adaptation of eating pattern and diarrhea. Adapted eating pattern and diarrhea were statistically significant in multivariate analysis. If none of these four risk factors were present, the probability of CSS was 13%, if all were present the probability still was only was 60%. Adapted eating pattern and diarrhea were statistically significant in

multivariate analysis. It was concluded that in patients with splanchnic artery stenosis the clinical history is of limited value for detection of CSS. This study once again emphasizes the need diagnostic test to detect ischemia to allow proper selection of patients with splanchnic artery stenosis who indeed have CSS and might therefore benefit from treatment.

In **chapter 9,** the distribution of cardiovascular risk factors in patients with chronic gastrointestinal ischemia due to atherosclerosis of the splanchnic vessels was studied. Currently, little is known about the cardiovascular disease risk factors of patients with CSS. It seems reasonable that a certain risk profile applies in these patients as differences in the risk profile between coronary artery disease, cerebral vascular disease and peripheral artery disease have been assessed. From April 2003 to September 2007 we prospectively analysed atherosclerotic risk factors in consecutive patients referred for suspected gastrointestinal ischemia. Data of 90 CSS patients were available, of whom 74% was female. Smoking was reported in 57 %, increased body weight in 21%. Hypercholesterolemia was present in 53%, hypertension in 62%. Diabetes was present in 21%. Compared to the overall atherosclerotic risk profile in Western Europe, a strong female preponderance and a significant lower prevalence of increased bodyweight, diabetes and hypercholesterolemia was observed in CSS patients. The management of cardiovascular risk factors in CSS was suboptimal.

The female preponderance has been recently confirmed but is still unexplained. The difference in prevalence overweight, diabetes and hypercholesterolemia might be well explained by the reduced caloric intake in patients with CSS due to fear of eating. As treatment of CSS results in restoration of normal caloric intake, development or even acceleration of atherosclerosis may be expected which warrants follow-up and active treatment of cardiovascular risk factors.

Chapter

11

Samenvatting en conclusies

Samenvatting en conclusies

Dit proefschrift onderzoekt drie geheel verschillende aspecten van maagdarmischemie. **Hoofdstuk 1** is de introductie van dit proefschrift. De onderzoeksdoelen worden in dit hoofdstuk uiteengezet.

De focus van het eerste deel van het proefschrift is gericht op **de rol van maagdarmischemie in de pathofysiologie van inspanningsgebonden maagdarmklachten.**
In **Hoofdstuk 2** wordt een uitgebreid overzicht gegeven van de pathofysiologie en behandeling van de meest voorkomende inspanningsgebonden maagdarmklachten. Eerst worden de effecten van lichamelijke inspanning op de gastrointestinale motiliteit en secretie/absorptie beschreven. Zowel de toegenomen sympatische zenuwactiviteit als maagdarmischemie kan de motiliteit van het maagdarmkanaal verstoren. De secretie en absorptie van maag- en darmsappen is vermoedelijk tijdens normale lichamelijk inspanning ongestoord, maar zou verstoord kunnen raken tijdens extreme inspanning.
De toegenomen sympatische zenuwactiviteit door lichamelijke inspanning is waarschijnlijk een belangrijke factor in de veranderde fysiologie van het maagdarmkanaal tijdens lichamelijke inspanning. Door vasoconstrictie van de splanchnische vaten wordt bloed van de buikorganen naar de actieve spieren gedistribueerd. Dit kan maagdarmischemie veroorzaken. Maagdarmischemie kan leiden tot verhoogde permeabiliteit van de darmwand met daardoor endotoxemie, micro- en macroscopische gastrointestinaal bloedverlies en diarree door schade aan het darmslijmvlies. Diarree tijdens of na lichamelijke inspanning wordt waarschijnlijk veroorzaakt door meerdere factoren, zoals een veranderde darmmotiliteit en disfunctie van de darmmucosa door maagdarmischemie. Klachten van de bovenste tractus digestivus, zoals regurgitatie, retrosternale pijn, boeren, misselijkheid en braken worden vermoedelijk vooral door dysmotiliteit veroorzaakt. Verlaging van de inspanningsintensiteit en preventie van uitdroging zijn belangrijke adviezen om inspanningsgebonden maagdarmklachten te voorkomen.
De prevalentie van inspanningsgebonden maagdarmklachten is het hoogste in topsporters. De prevalentie in de grootste groep sporters, de recreatieve atleten, is weinig onderzocht.
In **hoofdstuk 3** worden de resultaten van studie beschreven waarbij deelnemers van de 'Enschede Marathon' in 2006 werden onderzocht. Bij dit onderzoek werd gebruik gemaakt van een vragenlijst welke via e-mail onder de deelnemers werd verspreid. Bij de 'Enschede Marathon' konden de 7000 deelnemers kiezen tussen vier afstanden; 5, 10, 21 of 42 kilometer. Het onderzoek was opgezet om de prevalentie van de meest voorkomende maagdarmklachten tijdens, en gedurende de eerste 24 uren na de gelopen afstand vast te stellen. De vragenlijst werd naar 2076 deelnemers verstuurd waarbij 68% de vragenlijst retourneerde. 45% van de respondenten had tenminste één maagdarmklacht tijdens de lichamelijke inspanning bemerkt, 11% had ernstige klachten gehad. Ernstige klachten kwamen vaker voor bij jonge atleten, vrouwen, atleten die hadden gegeten en gedronken tijdens de loop maar dit niet gewend waren,

en atleten die waren uitgevallen. Bijna 3% had klachten gedurende de eerste 24 uren na de gelopen afstand. Dit was significant gerelateerd aan het vrouwelijk geslacht en het hebben van klachten tijdens de loop. De prevalentie van maagdarmklachten in deze studie was laag vergeleken met andere studies. Dit wordt vermoedelijk deels veroorzaakt door een andere definitie van 'de aanwezigheid van een klacht'. De risicofactoren om klachten te krijgen verschilden niet van andere studies. De relatie tussen het hebben van maagdarmklachten tijdens en na de loop suggereert een rol voor maagdarmischemie in de pathofysiologie van door hardlopen veroorzaakte maagdarmklachten.

In de afgelopen tien jaar zijn verscheidende atleten naar het Medisch Spectrum Twente te Enschede verwezen voor evaluatie van hun inspanningsgebonden maagdarmklachten. Bij de meesten werd vermoed dat hun klachten werden veroorzaakt door maagdarmischemie als gevolg van lichamelijke inspanning.

In **hoofdstuk 4** beschrijven we de diagnostiek en behandeling van drie patiënten met inspanning gerelateerde maagdarmischemie. We laten zien dat de klinische presentatie van deze aandoening erg kan variëren. Bij deze drie patiënten werd maagdarmischemie aangetoond door gebruik te maken van inspanningstonometrie. Volgens ons is tonometrie noodzakelijk voor een juiste diagnostiek en behandeling van deze complexe patiënten groep. Bij de eerste patiënt werd een stenose van de truncus coeliacus vasgesteld op basis van een zogenoemd truncus coeliacus bandje. Na het klieven van dit bandje was ze klachtenvrij en verbeterde de inspanningstonometrie. De overige twee patiënten hadden maagdarmischemie zonder aantoonbare stenosen van de splanchnische vaten en werden gediagnosticeerd met niet obstructieve maagdarmischemie veroorzaakt door een hoge inspanningsintensiteit. Verlaging van de inspanningsintensiteit resulteerde in het verdwijnen van de klachten. Deze klinische les toont aan dat maagdarmklachten tijdens en na lichamelijke inspanning kan worden veroorzaakt door maagdarmischemie. Deze diagnose kan worden gesteld na nauwkeurige anamnese, afbeelding van de splanchnische vaten en inspanningstonometrie.

In **hoofdstuk 5** beschrijven we onze ervaringen met de verlengde inspanningstonometrie in de diagnostiek naar inspanningsgebonden maagdarmklachten. Verlengde inspanningstonometrie bestaat uit een dertig minuten durende inspanningstest in toenemende intensiteit gericht op het vaststellen van a) maagdarmischemie tijdens submaximale inspanning, b) de aanwezigheid en ernst van maagdarmischemie tijdens maximale inspanning en c) de relatie tussen het optreden van maagdarmklachten en de aanwezigheid van maagdarmischemie. In totaal werden in tien jaar tijd twaalf patiënten onderzocht. 50% had maagdarmischemie tijdens submaximale inspanning en tijdens maximale inspanning hadden alle onderzochte atleten maag- en jejunumischemie. We konden geen verschil aantonen tussen de ernst van ischemie en de aanwezigheid van klachten tijdens de inspanningstest. Atleten met klachten tijdens de inspanningstest neigden naar een sterkere stijging van de maag CO_2 gradiënt in reactie op een stijging van de inspanningsintensiteit. Adviezen gericht op reductie van maagdarmischemie tijdens inspanning waren effectief om maagdarmklachten te voorkomen. Het hoge percentage van maagdarmischemie tijdens submaximale in-

spanning en de hogere maaggradiënten bij de atleten met klachten tijdens de inspanningstest suggereren mogelijk een toegenomen kwetsbaarheid op het ontwikkelen van maagdarmischemie tijdens lichamelijke inspanning.

Het tweede deel van het proefschrift omvat twee studies die de **methoden van CO_2 meting in het maagdarmkanaal** onderzoeken. Luchttonometrie wordt al vele jaren met succes gebruikt om een stijging van luminaal CO_2 te meten. Een dergelijke stijging is sterk geassocieerd met de ontwikkeling van maagdarmischemie. De luminale CO_2 concentratie stijgt als gevolg van buffering van protonen welke worden geproduceerd tijdens anaerobe glycolysering en een verminderde klaring van CO_2 door de verminderde splanchnische doorbloeding. Inspanningstonometrie is een tien minuten durende inspanningstest met een submaximale inspanningsintensiteit welke wordt gebruikt om maagdarmischemie uit te lokken. De door inspanning geprovoceerde splanchnische vasoconstrictie in aanwezigheid van splanchnische vaatstenosering is een accurate methode gebleken om maagdarmischemie aan te tonen. Echter, het tien minuten meetinterval van de tonometer is intrinsiek ongunstig in klinische situaties waar continue CO_2 meting dringend gewenst is.
In **hoofdstuk 6** wordt beschreven hoe de gebruikte tonometer, de Tonocap® uitgebreid getest werd waarbij de invloed van de timing, lengte en amplitude van een CO_2 piek tijdens het 10 minuten meetinterval op de meetuitkomst wordt onderzocht. Verder wordt vastgesteld wat de invloed is van het bedekken met water van de tonometrie ballon op de meetkarakteristieken van de Tonocap®. Het bleek dat de timing, lengte en amplitude van een CO_2 piek inderdaad een grote invloed had op de meetuitkomsten. Veranderingen in pCO_2 tijdens de laatste minuten van het meetinterval resulteerden in de grootste veranderingen in de meetuitkomst. Uit de testen met de wisselende amplituden van de CO_2 piek kon worden opgemaakt dat de snelheid van CO_2 diffusie over het membraan van de tonometrie ballon geen beperkende factor was. Het bedekken van de tonometrie ballon met water gaf duidelijke effecten op de meetuitkomst welke verklaard kunnen worden door buffering van CO_2 in het water. In de dagelijkse praktijk is bewezen dat de Tonocap® een hoge accuratesse heeft in het aantonen van maagdarmischemie. Desondanks blijft de wens tot continue CO_2 meting bestaan.
In **hoofdstuk 7** wordt een hydrogel bevattende CO_2 sensor, speciaal ontwikkeld voor continue CO_2 meting in de tractus digestivus zowel in vitro als in vivo getest en vergeleken met de Tonocap®. De nieuwe sensor is ontwikkeld door de Mesa+ groep van de Universiteit Twente (S Herber, project leider prof P. Bergveld en prof A. van de Berg). De genoemde sensor bestaat uit een pH-gevoelige hydrogel in een bicarbonaat oplossing gemonteerd op een druksensor. Het geheel wordt omvat door een gasdoorlatend membraan. De hydrogel zwelt en krimpt afhankelijk van de pCO_2 en dit wordt door de druksensor waargenomen.
De hydrogel sensor werd head-to-head vergeleken met de Tonocap® tijdens een in vitro test waarbij in een testopstelling geleidelijke en plotselinge CO_2 veranderingen werden geproduceerd. Tijdens de in vivo test verrichtten drie gezonde vrijwilligers een 30 minuten durende inspanningstest met oplopende inspanningsintensiteit, een

hyperventilatietest en werd een kunstmatige CO_2 piek in de maag gecreëerd. De hydrogel sensor was gedurende de in vitro testen goed in staat om snel en accuraat CO_2 veranderingen te meten. Bij de in vivo testen bleek de sensor erg temperatuursgevoelig en te instabiel om in de dagelijkse praktijk te gebruiken. Vermoedelijk worden deze problemen vermoedelijk veroorzaakt door de handmatige montage van de sensor. Machinale montage en correctie van de voorspelbare temperatuursgevoeligheid zou deze problemen kunnen aanpakken.

In het laatste deel van het proefschrift worden studies beschreven die de **klinische presentatie en atherosclerotisch risicoprofiel van patiënten met chronische maag-darmischemie** onderzoeken.
In **hoofdstuk 8** wordt onderzocht of de anamnese van patiënten met bewezen stenosen van een of meer splanchnische vaten bepaalde kenmerken bevat die het mogelijk maakt een risicoinschatting te geven op de aanwezigheid van chronische maagdarmischemie (ook genoemd chronisch splanchnisch syndroom, CSS). Data werden verzameld door statusonderzoek en een vragenlijst die door de patiënten werd ingevuld en in een database verwerkt. De anamnese van CSS patiënten werd vergeleken met niet-CSS patiënten. De diagnose CSS werd gesteld door een combinatie van anamnese, vaatafbeelding en tonometrie waarbij de diagnose na follow-up werd gebruikt in de analyse. Met de resultaten van de analyse werd een risico-model geconstrueerd. 109 van de 270 patiënten werd met CSS gediagnosticeerd. CSS patiënten rapporteerden vaker postprandiale pijn, gewichtsverlies, een verandering van eetpatroon en diarree. Een verandering van eetpatroon en de aanwezigheid van diarree waren statistisch significant in de multivariate analyse. Als geen van deze vier factoren aanwezig was in de anamnese, was de kans op CSS 13%. De kans op CSS was 60% als alle factoren aanwezig waren in de anamnese. Wij concluderen naar aanleiding van deze studie dat de anamnese alleen onvoldoende vermogen heeft om bij patiënten met bewezen vaatstenosen de categorie met CSS te onderscheiden van de patiënten met asymptomatische vaatstenosen. Deze studie onderstreept nogmaals de noodzaak om mucosale ischemie aan te tonen om de juiste patiënten te selecteren die baat hebben bij behandeling van de splanchnische vaatstenosen.
In **hoofdstuk 9** wordt het cardiovasculair risicoprofiel van patiënten met maagdarmischemie door atherosclerotisch splanchnisch vaatlijden onderzocht. Momenteel is slechts weinig bekend over het cardiovasculaire risicoprofiel van patiënten met CSS. Het lijkt logisch dat, analoog aan coronaire hartziekte, cerebrovasculaire aandoeningen en perifeer vaatlijden, een typisch risicoprofiel bestaat. Van april 2003 tot september 2007 werd bij patiënten, verwezen vanwege het vermoeden op CSS, het cardiovasculair risicoprofiel prospectief geanalyseerd. Data van 90 patiënten waren beschikbaar, waarvan 74% van het vrouwelijk geslacht. 57% rookte, 21% had een toegenomen body mass index (BMI). Hypercholesterolemie, hypertensie en diabetes mellitus was aanwezig bij 53, respectievelijk 62 en 21% van de geincludeerde patiënten. Vergeleken met het atherosclerotisch risicoprofiel in West Europa, typeerden CSS patiënten zich door en sterke vrouwelijk overwicht en een significant lagere prevalentie van toegenomen BMI, diabetes mellitus en hypercholesterolemie. De behandeling

van de cardiovasculaire risicofactoren was suboptimaal. Het vrouwelijke overwicht bij patiënten met CSS is recentelijk bevestigd in een andere studie maar is nog steeds onverklaard. Het verschil in overgewicht, diabetes en hypercholesterolemie kan mogelijk worden verklaard door de verminderde inname van calorieën door postprandiale pijn en eetangst. Behandeling van de vaatstenosen zal leiden tot normalisatie van de inname van calorieën waardoor ontwikkeling of versnelde atherosclerose in andere vaatbedden verwacht kan worden. Dit rechtvaardigt nauwkeurige follow-up en actieve behandeling van de diverse cardiovasculaire risicofactoren.

Curriculum Vitae

Rinze Willem Frederik ter Steege werd op 29 juni 1978 geboren in Hoogeveen. In 1996 behaalde hij het diploma Voorbereiden Wetenschappelijk Onderwijs (atheneum) aan het Menso Alting College te Hoogeveen. Hij studeerde Geneeskunde aan de universiteit in Groningen. Het doctoraal examen werd behaald in juni 2000 en het arts-examen in augustus 2002 na de co-schappen te hebben doorlopen in het Medisch Centrum Leeuwarden en het Martiniziekenhuis te Groningen. In september 2002 tot 1 april 2004 werkte hij als arts-assistent longziekten, interne geneeskunde en maag-darm-lever-ziekten in het Martiniziekenhuis te Groningen. Van 1 april 2004 tot 1 oktober 2004 werkte hij als poortarts in het Refajaziekenhuis te Stadskanaal waarna hij van 1 oktober 2004 tot 1 januari 2005 weer als arts-assistent MDL in het Martiniziekenhuis Groningen werkte.
Van juli 2005 tot juli 2006 deed hij onderzoek op de afdeling MDL van het Medisch Spectrum Twente. Van januari 2007 tot januari 2008 deed hij zijn vooropleiding interne geneeskunde in het Medisch Spectrum Twente (opleider dr WM Smit) en vervolgens het perifere deel van de opleiding tot maag-darm-lever arts onder leiding van prof dr JJ Kolkman. Van februari 2010 tot en met januari 2012 werkte hij als maag-darm-lever arts in opleiding in het Universitair Medisch Centrum Groningen (opleider prof dr JH Kleibeuker). Vanaf 1 mei 2012 zal hij als maag-darm-lever arts in het Medisch Spectrum Leeuwarden gaan werken.

Rinze is getrouwd met Rinske en ze hebben twee dochters, Lynke en Marin.

Dankwoord

Dankwoord

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