The Clinical Impact of Tonometry on the Diagnosis and Treatment of Gastrointestinal Ischemia

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The Clinical Impact of Tonometry on the Diagnosis and Treatment of Gastrointestinal Ischemia

De rol van tonometrie bij de diagnose en behandeling van maag-darm ischemie

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CONTENTS

LIST OF ABBREVIATIONS

AUC = area under the curve
BMI = body mass index
CA = celiac artery
CACS = celiac artery compression syndrome
CO2 = carbon dioxide (gaseous)
CSD = chronic splanchnic disease
CSS = chronic splanchnic syndrome
DSA = digital substraction angiography
GET = gastric exercise tonometry
IMA = inferior mesenteric artery
MT-GI = multidisciplinary team on gastro-intestinal ischemia
NOMI = non-occlusive mesenteric ischemia
PCO2 = tension of carbon dioxide in kPa
SD = standard deviation
SMA = superior mesenteric artery

1 Aims and outline

AIMS AND OUTLINE

Intragastric production and accumulation of CO2 is an early marker of gastrointestinal ischemia. This CO2 can be easily measured using gastrointestinal tonometry. Until now evidence of the clinical impact of tonometry is sparse. The development of gastric exercise tonometry (GET) by Kolkman led to a practical diagnostic test. Recent work by Otte validated this GET in healthy subjects. In a first group of patients suspected for the chronic splanchnic syndrome (CSS), GET showed its additional diagnostic value.

In this thesis we challenged the use of GET in a broader clinical perspective. First in a notoriously 'difficult' patient group: patients with unexplained upper abdominal pain and a single vessel splanchnic stenosis. Secondly in a large cohort of patients with unexplained abdominal pain, suspected of CSS.

Finally, we studied tonometry for prolonged periods after meals. Earlier studies using tonometry after meals showed unreliable results. Still, the majority of patients with CSS have postprandial pain, and less during or after exercise. Further, some patients are unable to perform exercise. We therefore decided to give gastrointestinal tonometry before and after meals a second chance. The initial problems with postprandial tonometry were related to gastric acid production and meal-based CO2 production. With this in mind, we firstly tested different meals for their CO2 production and absorption in a stomach-like in vitro model. This was followed by a healthy subjects study using the most ideal (standard) test meals, combined with high dose proton pump inhibition. Finally, we tested the potential clinical value of prolonged tonometry in patients suspected of CSS, using the analysis derived from the healthy subjects study.

PART 1: INTRODUCTION

Chapter 2 is a review on non-occlusive mesenteric ischemia (NOMI).This disorder is well-known and frequently diagnosed on the intensive care unit. The physiological background of splanchnic vasoconstriction as response to intravascular volume reduction, and its gradual transition into NOMI are highlighted. Using these insights, derived from intensive care literature, the clinical features of ischemic colitis and non-occlusive bowel infarction are finally discussed. It is postulated that NOMI is not rare, as often assumed, but a frequent phenomenon in gastroenterology.

Chapter 3 gives an interim analysis of the first group of CSS patients. In this paper our experience and opinion concerning diagnostic procedures and therapeutic options are presented. The difference between single and multivessel disease, between CSD and CSS, and the crucial role of gastric exercise tonometry and the possible role of prolonged tonometry before and after meals in these patients are highlighted.

PART 2: METHODOLOGY

In **chapter 4** different standard meals were tested in a 'stomach-like-model' for their CO2 profile: ability to absorb and / or produce CO2. In this way the, theoretically, most ideal meal(s) were selected, to be used in future studies with prolonged tonometry.

In **chapter 5** the results of a healthy volunteers study with prolonged gastric and jejunal tonometry are presented. The selected standard meals were used in a maximally controlled environment, including maximal acid suppression and standardized meals. The prolonged gastric and jejunal tonometry was performed for 24 hours, and 3 standard meals were tested.

PART 3: CLINICAL STUDIES

In **chapter 6** we evaluated the outcome of patients with a significant, isolated, celiac artery stenosis. A comparison was made between patients with ischemic complaints, single-vessel CSS, or not, in a large patients group with a significant celiac artery stenosis. GET was used as indicator of gastrointestinal ischemia and decisions on diagnosis and treatment were made by a multidisciplinary working group. The patients had follow-up and GET was repeated after the revascularization.

In **chapter 7** a large cohort of patients with splanchnic stenosis is described. The patient characteristics, clinical presentations and outcome of treatment are presented. All patients had a standardized diagnostic work-up, and decisions on diagnosis and treatment were made by a multidisciplinary team. A practical guideline for patients with abdominal complaints and (possible accidental) splanchnic stenosis is provided.

Chapter 8 shows the results of the first, retrospective, study of the use of prolonged tonometry in a group of patients evaluated for possible CSS.

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Non-occlusive mesenteric ischaemia: a common disorder in gastroenterology and intensive care

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ABSTRACT

Non-occlusive mesenteric ischaemia is characterised by gastrointestinal ischaemia with normal vessels. In gastroenterology it is recognised as rare disease occasionally causing acute bowel infarction or ischaemic colitis. From intensive care literature this disorder is recognised as early phenomenon during circulatory stress. This early mucosal ischaemia then leads to increased permeability, bacterial translocation, and further mucosal hypoperfusion. The damage is mainly produced during reperfusion following ischaemia with fresh inflow of oxygen and outflow of waste products into the systemic circulation.

The mechanisms underlying non-occlusive mesenteric ischaemia include macrovascular vasoconstriction, hypoperfusion of the tips of the villi and shunting. It is very common in critically ill and perioperative patients, but also in pancreatitis, renal failure and sepsis.Treatment options include aggressive fluid resuscitation and careful choice of vasoactive drugs. Control of reperfusion damage and new endothelin-antagonist are potentially useful new treatment options.

INTRODUCTION

There is a striking difference between the perception of gastroenterologists and intensivists on non-occlusive ischaemia (NOMI). In gastroenterology, NOMI is recognized as possible cause of ischaemic colitis[1] and as a rare cause of acute mesenteric infarction[2]. It is well established that different drugs (including ergotamine, digitalis and vasoactive agents) and underlying cardiovascular and renal disease predispose to this condition. In contrast, in intensive care medicine and anaesthesiology, NOMI is regarded as a very common disorder in critically ill patients or during major operations. In the majority of studies NOMI was strongly associated to an adverse outcome[3]. It is generally referred to as mucosal acidosis, gastrointestinal hypoperfusion or mucosal ischaemia. Still, it is currently unclear whether these patients, NOMI is just another expression of their severe illness, or whether it is a major factor in development of multiple organ failure (MOF) syndrome. The mechanisms underlying mucosal ischaemia are increasingly well established. The aim of this chapter will therefore be to review the literature on both ends of the spectrum of this disorder, characterized by insufficient oxygen delivery despite normal vessel patency. We will go beyond the commonly accepted NOMI features of acute mesenteric infarction and ischaemic colitis and look at the mechanisms of mucosal perfusion, cytokine production, bacterial translocation and ischaemic / reperfusion damage control.

NON-OCCLUSIVE ISCHAEMIA: AN EXTENSION OF THE NORMAL PHYSIOLOGICAL RESPONSE

Normal blood flow: introduction

The ultimate goal of perfusion of any organ is to maintain its metabolism and integrity. The metabolism is dependent upon delivery and utilisation of sufficient amounts of oxygen to meet metabolic demands. With ischaemia, or dysoxia, the amount of oxygen utilised by the organ is insufficient to maintain the aerobic glycolytic processes with onset of anaerobic metabolism. Dependent on the severity and time this may result in ischaemic damage and propensity for ischaemia / reperfusion damage. At first glance this seems a straightforward problem: reduced perfusion by mesenteric vasoconstriction simply causes reduced flow and finally ischaemia; sufficient blood flow prevents or restores this mesenteric ischaemia. However, several factors, with complex interference patterns, determine the balance between oxygen demand and delivery in the GI-tract. The most important factors are (1) blood flow through the main arteries, (2) blood oxygen and haemoglobin content, (3) blood distribution in the bowel wall, (4) oxygen exchange within the mucosa from base to tip, (5) matching of metabolism and perfusion within the mucosa and (6) the cell's capacity to utilize oxygen (see Table 2.1 for examples).

Table 2.1. Pathophysiological mechanisms in gastrointestinal ischaemia

Pathophysiological mechanism	Examples of disorders	Importance
Reduced blood flow in mesenteric arteries	Occlusions of CA and SMA	Frequent, frequency of chronic mesenteric ischaemia unclear
	Occlusion of the IMA	Frequent with aortic surgery or spontaneous, rarely symptomatic
	Low flow states	Frequent: almost any (pre)shock syndrome causes mesenteric vasoconstriction
	Medications (epinephrine, digitalis)	Frequent on ICU's
	Drugs (cocaine)	Infrequent in hospital setting
	Strenous exercise	Probably frequent, may underly GI symptoms after exercise
Blood oxygen & haemoglobin	Anaemia, Severe hypoxia	None, other organs define outcome (heart, brain)
Cell capacity to utilize oxygen	Sepsis	Frequent in critically ill patients, may underly M.O.F. an bacterial translocation
Blood distribution in bowel wall	Low flow states (cardiogenic, septic, hemorrhagic shock)	Mucosal < serosal perfusion. Assessment of ischaemia only by intraluminal techniques (endoscopy, tonometry f.e.) not serosal inspection (laparatomy)
Oxygen exchange base to tip	Low flow states (cardiogenic, septic, hemorrhagic shock)	Probably frequent: 1) areas of low perfusion within normal regions 2) tips of villi ischaemic with normal crypts
Mismatch of metabolism & perfusion	Sepsis and other low flow states	Probably frequent: 1) areas of low perfusion within normal regions 2) tips of villi ischaemic with normal crypts

The main vessels: coeliac artery, superior mesenteric artery and inferior mesenteric artery

The gastrointestinal tract is perfused by three aortic branches: the coeliac artery (CA), superior mesenteric artery (SMA) and inferior mesenteric artery (IMA). Branches of these arteries enter the serosa of the gut on the mesenteric side to form a serosal vascular plexus around the gut. After penetration of the bowel wall, a dense submucosal plexus is formed. From this plexus arterioles penetrate the muscalaris mucosa to the superficial mucosal layers. At the mucosal tip they branch into an intense capillary network of capillaries and venules. Under fasting, basal conditions approximately 20% of the cardiac output goes through the splanchnic vasculature. The celiac artery is a large artery which supplies stomach, liver, part of the pancreas and proximal part of the duodenum. It receives 800 ml blood /min, divided in 350 ml/min to both the splenic and hepatic artery. The remaining 100-150 ml/min supplies stomach, duodenum and part of the pancreas. After a meal the celiac artery flow increases by 30% to 1100 ml/min[4]. The superior mesenteric artery has a similar diameter as the CA and supplies the distal part of the duodenum, the entire small bowel and the proximal colon. The basal SMA fllow is 500 ml blood /min, but increase by more than 150% after a meal with volumes up to 1400 ml/min[4]. The inferior mesenteric artery is relatively small and supplies

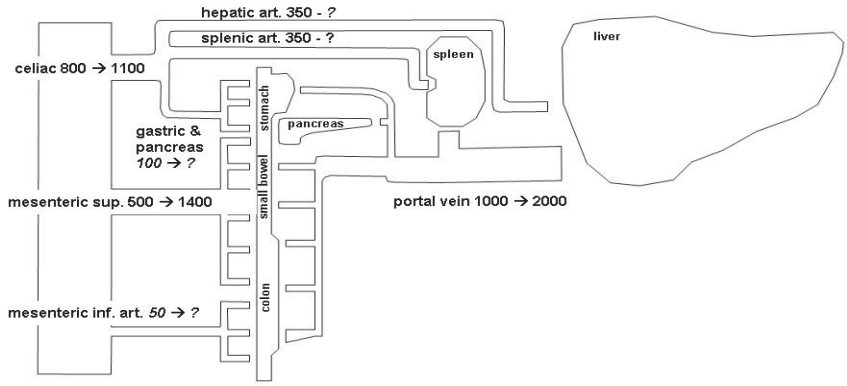

Figure 2.1. Distribution of basal and postprandial mesenteric blood flow.
The amounts are the mean from the literature, the numbers in italic have been calculated. The question marks indicate that solid figures for these vessels have not yet been established.

the distal colon. The blood enters the liver by two ways: 80% from the intestines and pancreas through the portal vein and 20% directly from the hepatic artery. The portal venous blood flow is 1200 ml in the fasting state, but may increase up to 2000 ml/min following a meal. The double vascularisation renders the liver relatively resistant to ischaemia.

Blood flow within the bowel wall layers

During hypoperfusion, the blood flow within the bowel wall is not evenly distributed and the relative flow to the mucosa or serosa my vary widely. In general, the metabolic active and vulnerable mucosa is protected at the expense of the serosal layers[5], probably by mucosal production of nitric oxide (NO), prostaglandins[6] and dopamine-1 receptor stimulation[7]. These receptors exert their effects through sphincters located immediately after the arteriole divides into several capillaries[8]. Despite this preserved mucosal flow, the villi of the mucosal layer are the most vulnerable area to hypoperfusion[9,10]. This is a direct consequence of the microvascular organisation with oxygen exchange over the entire length of the villus, with ischaemia at the tip, and adequate perfusion at the crypts.

Regulation of bowel wall blood flow

Vasoconstrictors

Endothelin-1. ET-1 is a potent vasoconstrictor that regulates vascular resistance. It is generated from endothelial cells and acts, after conversion by endothelin-converting enzyme, locally on the myogenic cells of the vascular wall[11]. ET-1 triggers either ETA receptors that cause vasoconstriction or ETB receptors that induce mild vasodilatation. In the bowel ETA receptors are present in the mucosa, submucosa and muscularis and play a pivotal role in the vasoconstrictory response of the mesenteric vessels[12]. In ischaemia-reperfusion and severe hemorrhagic shock, endothelin-1 levels were elevated and related to development of mu-

cosal ischaemia and ulcerations[13]. Inhibition of ET-1 increased the bowel hypoperfusion and ischaemia from circulatory stress[11].

Renin-angiotensin axis: ACE, AT-I and AT-II. The selective splanchnic vasospasm during many shock states may relate to a high sensitivity of the mesenteric vasculature to the renin-angiotensin axis[14], especially AT-II. In CABG patients an increased angiotensin II level was indeed associated with mesenteric ischaemia[15].

Catecholamines. Three catecholamine-like receptors can be identified in the mesenteric circulation. Stimulation of the α-1 receptors causes vasoconstriction, whereas β-2 and dopamine-receptor stimulation leads to mesenteric vasodilatation.

Vasodilatators

Nitric oxide (NO). NO has paradoxal effects on gastrointestinal perfusion and integrity. In physiological, low concentrations it is produced mainly by the mucosa and acts as vasodilator. Increase of NO can have beneficial effects in primary vasoconstrictive conditions, for example in prevention of nicotine-induced gastric mucosal hypoperfusion or gastric ulcerations. In pathological high concentrations, NO acts a free radical, similar to oxygen free radicals, with deleterious effects by direct impairment of mitochondrial energy production[16]. In many shock states NO is grossly elevated and indeed harmful, and in animal models inhibition of NO-production was beneficial[17].

Prostaglandins. Locally formed prostaglandins act as mucosal vasodilators especially during low flow states or following mucosal injury. Inhibition of cycloxygenase inhibition, the central action of all non-steroidal anti-inflammatory drugs, reduced mucosal vasodilation following shock; mucosal vasoconstriction and hypoperfusion is an important factor in NSAID-gastropathy.

Mesenteric vasoconstriction as physiological response in shock

All the above receptors and messengers act to balance perfusion to metabolic demands on any given occasion. The mesenteric circulation can be regarded as one of the prime reservoirs of blood volume to be utilized in circulatory stress. Already at the onset of circulatory shock, from whatever cause, the blood flow distribution changes by selective constriction and dilatation of different vascular beds. Almost invariably, the blood flow to the heart muscle increases, the brain perfusion is maintained, and perfusion of the muscles, skin and gut are reduced. Of these, the mesenteric vasoconstriction occurs early and profoundly[14] and even before haemodynamic instability arises[18]. This preferential splanchnic vasoconstriction can be triggered by different shock states, or by direct stimulation with vasoactive medications or nicotine and cocaine abuse. Only when the blood flow is reduced to less than 50% of normal basic flow, ischaemia of the gastrointestinal tract develops[3,10,19].

NON-OCCLUSIVE ISCHAEMIA: REDUCED FLOW AND MISMATCH

Splanchnic hypoperfusion and circulatory stress

The term NOMI indicates insufficient oxygen consumption for a given metabolic demand (dysoxia) despite normal arterial and venous vessel anatomy. As indicated above NOMI is recognized in surgery, radiology and gastroenterology as cause of acute mesenteric infarction and ischaemic colitis[2,20]. The same condition is described in intensive care medicine and anaesthesiology, but referred to as intramucosal acidosis or mucosal hypoperfusion. It was associated with poor outcome or the development of multiple organ failure. The main difference between NOMI as described in clinical gastroenterology and surgery and mucosal ischaemia / acidosis as appearing in the intensive care literature is the presentation of the patients. In gastroenterology and surgery patients are reported that presented with abdominal complaints, diarrhoea or abdominal pain. In the intensive care literature patients in the intensive care and operation theatre for mostly non-GI disorders, developed NOMI as a complication of their critical illness or major operation. The relative unawareness of the latter condition by gastroenterologists is illustrated by recent reviews where NOMI was identified only as a rare cause of infarction, to be diagnosed by angiography[2,20]. Not a single word was used to describe the role of NOMI as extension of the normal adaptive mechanism in circulatory stress.

Mismatch of mucosal blood and metabolism

During situations of limited blood flow, either locally or in the systemic circulation, a mismatch between metabolic demands and oxygen delivery has been shown in the gut, as in most organ systems. With microspheres infusion, fluorescent microscopy and vascular casting, the initial mesenteric damage is patchy and limited to the upper layers of the mucosa, away from the central arteriole[8]. With intravital microscopy during sepsis in rats wider variations in erythrocyte velocity moving through the villous capillaries and arterioles were observed[21,22]. During haemorrhage and sepsis, a striking difference in blood flow and oxygenation between different villi was seen, with some well-perfused villi, amid de-oxygenated and ill-perfused villi. All these observations indicate microcirculatory disturbances and shunting during GI hypoperfusion[22-24]. This pattern of patchy ischaemia amid normally perfused areas may provide the explanation of findings in earlier sepsis studies that described normal overall mucosal oxygenation during mucosal ischaemia, and has been confirmed in septic patients[25]. Simply stated: some erythrocytes remain in capillaries far too long and will be completely desaturated, others will rush by in arteriolar shunts without any oxygen exchange, leaving the mucosa ischaemic.

Ischaemic damage: the crucial role of reperfusion

After the onset of ischaemia, three different processes can be distinguished. In acute arterial occlusion these processes occur sequentially; in non-occlusive ischaemia different stages can occur simultaneously, intermittently, or even repeatedly. For better understanding of their role in the complications of gastrointestinal ischaemia they will be discussed in chronological order.

The ischaemic phase

The effect of dimished oxygen utilization is a decrease in ATP formation causing ATP depletion and distortion of ATP-dependent cell membrane-bound enzymes. This results in distorted cell homeostasis causing cell swelling by electrolyte and water influx, which may lead to necrosis. The intestinal epithelial barrier function is reduced by weakening of the tight junctions, and bacterial translocation may be an early event[26]. The necrotic cells trigger an inflammatory response with release of several cytokines. In the swollen cells, calcium accumulates and this triggers hydrolysis of enzyme xanthine dehydrogenase into xanthine oxidase (XO)[27]. In this phase XO does not cause damage, but will later become crucial in free radical production.

Reperfusion

After restoration of perfusion, by reperfusion in occlusive disease and restoration of volume depletion or shock in NOMI, oxygen enters the ischaemic tissue. This is rapidly reduced by the abundantly present XO into several reactive oxygen species (ROS), all capable of oxidating DNA, enzymes, and receptor and membrane bound phospholipids[28]. Membrane integrity is lost, with further cell necrosis; damaged microvasculature leads to interstitial oedema. Not only is the damaging effect of ROS greater than pure ischaemia, the damage is no longer restricted to the ischaemic area. By diffusion of these small ROS molecules into surrounding, previously healthy tissues the damaged area expands considerably. Recently poly (ADP-ribose) synthetase (PARS), or poly (ADP-ribose) polymerase (PARP) were identified as major intermediates in I/R damage[29]. Both are DNA-repair enzymes that are abundantly present in the cell, and are activated by ROS-induced DNA-damage. PARS and PARP activation lead to severe energy depletion of the cells, and necrotic-type cell death. Recent studies show that inhibition of PARS can prevent injury associated with inflammation, shock and ischaemia and reperfusion[30]. The deleterious effects of ROS are limited by endogenous scavengers, which bind and eliminate ROS. Endogenous scavengers include glutathione, catalase, superoxide dismutase and NO. Most endogenous scavengers have high affinity for ROS, but low concentration and therefore have limited scavenging capacity. Only in very limited ischaemia endogenous capacity will balance ROS production. In prolonged ischaemia the endogenous capacity will be insufficient to bind ROS and thus to prevent this damage on a local and systemic level.

The onset of reperfusion not only results in inflow of oxygen, but also in outflow of ischaemic and reperfusion waste products, including ROS, NOS, mediators, cytokines and activated neutrophils into the systemic circulation[31]. In animal studies, liver and lung damage could be attributed to activated neutrophils coming from reperfused ischaemic bowel[28].

Detection of non-occlusive ischaemia

Introduction

Some decades ago, it was assumed that the main problem in critically ill patients was their inability to increase their oxygen delivery (cardiac output and oxygen content) to meet the increased demands during their illness. Studies that were aimed at increasing the global oxygen delivery with fluid resuscitation and vasocative medication, showed disappointing results[32]. Later it became apparent that changes in systemic perfusion changed different vascular areas, and especially the mesenteric circulation, in unpredictable manners. By using gastric tonometry, which measures luminal PCO2 or mucosal pH (pHi), the role of NOMI in gastric stress ulceration[33], in complications after aortic surgery, bacterial translocation, development of multiple organ failure and adverse outcome in critically ill or operative patients was shown[3,34]. This changed the view from systemic parameters and interventions towards measurements and interventions aimed at increasing gastrointestinal perfusion[35,36]. As a result, the central role of GI-perfusion in shock patients was identified, and the poor correlation with systemic parameters established.

Various diagnostic techniques are in use for assessment of splanchnic perfusion. They can be divided upon the information acquired: (1) anatomy of the major splanchnic vessels (angiography, duplex ultrasound, MRA and CT angiography),(2) flow patterns (duplex ultrasound), (3) flow volume (MRA), (5) perfusion of the mucosa (mucosal laser Doppler flowmetry, endoluminal pulse oximetry, endoscopy, intravital microscopy), (6) perfusion of the entire gut wall (laparoscopy, laparotomy) or (7) assessment of actual ischaemia irrespective of flow (tonometry).

Assessment of the vessels and flow: angiography, duplex ultrasound, MRA and CT angiography

Because vasoconstriction of the major mesenteric vessels is but one of the mechanisms of NOMI, investigations aimed at the origins of the CA and SMA therefore have little to no role in the ICU patient. Splanchnic angiography has been mentioned as "only diagnostic" in NOMI[2]; however, it should be stressed that angiography can only exclude occlusion. The only role might be as a route for intra-arterial treatment of the vasoconstriction[2].

Assessment of mucosal appearance: endoscopy and histopathology

Because the earliest ischaemic changes in the bowel wall appear on the superficial mucosal layers[10], endoscopy has great potential in its diagnosis. The endoscopic appearance of ischaemic colitis may mimic ulcerative colitis or Crohn's disease, in which cases histopathol-

ogy can be very helpful. In contrast to IBD, the histopathological abnormalities in ischaemic colitis are characterized by a ghost-like appearance of the superficial layers and absence of a neutrophil infiltrate.

Tonometry

Because mesenteric ischaemia is one of the earliest events in circulatory stress, at a stage where all other systemic parameters remain within the normal range, it has been referred to as "the canary of the body"[37]. Like the canary that was once used in the coal mines for its hypersensitivity for mine gas, tonometry may be "a good, inexpensive and relatively early warning of impending trouble"[38]. One of the unique properties of tonometry is that it measures ischaemia, defined as insufficient oxygen delivery and/or consumption for the metabolic demands, not perfusion[3]. Initially, tonometry was expressed as a calculated mucosal pH or pHi from the intraluminal PCO2 and blood bicarbonate; this compound and indirect parameter has major drawbacks and is increasingly replaced by the luminal-blood PCO2 difference[3]. The PCO2 gradient is very specific for mucosal ischaemia and less influenced by systemic variation. It should be emphasized that detection of reduced blood flow does not prove ischaemia, which will become relevant below app. 50% of basal blood flow (Figure 2.2)[10,39]. Gastrointestinal PCO2 tonometry is currently the only commercially available diagnostic technique capable of detecting early mesenteric ischaemia. The physiological background of tonometry is that with insufficient oxygen utilization in the cells inefficient glycolysis results in production of lactate and free protons (H^+) (Figure 2.3). These are buffered by tissue bicarbonate under formation of CO2. In the GI-tract this CO2 easily diffuses into the lumen and can be measured with a specialised tube, the tonometer, which can be positioned in the stomach, jejunum or colon[3] (Figure 2.4). The PrCO2 can be measured ex vivo by attaching an automated measurement device, the Tonocap to the tonometer. In the absence of ischaemia

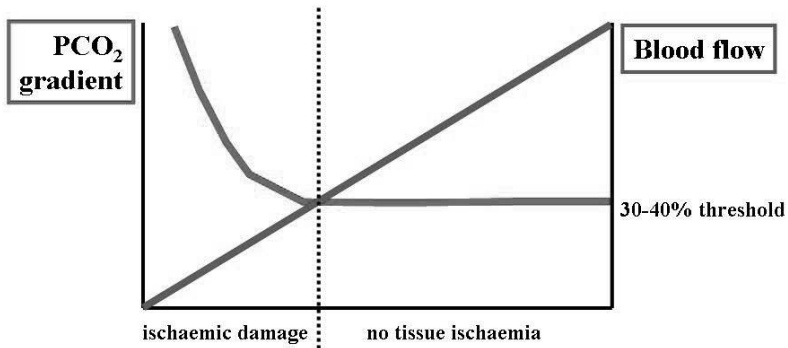

Figure 2.2. Blood flow, ischaemia and luminal PCO2

Reduction of the mesenteric blood flow to approximately 50% does not increase the luminal PCO2 nor cause tissue damage. Further reduction below approximately 30% of basal blood flow causes a gradual increase in luminal PCO2 and characteristic ischaemic tissue changes. The blood flow is indicated by the blue line. The tonometric PCO2 by the red line. The dotted lines indicates the anaerobic threshold of the tissue.

the PrCO2 equals arterial values (PaCO2); in mucosal ischaemia PrCO2 is higher than PaCO2 (threshold around 0.8 kPa). The unique property of tonometry is its capability to detect ischaemia at early stages. In a recent study in sepsis, it was shown that disturbed microcirculation and focal ischaemia was closely associated with an increase in the PCO2 gradient[22]. Unfortunately, performing tonometry is not as easy as once claimed, and is very sensitive to large

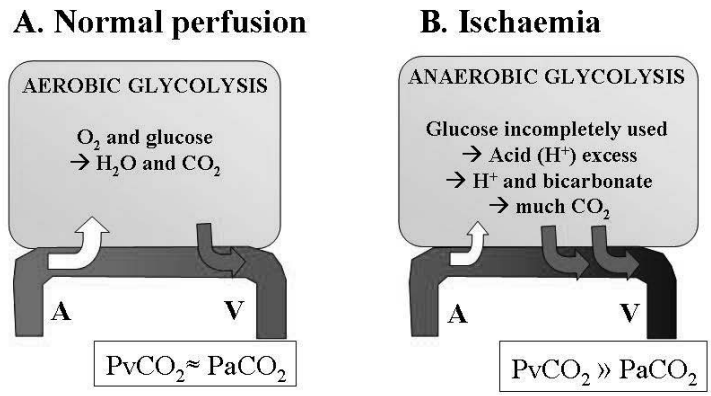

Figure 2.3. The tonometric principle

A. During normal or moderately reduced blood flow the tissues show aerobic oxygenation with efficient glucose utilisation under formation of water and CO2. The tissue PCO2 equals arterial values because of very rapid diffusion across the gastrointestinal epithelium and efficient CO2 disposal by the lungs.

B. With reduced blood flow the oxygen delivery is reduced so that glucose can no longer be completely burned and anaerobic glycolysis results. Now, a large number of H+ ions are formed leading to tissue acidosis (lactic acidosis). These H+ ions are immediately buffered by tissue bicarbonate under formation of CO2. The end result of this process is an elevated tissue –blood PCO2 difference. In the gastrointestinal tract this leads to an increased luminal PCO2 as well. In the absence of intraluminal CO2 production (f.e. by acid secretion or bacterial overgrowth) this increased PCO2 gradient is an accurate indicator of tissue ischaemia.

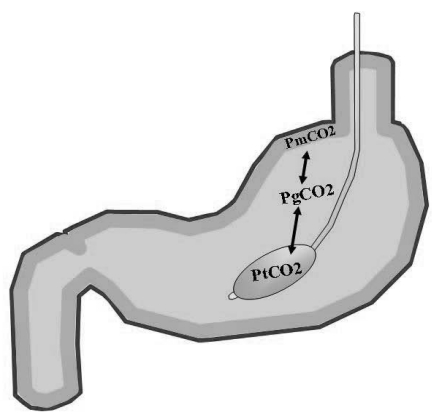

Figure 2.4. Tonometry of intraluminal PCO2.

The PCO2 can be measured from a specialized balloon tipped catheter placed in stomach, small or large bowel. Because CO2 diffuses rapidly over different membranes the mucosal PCO2 (PmPCO2) will equal the gastric lumen PCO2 (PgCO2). Because the tonometer balloon is CO2 permeable as well the tonometric PCO2 ultimately reflects mucosal values. This tonometric PCO2 is measured from air aspirated and inflated automatically into the balloon using a modified capnograph, the Tonocap (Datex-Engström).

measurement errors. Introduction of automated air tonometry has improved accuracy and reliability. Some precautions should be taken with tonometry: (1) measurement in the stomach requires acid suppression with a gastric pH >4-5, and (2) in the colon CO2 production by the microflora can cause false-positive readings. Recently, sublingual tonometry has been advocated as a simple tool that may avoid these persistent drawbacks. In animal models with severe hemorrhagic and septic shock, the correlations of sublingual tonometry with gastric tonometry and blood lactate during hemorrhagic shock were good[40]. This correlation between sublingual with gastric tonometry with lactate acidosis, indicating severe shock, was confirmed in ICU patients[9]. Further studies are needed to confirm that sublingual tonometry indeed parallels NOMI and is applicable, as well as reliable, in the daily practice of the ICU. For the moment, gastric and / or sigmoid tonometry remain the only proven diagnostic tools for detecting ischaemia at a reversible stage.

CLINICAL PRESENTATIONS AND SETTINGS OF NOMI

Critically ill patients and major operations

It has been shown repeatedly that major operations, especially aortic surgery are associated with mesenteric ischaemia, and that the latter carries an adverse prognostic significance[41,42]. In individuals with mucosal ischaemia, increased levels of cytokines, including IL-6 and TNG-alpha, and endotoxin levels were observed which peaked during reperfusion[43]. In severe acute pancreatitis, the occurrence of gastric mucosal ischaemia carries an adverse prognosis. In these patients the occurrence of mesenteric ischaemia was associated with increased cytokine levels, including IL-2, IL-6, IL-8 and TNF; increased serum endotoxin levels were less common[44]. During sepsis and endotoxinaemia a vicious cycle can develop because endotoxinaemia directly triggers the release of various vasoactive compounds causing splanchnic vasoconstriction[45] and profoundly disturbed microcirculation at the mucosal villi level[22], which leads to impaired mucosal barrier function and further bacterial translocation.

Ischaemic colitis

Ischaemic colitis is a well-defined disease with somewhat mysterious aetiology. It is generally considered non-occlusive in nature since angiograms are almost invariably normal[1,2]. On the other hand, most cases of ischaemic colitis are not preceeded by shock states (Table 2.2) and ischaemic colitis in the ICU is limited to patients with aortic surgery with loss of the inferior mesenteric artery[46].

Moreover, it was recently reported that the majority of patients with ischaemic colitis may have thrombogenic disorders[47] or cardiac or vascular emboli[48]. Thus, ischaemic colitis is indeed not associated with major vessel occlusion, but with transient hypoperfusion or occlusion of small vessels. Ischaemic colitis is usually left-sided and may extend up to the splenic

Table 2.2. Clinical features ischaemic colitis, Enschede the Netherlands 1998-2001

Lokalisation	Cause	History	Angiography	Course	Mortality
Right-sided (n=3)	Spontaneous (n=3)	Chronic splanchnic syndrome (1) None (2)	SMA stenosis (1) SMA and CA stenosis (2)	operated and recovered (1) died from bowel gangrene (2)	67 %
Left-sided (n=19)	Spontaneous (n=11)	Cardiovascular history (5) Trigger event or hypotension (0) None (6)	normal angiogram (2) no angiogram made (9)	Died from gangrenous colitis (3) Operated and recovered gangrene (1) Resolved spontaneously (7)	27%
	Postoperative (n=8)	After acute aortic surgery (7) After elective aortic surgery (1)	no angiogram made (8)	Recovery without operation (5) Operated and recovered gangrenous colon (1) Died from ischaemic colitis (2)	25%

Patients characteristics of 22 patients presenting with ischemic colitis in Enschede, the Netherlands between 1998 and 2001.
CA = celiac artery
SMA = superior mesenteric artery

flexure. It can develop spontaneously or after aortic surgery (Table 2.2). The incidence after aortic operations ranged from 1 – 2% after selective up to 20% after acute aortic surgery, and was associated with hypovolaemic shock[49] or sigmoid ischaemia[46,50]. In most cases the disease will resolve spontaneously with fluid resuscitation and antibiotics. Surgery is restricted to patients with gangrene, or transmural ischaemia, but then still carries a poor prognosis. Endoscopy is crucial in the diagnosis. Most authors agree that endoscopy is indicated in patients with aortic surgery who remain unstable > 48 hrs postoperatively. It has even been advocated to perform routine sigmoidscopy repeatedly on high-risk patients after aortic surgery. These high risk patients were characterised by severe pre-operative shock or large infusion volumes[49]. Angiography is rarely indicated. Treatment is aimed at aggressive fluid resuscitation, antibiotics and bowel decompression if indicated.

A distinction should be made between the above mentioned pattern of ischaemic left-sided colitis, and patients with right-sided colitis[51]. Right-sided ischaemic colitis is a symptom of acute SMA occlusion and thus acute mesenteric infarction, and requires immediate treatment. In our opinion a pre-operative angiography is indicated to plan the appropriate revascularisation approach or embolectomy, although others would prefer immediate surgery. As the time between onset of acute small bowel ischaemia and irreversible gangrene is only 6-8 hours, many patients present with gangrene, and the prognosis is poor (Table 2.2).

Medication

Many drugs have been implicated as causative agents in NOMI. NSAID's affect the integrity of the gastrointestinal mucus and bicarbonate layer, and reduce mucosal perfusion[52]. In general, alpha-adrenergic agents, like epinephrine and dopamine, reduce the gastrointestinal perfusion, whereas predominantly beta-adrenergic agents, like dobutamine and dopexamine,

tend to sustain the mucosal perfusion. Still, when comparing studies performed on the influence vasoactive drugs on mesenteric ischaemia or perfusion with identical drugs, including dobutamine, norepinephrine and dopexamine, completely opposite results can be found. Although these differences can be explained by different patient groups (trauma, surgery or sepsis patients), dosage regimens and fluid resuscitation, interpretation remains difficult.

Haemodialysis patients

A high incidence of NOMI was found in haemodialysis patients[53], leading to bowel infarction in 2%[54], with a 45% mortality rate. The onset of NOMI was associated with hypotension, and close monitoring was therefore advised[54].

Treatment

The first step towards successful treatment is early detection of mucosal ischaemia[1]. Because microcirculatory disturbances are pivotal in NOMI, angiography, CT scan or ultrasound are useless. Currently, only tonometry in the stomach or sigmoid colon would enable this task.

Vasocative drugs

Medical treatment aimed at improvement of mucosal perfusion should include aggressive fluid resuscitation as first and most important step[55,56]. Catecholaminic agents should only be instituted after sufficient fluid resuscitation[55]. Following the recognition of mucosal ischaemia as major factor in these patients, studies have been performed aimed at restoring the ischaemia or pHi, with limited success[57,58]. This might be explained by the difficulty of redirecting the blood flow towards the gut, without affecting other organ systems, or because reperfusion damage remains or increases. Because the negative effects of ischaemia are mediated mainly by reperfusion damage, and reperfusion damage is almost always present in NOMI patients, I/R management approach deserves further exploration. ACE-inhibition was shown to be beneficial in experimental stress ulceration models, but in clinical studies, only one of three showed some improvement in mesenteric ischaemia. Endothelin-antagonists are probably the most promising new drugs, as they block the final common pathway of mesenteric vasoconstriction. Animal data point to their potential effectiveness specifically on gastrointestinal ischaemia following ischaemic, hypovolaemic and septic shock[12,59]. Finally, prostaglandins have been successfully used in an experimental sepsis model in cats[60], to be confirmed in patients with septic shock[61].

Enteral nutrition

Early institution of enteral nutrition may improve perfusion, besides the well-established immunological effects. In no flow states, complete arterial occlusion, enteral nutrition proved harmful in animal models[62]. Enteral nutrition augmented mesenteric perfusion in experimental shock models characterised by low-flow[63], in post-operative[64] and severely burned

patients. As the low-flow is far more common than no-flow, enteral nutrition should be considered in all patients with circulatory stress. The mechanism probably involves mucosal vasodilatation driven by the metabolic demands of the food in the lumen, counteracting the circulatory stress induced vasoconstriction.

Reperfusion damage control

Treatment of reperfusion damage is a promising, but clinically underappreciated approach. Several new compounds[65-67], and established drugs including N-acetylcysteine[68] and vitamin E[69] used in animal models reduced I/R damage. The best-known scavenger, N-Acetyl-L-cysteine, causes increases of intracellular glutathione and increased NO release, leading to vasodilatation of small blood vessels[70]. When given in early sepsis it caused improvement of hemodynamic parameters[71] and mesenteric ischaemia[72].

New ways

Through the years some sporadic papers have emerged on intraluminal or intraperitoneal administration of pure oxygen[73,74]. Interestingly, significant mesenteric hypoperfusion could be treated by fluid or gas installation with pure oxygen. We have recently confirmed the potential of intraluminaal oxygenation in a large animal model[75].

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3

The clinical approach to chronic gastrointestinal ischemia: from "intestinal angina" to the spectrum of chronic splanchnic disease

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ABSTRACT

Stenotic disorders of the splanchnic arteries are not rare, and it is generally assumed that symptoms are rare in patients with a single splanchnic stenosis, and even in patients with multiple vessel stenoses. Currently, only gastric exercise tonometry aids to the diagnostic evaluation as it indicates actual ischemia. Patients with stenotic disorders without complaints are referred to as chronic splanchnic disease (CSD), and those with ischemic complaints as chronic splanchnic syndrome (CSS). The classical presentation of CSS, including the trias postprandial pain, weight loss, and upper abdominal bruit is also known as "intestinal angina". From the experience of our multidisciplinary working team on gastrointestinal ischemia in 110 patients with stenoses of at least 1 splanchnic artery two different clinical patterns were observed. In our series app. 60% of patients with single vessel stenosis, including the celiac artery compression syndrome, have CSS. They have fewer complications, very low mortality, but most can be successfully treated by stenting or surgical treatment. Patients with multivessel splanchnic stenoses have more classical ischemic complaints. Progression to a bowel infarction was seen in 34%, and mortality was 21%, mostly from bowel or myocardial infarction. Treatment should be tailored based upon peri-operative risk assessment and local vascular anatomy. It may consist of autologous arterial bypass of one or two vessels, preferably antegrade, stenting or a combination of both.

This differentiation between single and multivessel splanchnic disease has large consequences for optimal work-up and treatment.

INTRODUCTION: ANATOMY AND PHYSIOLOGY OF SPLANCHNIC PERFUSION

Three major aortic branches provide the gastrointestinal blood supply. The coeliac artery (CA) provides the stomach, proximal duodenum, liver and spleen; the superior mesenteric mesenteric artery (SMA) supplies the distal duodenum, small bowel and proximal colon. Both arteries are large vessels with basal blood flow of 800 and 500 ml, respectively. After meals this flow can increase by 50 to 100%. The third vessel, the inferior mesenteric artery (IMA) is small and provides the distal colon and rectum by blood. Between these vessels a large collateral vascular network may protect against the effects of stenoses in one of the main branches.

That stenoses of splanchnic vessels do not necessarily cause symptoms has led to the notion of differentiation between chronic splanchnic disease (CSD) and chronic splanchnic syndrome (CSS)[1]. In CSD significant stenoses of at least one of the splanchnic arteries is not accompanied by complaints. In CSS, the existence of splanchnic stenoses is associated with typical complaints of ischaemia, notably postprandial pain, which may lead to weight loss typically caused by fear of eating. The differentiation between these entities is still difficult, especially in patients with single vessel abnormalities. Because of the abundant collaterals it is generally assumed that a single stenotic lesion rarely, if ever, causes complaints. Even with stenoses in two vessels, some experts doubt on the relation between pain and these vascular abnormalities. To complicate matters even more, ischaemia can develop in patients with normal splanchnic vessel anatomy, the so-called non-occlusive mesenteric ischaemia (NOMI)[2]. In these patients the normal adaptation of the vasculature to circulatory shock leads to preferentially splanchnic vasoconstriction and ischaemia. The splanchnic vasculature is even more sensitive to (pre) shock than for example the renal vasculature. Almost 20 years ago, Marston stated, after careful analysis of his wide expertise and world literature, that a test that may show ischemia and risk for bowel infarction is needed[3].

In our hospital we have formated a multidisciplinary team for analysis, advice and treatment of gastrointestinal ischaemia in 1997. It was the result of longstanding clinical and scientific interest of the gastroenterologist (JJK), vascular surgeon (RHG) and interventional radiologist (ABH) currently all working in the Enschede hospital. This team combines the insights of the gastroenterology, vascular surgery and interventional radiology world. In our view this multidisciplinary approach has enhanced our understanding of CSD and CSS and enabled us to unravel new disease patterns. In this review we will try to summarize our insights and views on the clinical aspects of chronic occlusive splanchnic or mesenteric ischaemia.

DIAGNOSTIC TOOLS

Questions on vessels, flow and ischaemia and natural course

When considering perfusion adequacy of organ systems, the assessment of vessel anatomy, perfusion and ischaemia are separate, but interrelated issues. Stenoses may or may not lead to ischaemia and complaints, may be progressive with risk of infarction or remain indolent for long times. Since gastrointestinal ischaemia is relatively rare, and research is sparse, it may be worthwhile to consider the current views on vessels, flow and ischaemia assessment and treatment in other, more common, vascular systems. Ischaemic disorders of the brain, heart, extremities, or kidneys are far more common, and therefore diagnostic and therapeutic strategies are well established and mostly evidence based. We will briefly discuss these main considerations in treatment of ischaemic disorders in these vascular areas where research is abundant, and will then come back to the gastrointestinal tract to apply these mechanisms.

It is widely recognised that the finding of a hemodynaemic significant stenosis (defined as a stenosis causing insufficient perfusion of the outflow area) in the coronary or carotid artery does not automatically indicate ischaemia. In general, five questions should be answered before a sound decision on treatment of any vascular stenosis can be made: 1) does this stenosis cause ischaemia and complaints, 2) what is the natural history of this stenosis (how often and how rapid does it progress even to occlusion), 3) what are the consequences of progression and / or occlusion, 4) can it be treated with life-style measures or medication, 5) is a safe and durable revascularisation technique available. In general, in situations with a low risk for infarction, revascularisation will be required only to those with ischaemic complaints unresponsive to medical treatment. In cases where the risk of infarction is larger, and especially when infarction has grave consequences, revascularisation may be the first choice, unless conservative treatment could prevent infarction.

The choice, aim and acceptable risk of therapeutic procedures is dependent on these clinical considerations as well. In patients with symptomatic disease without risk for infarction, disappearance of symptoms is the main goal, and treatment should have minimal complications. In patients with imminent infarction the restoration of sufficient blood flow to is the primary goal, and less so the disappearance of symptoms. These considerations are valuable in the gastrointestinal tract, as well and the diagnostic tools should therefore be aimed at these tasks and provide information on anatomy, flow, ischaemia or prognosis (Table 3.1).

Medical History

Most patients present with postprandial pain and sometimes fear of eating due to this pain. Weight loss may be an early and progressive feature, but in most it develops slowly over years. Some patients present with mainly atypical complaints of nausea and vomiting, and far less pain.

Table 3.1. Information obtained from different diagnostic tools / methods

Diagnostic tool	Anatomical	flow	ischaemia	Prognosis
Clinical presentation#	– –	– –	– –	++
Duplex-ultrasound	++	+++	– –	+
Angiography	+++	++	–	++
Magnetic resonance Angiography	++	+	– – (++*)	+
Exercise tonometry	– –	– –	++	+
24 hr tonometry	– –	– –	++?	++

Presentation with vascular abdominal rest pain, right sided ulcerative colitis or gastric ulceration.

* Measurement of percentage of increased of portal venal flow following a meal.

In some, but not all, patients a medical history of vascular disease might be present. As in all vascular diseases, a combination of a positive family history and risk factors, like smoking and / or hypercholesterolemia can be found.

Physical examination

Two major clues can be obtained by physical examination. First, an epigastric arterial bruit can be heard, but unfortunately in less than 50% of patients with arterial stenosis[4]. In patients with the celiac artery compression syndrome the bruit may vary with respiration. Dependent on anatomy it can increase with either inspiration or expiration. Second, a significantly lowered body weight can be found, which is usually caused by reduced food intake because of fear of eating.

Duplex-ultrasound

Duplex-ultrasound is the most widely used screening tool for detection of splanchnic stenosis. In experienced hands the CA and the SMA can be visualised in 80 to 90% of patients. Proper visualisation can be difficult because of the location behind the, often air-filled, stomach. With duplex ultrasound B-mode information on anatomy is obtained first. This is followed by assessment of blood flow pattern and velocity. The arterial blood flow in the splanchnic vessels varies during the cardiac cycle. The normal CA has a biphasic signal. In case of severe stenosis or occlusion of its origin, retrograde blood flow in the common hepatic artery can sometimes be found. The SMA normally has a triphasic signal. A biphasic signal in the SMA may indicate a stenotic lesion at its origin, but can also occur physiologically after a meal or in patients in whom mainly the right hepatic artery originates from the SMA instead of the CA. The latter is the most frequent of the many anatomic variants in the splanchnic vasculature with a frequency of 25%. Blood flow measurement is then performed using a measurement angle of less than 60 degrees between vessel and probe. This enables quantitative assessment of compromised perfusion over stenotic areas, caused by the phenomenon that a decreased lumen diameter causes the blood flow to become accelerated and turbulent. On duplex ultrasound this is shown as high-speed jets and increased flow velocity. Using either

the end diastolic velocity (EDV) or the peak systolic velocity (PSV) discrimination can be made between patients with normal or stenotic vessels. The mostly used cut-off values are for PSV and EDV in the CA 200 m/s and 55 m/s, and in the SMA 275 and 45 m/s in the SMA[5]. The optimal cut off values depends on patient selection, in or expiration measurements and a diagnostic or screening intention of the test. In our own centre, in over 200 patients evaluated for the existence of chronic splanchnic syndrome, the optimal screening parameter seemed the PSV with cut-off values for inspiration CA of 135 cm/sec and expiration CA of 190 cm/s. For inspiration SMA the cut-off values were 140 cm/s and for expiration SMA 135 cm/sec. Using this threshold value the sensitivity and specificity for stenoses > 70% were 89% and 44% for the inspiration CA, 89 and 62 for the expiration CA, 100% and 61% for the inspiration SMA, and 80% and 42% for the expiration SMA.

In patients who were operated or had stent placement for stenotic lesions duplex ultrasound was performed in the follow-up. Pre-intervention cut off values could not be extrapolated to post-intervention duplex ultrasound measurements. Duplex-ultrasound is a validated and valuable screening tool for patients suspected for CSS or CSD.

Angiography

Biplanar selective splanchnic angiography is still gold standard for detection of vascular anatomy and stenoses. A state-of-the-art investigation consists of: 1) anterior-posterior aselective aortic abdominal angiography, 2) lateral aortogram during maximal inspiration and expiration for detection of external compression of the celiac axis and/or rarely the superior mesenteric artery 3) selective angiography of all three splanchnic vessels 4) a late angiographic picture with visualisation of the venous phase. When collaterals between the main arteries already appear on anterior-posterior aortic angiography they indicate origin stenosis and can therefore be considered pathological. A well-known example is the meandering artery, or artery of Riolan, which fills the superior mesenteric artery or even the celiac axis from the inferior mesenteric artery in case of SMA and/or CA stenosis. In our experience these pathological collaterals can be easily recognized in patients with significant proximal stenosis of the splanchnic arteries. With subsequent selective angiography detailed information on the vascular anatomy, stenosis, variations and collateral anatomy can be obtained. This information is essential in preparation for an optimal revascularization strategy in view of the wide anatomic variations of the splanchnic circulation.

Magnetic resonance angiography

After standard magnetic resonance imaging of the abdomen, a "virtual" reconstruction of the splanchnic vessels can be obtained by software analysis. With this so-called MRA, a 360 degrees examination of the splanchnic vessels can be obtained. In a small pilot-study of 14 patients with correlative angiograms overall sensitivity and specificity of MRA was 100% and 95%[6]. In many clinics MRA is already considered the gold standard investigation for detec-

tion of splanchnic stenosis. Still, in our experience in over 30 subjects with biplanar selective angiography and MRA, the latter has lower spatial resolution and tends to overestimate the degree of stenosis. Moreover, because MRA only shows the vessels within a couple of centimetres of the aorta, collaterals cannot be fully evaluated, nor can their flow direction be ascertained. With MRI, functional information on splanchnic blood-flow can also be obtained. Flow velocities and total flow volumes can be measured in the mesenteric vessels using two-dimensional cine phase contrast velocity mapping. MRI has also been used to measure the oxygen saturation of haemoglobin in the blood. Combining morphological evaluation of the splanchnic vessels by MRA with a functional test (either by measurement of flow or %HbO2) in a single session may become important in the detection of patients with chronic splanchnic syndrome. Thus, MRA seems to be a valid screening tool, and may provide important information on blood flow reserve. Still, the gold standard for assessment of splanchnic anatomy and stenoses is biplanar selective splanchnic angiography.

Tonometry: detection of ischemia

Tonometry of the gastrointestinal tract has the unique potential to the detect ischemia, irrespective of flow or metabolism. Tonometry is based on a general characteristic of ischaemic tissues in which lack of oxygen results in increased production of acids, which are buffered locally leading to increased PCO2. This relation between ischaemia and increased PCO2 has been observed in all ischemic models and animals studied[7]. Because CO2 is a small molecule it rapidly diffuses over different membrane layers; the PCO2 in the gastrointestinal lumen will equal the PCO2 in the gastrointestinal mucosa. Therefore, mucosal ischemia is invariably associated with increased gastrointestinal PCO2. The latter can be measured using a balloon-tipped catheter, the tonometer, which is attached to a modified capnograph, the Tonocap. Historically, a compound parameter was used called the pHi. It was calculated from arterial bicarbonate and luminal PCO2, but its value is questioned, and is increasingly abandoned as measure of tissue ischaemia. The currently preferred tonometric parameter for ischaemia detection is the PCO2 gradient, defined as the difference between luminal and arterial PCO2. An increased PCO2 gradient indicates luminal or mucosal CO2 production and therefore ischaemia[7].

In gastroenterology, tonometry was first used by Fiddian Green in the evaluation of gastric stress ulcers[8]. Tonometry was evaluated as test for ischaemia using meals as provocative manoeuvre, but the accuracy ranged from 100%[9] to 0% accuracy[10], probably due to ongoing acid production and direct influence of the meal on gastric PCO2 by dilution[11].

In search for an alternative provocative manoeuvre we have shown that tonometry during exercise can be used to provoke ischemia in patients with chronic splanchnic syndrome[12]. We have later established the normal values in exercise tonometry as well as the optimal exercise intensity in healthy volunteers. Using these data we have developed a 10 minutes exercise test using a constant workload bicycle ergometer, an aimed exercise level of 70% maximal

workload using stepwise increase in workload. The aim should be to reach an arterial lactate concentration between 3 and 8 mmol at the end of exercise[13]. The upper limit of normal gastric PCO2 gradient was 0.8 kPa. We have now performed over 300 gastric exercise tonometry tests in patients suspected of gastrointestinal ischemia sensitivity and specificity approach 80 and 75%, respectively. Using jejunal tonometry we were able to show isolated small bowel ischemia in patients with SMA stenosis. In some patients with CA stenosis, only jejunal ischemia with normal gastric tonometry was observed, indicating intramesenteric shunting.

Because the technique of tonometry has much improved, allowing more frequent and more accurate measurements, and because adequate acid suppression after meals can be reached by high-dose omeprazole, prolonged and postprandial tonometry can now be performed. This 24-hour tonometry has the advantage of potentially showing postprandial and fasting PCO2 levels. As mentioned, postprandial measurements were proven to be unreliable[11]. These measurement problems were analysed by in vitro experiments on CO2 production and resorption by different meals, followed by a volunteer study (Papers in preparation). The first results show very promising results and a comparative study between exercise tonometry and 24-hr tonometry for detection of ischaemia, or differentiation between CSS and CSD, is ongoing.

CLINICAL PRESENTATION OF ISCHEMIA: TWO DIFFERENT PATTERNS

The current literature normally refers to splanchnic ischemia as "intestinal angina" characterised by an epigastric bruit, weight loss and postprandial pain. However, in the majority of patients this syndrome is incomplete or absent[4,14]. This clinical picture is more common in the severe patients, but rarely so in the earlier stages of the disease. A clinically more important

Table 3.2. Difference between single and multivessel splanchnic disease

Single vessel splanchnic disease (n=76)		**R Remarks**
Ischemia (CSS)	45 / 76 (60%)	Mean body mass index 22.1 (normal)
Abnormal tonometry	45 / 76 (60%)	
Complications	8 / 76 (11%)	1 infarction (limited small bowel infarction after severe diarrhea) 7 ulcers (4 stomach, 3 duodenal, NSAID and Hp excluded as cause)
Mortality	0 / 76 (0%)	
2 and 3- vessel splanchnic disease (n=34)		**Remarks**
Ischemia (CSS)	32 / 34 (94%)	Mean body mass index 22 in 2 vessel- and 17.5 in 3 vessel-disease
Abnormal tonometry	22 / 26 (85%)	8 patients were too weak / cachectic for exercise tonometry.
Complications	13/ 34 (38%)	12 infarctions (3 as presentation of the disease, 9 during work-up) 1 persistant cachexia, even after revascularisation
Mortality	7 / 34 (21%)	2 postoperative from multi-organ failure (both extreme cachexia) 2 from CSS, no treatment possible (neither operative nor stenting) 3 from other causes (2 myocardial infarctions, 1 from unrelated cancer)

distinction can be made between single- and multivessel CSS. In the last years we saw 222 patients referred for analysis of suspected ischemia or proven stenoses. In 112 no stenosis was found; 110 showed stenosis of one single vessel (n=76) or two-or three vessels (n=34). This distinction between these groups is remarkable and includes clinical presentation, course, risk for bowel infarction and prognosis (Table 3.2).

I. SINGLE VESSEL DISEASE

Clinical presentation and diagnosis

It is disputed among experts if a stenosis in only one of the three splanchnic arteries can cause symptoms[15-17]. On the one hand, smaller series of successful treatment in single vessel stenosis, mostly coeliac artery compression syndrome (CACS), have been published[18,19]. On the other hand it has been shown that in patients with single vessel disease, revascularization treatment often fails to reach long-term disappearance of symptoms[20,21]. The syndrome is deemed curious and very rare and it was recently stated that "the diagnosis of CA compression syndrome ultimately depends on the relentless elimination of other possible causes for abdominal pain and on the knowledge that this curious syndrome does indeed exist"[22]. It is widely assumed that the abundant collateral network in the splanchnic circulation effectively prevents ischaemia in single vessel stenosis. In a recent "AGA technical review" it was concluded that patients with chronic splanchnic ischaemia show 2 or 3 vessel stenosis in 91% of cases[14]. In view of the 4-fold more frequent occurrence of single vessel stenosis[23] it could be concluded that single vessel stenosis does indeed rarely cause symptoms. An alternative explanation may be that current literature focuses mainly on advanced "classical" disease and ignores earlier stages of CSS. That this may indeed be the case is suggested the study by Bron et al. who observed "otherwise unexplained abdominal complaints" in 49% of patients with isolated CA stenosis. This figure is very much in line with our experience in over 76 patients with single splanchnic stenosis in whom 60% was diagnosed as CSS. In our experience gastric exercise tonometry, with its unique capability to detect ischaemia, can indeed separate between patients with asymptomatic stenoses and patients that might benefit from treatment. We currently perform gastric tonometry exercise test[12] in all patients referred for analysis of potential CSS, or after a finding of an isolated CA or SMA stenosis. A revascularisation procedure is only advised in subjects in whom 1) the stenosis is considered significant on duplex ultrasound or angiography (>70%), 2) the clinical history is fitting CSS (pain or abdominal discomfort preferably but not exclusive after meals or exercise, duration up to several hours, no other explanation) and 3) abnormal exercise tonometry. Using these criteria, the over 70% of patients have improved or disappeared symptoms after successful revascularization of single vessel disease. A normalised post-procedure tonometry was associated with patent vessels and improved complaints in all cases. Thus, gastric tonometry

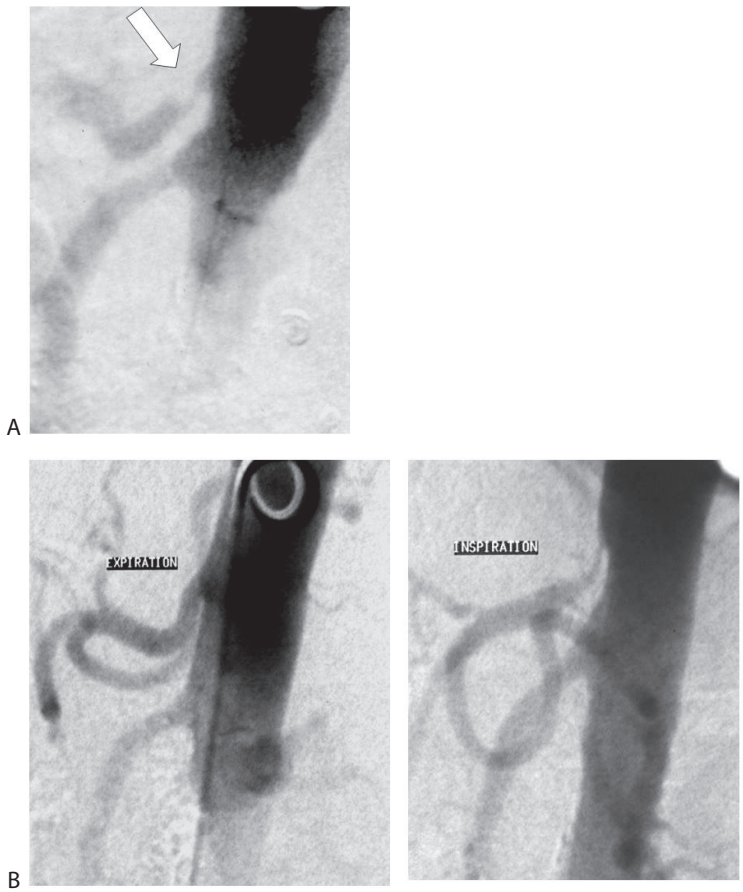

Figure 3.1. Celiac artery stenosis: atherosclerosis and celiax axis compression syndrome (CACS)
1A - stenosis with an arteriosclerotic origin (white arrow) with typical concentric appearance and presence of a calcified plaque.
1B - celiac artery compression syndrome (CACS) due to the ligament of the diaphragmal crux can cause either in expiration or in inspiration a significant compression from above. In this case expiration shows a completely normal coeliac trunc (left), while on inspiration a significant stenosis is demonstrated (right).

can be used to identify patients who might benefit from revascularisation in single vessel disease (paper in preparation).

The clinical presentation of these patients is characterised by pain, usually starting 10-20 minutes after the meal with duration of 1-3 hours. Weight loss is not obligatory, but patients can lose up to 20 kg of weight, even with single vessel disease, invariably caused by fear of eating leading too smaller and often more frequent meals. In some patients nausea, or dyspepsia are the prominent complaints. The main causes of single vessel stenosis in our series is the CACS as well as atherosclerosis and can be distinguished by angiographic appearance (Figure 3.1). Rarely SMA compression syndrome could be seen.

The course and prognosis in these patients varied from mild postprandial pain, often for many years to excruciating pain, increasing weight loss, physical impairment and social isolation. Not rarely these patients have been diagnosed as "nervous anorexia". Irreversible ischaemia or infarction is rare and was seen in 1 patient only. This patient developed a limited infarction of 60 cm small bowel during vacation after 2 days of severe diarrhoea and dehydration; coagulation disorders and cardiac emboli were excluded. He had a 90% CA stenosis without further abdominal complaints. His infarction can be explained by NOMI combined with the stenosis, and not from the stenotic disorder alone.

Treatment

The choice of treatment mainly depends on the nature of the stenosis. In CACS, release of the compressed CA by cleavage of the arcuate ligament and the coeliac plexus is indicated. Intra-operative duplex is essential in these patients because longstanding compression can cause localised and severe CA vessel wall damage that should be treated by a vascular reconstruction. The less favourable outcome in some series may indeed be explained by operative techniques, which consisted of release only, and did not ascertain vessel patency. In our series 5 out of 21 patients showed no improvement of symptoms after celiac artery release or reconstruction. Four of these patient had restenosis of the coeliac artery. In our opinion, stent placement is not indicated in the CACS because repeated pressure from the arcuate ligament with each respiratory cycle can damage the stents. Still, in 2 patients with suspected CACS an intravascular stent was placed in other hospitals. These patients were subsequently admitted to our centre for evaluation of recurrent and "unexplained" pain. Both patients had ischaemia, and on angiography fractured stents 1-2 years after stent placement for CACS. In patients with atherosclerosis in a single vessel, counting for app. 50% of our patients with single vessel involvement, operative or endovascular revascularization with stenting can both be considered. The results of PTA alone are short-lived in our experience in 6 patients, lasting some weeks to months. We currently use it as "diagnostic test" only, when in doubt on the diagnosis CSS in patients with very disabling symptoms.

II. MULTI VESSEL DISEASE

Clinical presentation and diagnosis

When 2 or 3 of the main splanchnic arteries are stenotic the potential collateral blood flow is reduced and complaints as well as complications are more common than in single vessel disease. In these patients weight loss is more common. The average body mass index (BMI) of patients we evaluated with the suspicion of CSS was 23 kg/m2 in the absence of stenosis, 22 kg/m2 in 1 vessel, 21 kg/m2 in 2 vessel and 17.5 kg/m2 in 3 vessel CSS.

Many patients report to have postprandial complaints for many years before presentation. In these patients postprandial pain becomes less typical and may resemble classic dyspepsia, including fullness and bloating. Still, in most patients the relation to the meal is typical with an interval of 10-30 minutes between the end of the meal and the onset of complaints. Most of our patients with 2- or 3-vessel disease indeed had CSS (Table 3.2), and tonometry was abnormal in most of them as well.

In our experience CSS in patients with multivessel disease may run a rapidly progressive course. Moreover, in contrast to patients with single vessel stenosis, patients with multivessel CSD have a high risk for bowel infarction. In a recent study patients were followed after abdominal angiography for "other indications" who had no bowel complaints at the time of angiography. Ten of 15 patients with 2- or 3-vessel disease developed a bowel infarction or CSS during 1-6 years of follow-up[24]. In our own series 9 / 34 patients (26%) developed a bowel infarction during the diagnostic work up, while 3 more presented with acute splanchnic syndrome and were diagnosed during laparotomy. Typically, the pain in these patients progressed from the postprandial to more prolonged periods, and is provoked by increasingly smaller meals or even drinks. Finally, pain occurs even without any meal or drink, indicating "abdominal vascular resting pain". The latter pattern, in our experience, has a poor prognosis and often precedes bowel infarction by only days to weeks. In 3 of these severe patients our attempts to improve their nutritional status by enteral or even parenteral nutrition resulted in increased pain and subsequent infarction. Thus, "abdominal vascular rest pain" leaves the clinician with little time, and in some of these patients a bowel infarction developed undetected even during admission for worsening CSS and while being carefully observed by experienced clinicians. In these patients our initial experience with 24-hour tonometry seems promising (Figure 3.2). The one-year mortality in multivessel CSD patients was 21%, and was mostly associated with their vascular status, not only of the splanchnic vessels, but their coronary arteries as well. In two of our patients a fatal myocardial infarction developed, whereas the 1 of 2 patients who died post-operatively from MOF, had a suboptimal cardiac output as well.

Treatment

In view of the high incidence of ischemic complaints and bowel infarction, most, if not all, patients with multivessel CSD have an indication for treatment. The goal is both to reduce pain and to prevent bowel infarction. Timing is pivotal because of the rapidly progressive nature of end-stage CSS. The occurrence of vascular abdominal resting pain, especially when associated with long and high PCO2 peaks measured with tonometry, indicates imminent infarction (Figure 3.2). In these cases treatment should be planned within 24 hours at maximum, not after days or weeks. Our current policy is to admit these patients, perform 24-hr tonometry with meal provocation, followed by selective angiography and starting immediately with intravenous fluid challenge to minimize NOMI. The treatment plan and timing can be made

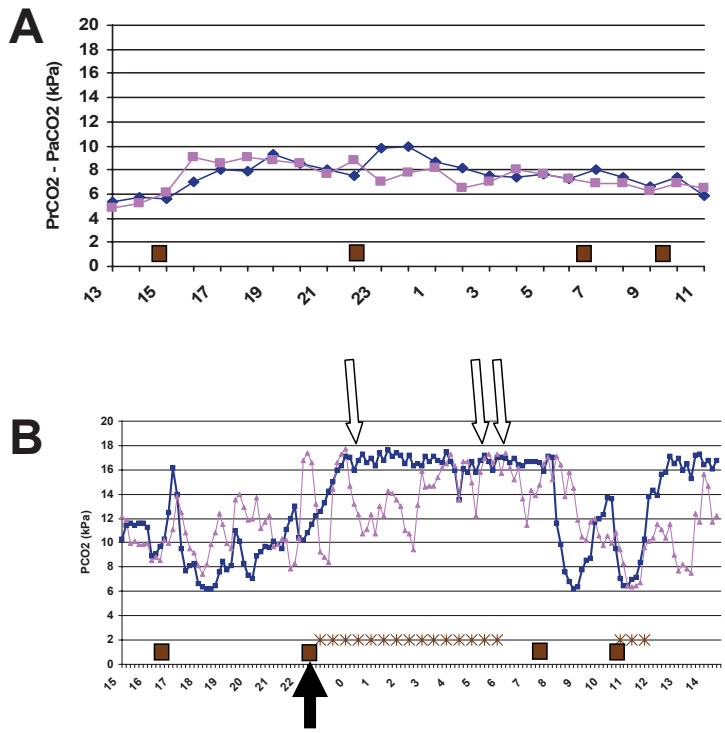

Figure 3.2. Imminent bowel infarction on 24-hr tonometry

24-hr tonometry of the stomach (gastric PCO2: diamonds) and jejunum (jejunal PCO2: boxes). PCO2 in kPa on the Y-axis and time on X-axis. Liquid meals (Nutridrink): boxes above the X-axis. Pain: asterix.

A. Normal tonometry in healthy volunteer with only minimal increase in PCO2 after meals.

B. Tonometry in a patient with abdominal vascular rest pain. After a small drink (solid arrow) the patient had pain for hours. At that time the gastric (single white arrow), and later jejunal PCO2 (double arrows) rose sharply to 14-15 kPa for several hours. The patient was treated by intravascular stent placement the next day with immediate resolvement of symptoms and normalisation of tonometry after the procedure.

within one day. The choice of treatment is mainly based upon the expected peri-operative risk and local anatomic abnormalities. As a rule we consider the antegrade autologous multi-vessel bypass as the surgical best choice. It has ideal anatomical positioning, has been shown to have superb long-term outcome as measured by patency and complaints[4]. Its drawbacks are the necessity for a short period of aortic clamping above the splanchnic vessels with resultant ischemia in the lower body and splanchnic and renal vascular beds. The reperfusion damage phase following release of the clamp is a major cardiovascular burden for these compromised patients, and may be just too much for the cachectic, elderly or cardiopulmonary compromised patients. Deviation of the first 500 ml portal blood after declamping may be considered as it could diminish reperfusion damage from outflow of endotoxines and cytokines from ischaemic bowel[25] after revascularisation. In severely compromised patients a retrograde bypass from the iliac artery to only one of the stenotic splanchnic vessels may an alternative option. The main drawback of this technique is that the bypass needs to be quite

long to avoid kinking by the overlying bowels. It is more susceptible to occlusion than the antegrade bypass. On the other hand, the perioperative stress from an iliac clamp is much less compared to the aortic clamp used in the antegrade technique.

Intravascular techniques provide many advantages over a surgical approach. There is no need for surgery or general anaesthesia, nor is aortic or iliac clamp necessary. As above mentioned, dilatation alone is rarely sufficient and almost all patients will need stent placement. Currently, the Bridge® stent (Medtronic AVE) and the Express® stent (Boston Scientific) in our opinion show the best properties regarding length, form, placebility and radial force for these vessels. We have an experience of splanchnic artery stenting in 27 patients with the suspicion of CSS with a mean follow up of 19 months. The primary clinical success rate (disappearance of symptoms and restoration of blood flow) was 77%. The well-known drawbacks of intravascular stents including occlusion from intimia hyperplasia and thrombus formation were observed in 19% of stents so far[26]. These patients should therefore be closely followed up and may need several duplex ultrasounds and angiographies with dilatation or even new stents even within the first years of follow-up. Also, the vascular access is not without complications. Because of the caudal direction of both SMA and CA, a vascular approach from above, using the brachial artery as entry site is preferred. In some patients pressure on the median nerve, either by puncture or from local pressure from a haematoma, may cause neuropathic damage.

As guideline we currently prefer stenting in severely cachectic patients or patients who are considered at high-risk for operation. Alternatively, retrograde single vessel bypass from the iliac artery can be considered.

After successful revascularisation of one of the arteries all but one of our patients regained weight and had mostly impressive improved overall condition. At that time more definitive treatment can be considered, including antegrade multivessel bypass. In our experience, however, most patients are quite happy with their status and prefer a "wait-and-see" policy.

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4

In vitro testing of CO2 production and absorption of standard meals

PBF Mensink and JJ Kolkman

INTRODUCTION

The principle of tonometry is based on ex vivo measurement of intraluminal carbon dioxide (PCO2). These PCO2 values represent the adequacy of the (sub-) mucosal blood flow. These measurements are performed with placement of the tonometer intragastric and / or in the first part of the small bowel (jejunum). Most studies using tonometry are performed in the empty stomach and / or jejunum, because of the disturbing effects of meals on the intraluminal CO2 content[1]. Boley and Fiddian-Green described the diagnostic potential of a meal as provocative manoeuvre in gastric tonometry[2,3]. It was later shown that postprandial PCO2 tonometry was very insensitive for ischemia detection, which can be explained by buffering as well as dilutional effects[4,5]. Consequently, Kolkman et al have developed the gastric exercise test as an alternative provocative maneuver, thus avoiding acid secretion and meal-effects on the intragastric PCO2[6,7]. The effect of exercise on provoking ischemia is explained by the redistribution of blood flow from splanchnic area to the exercising muscles. The provocative effect of a meal is based on increased metabolic demand, and is probably more 'physiological' as most patients with gastrointestinal ischemia experience postprandial pain, whereas only 40-50% of these patients experience pain during or after exercise[8]. Therefore, we reconsidered measurement of intragastric postprandial PCO2 as potentially superior test in this patient group. Together with the inability of some patients to perform exercise, this makes tonometry after meals an attractive diagnostic tool in this patient group.

Theoretically, every meal has a certain capacity to produce or absorb CO2. The (surplus) production and absorption of CO2 intervenes with the measurement of CO2, e.g. the PCO2 level as marker for intestinal mucosal blood flow. We decided to challenge these difficulties of interference of meals and gastric and / or jejunal fluids on the PCO2 level by designing a healthy subjects study where a maximal controlled gastric (and jejunal) environment had to be established. This maximal controlled environment also included the use of standard meals, which had been tested in vitro for their capacity to produce and absorb CO2. In this chapter the in vitro testing of the different standard meals is presented.

METHODS

Choice of meals

An 'ideal' standard meal for provocation of splanchnic ischemia would be a high protein and fatty meal, as this is associated with maximal gastrointestinal blood flow demand, with minimal disturbance of local PCO2[9,10].

Four commercially available liquid meals were chosen as test meals. The choice of the meals depended on the different composition of the meals. A carbohydrate-predominant meal (Nutrical®), a fat-predominant meal (Solagen®), a protein-predominant meal (Adamin G®)

Table 4.1. Test meal characteristics

Meal	Composition	pH	kcal/ml
Solagen	fat (100%)	3.5	4.32
Adamin G	proteins (100%)	4.8	4.79
Nutrical	carbohydrates (100%)	5.4	2.47
Nutridrink	fat (35%), proteins (16%), carbohydrates (49%)	7.3	1.50

Percentages in % of delivered energy (En %)

and a compound solution of carbohydrates, proteins and fat (Nutridrink®) were chosen; see Table 4.1.

In vitro experiments

A 750 ml Erlenmeyer flask was placed in a water bath with a constant temperature of 37ºC. The flask was air-tight sealed with a cock-stop which contained two holes, allowing passage

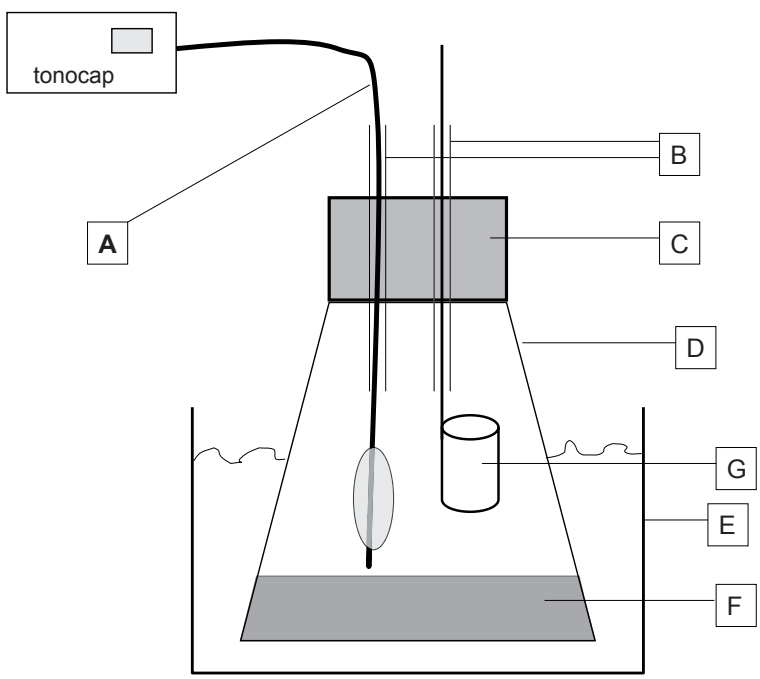

Figure 4.1. In vitro experiment.
Flask for in vitro determination of CO2 production an absorption by the various test meals.
A : tonometer catheter
B : tubes for tonometer and sample (installation of bicarbonate)
C : stopcock with two entry sites
D : glass flask
E : waterbath (37 ° Celsius)
F : test meal (250 ml)
G : extra glass for bicarbonate and acid mixing (CO2 absorption experiment).

of a tonometer catheter and a polyethylene tube. The tonometer was connected to a Tonocap (Datex Ohmeda, Helsinki, Finland) and PCO2 measurement was performed automatically every 10 minutes. In each experiment a standard volume of 250 ml liquid meal was placed in the flask. The CO2 production and absorption experiments were performed separately.

For the measurement of CO2 production, sodium bicarbonate (5 ml, 0.1 M) was suspended in 250 ml of the standard meal at t = 0 minutes. For the measurement of the CO2 absorption, hydrochloric acid (5 ml, 1.0 M HCl) and sodium bicarbonate (2.5 ml, 0.1 M) were mixed in a polyethylene basket placed in the flask above the standard meal at t = 0 minutes. This gaseous CO2 was suspended above and stirred into the meals. The meals and added contents were stirred every minute by hand. During both experiments the PCO2 was measured every 10 minutes for 2 hours. All tests were performed in triple; see Figure 4.1.

RESULTS

CO2 production

Adding bicarbonate to the various meals resulted in a PCO2 rise in all meals; see Figure 4.2. The largest rise of PCO2 was seen in the protein meal; almost no production of CO2 was seen in the fatty meal. The maximal change in PCO2 was just over 3 kPa, as seen in the protein meal.

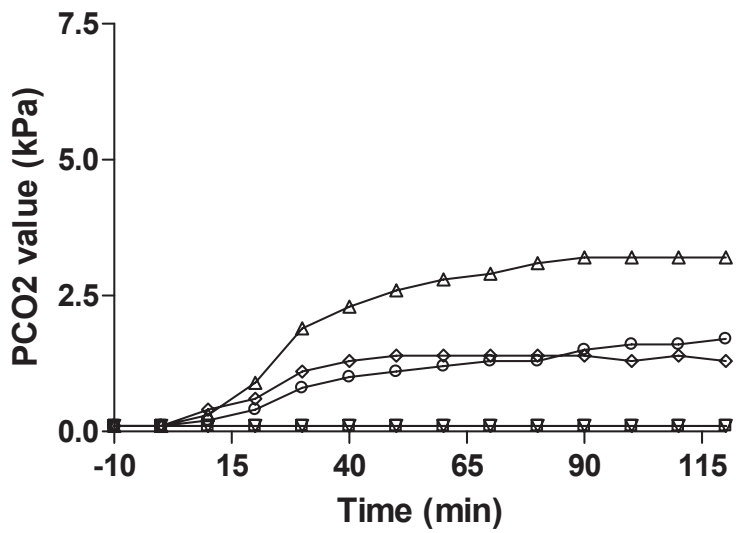

Figure 4.2. In vitro results: production of PCO2.
CO2 production curves of the different meals; protein-predominant (+), fat-predominant (×), carbohydrate-predominant (◊), compound solution (○) and control (□). On the horizontal axis time in minutes, on the vertical axis the measured PCO2 in kPa.

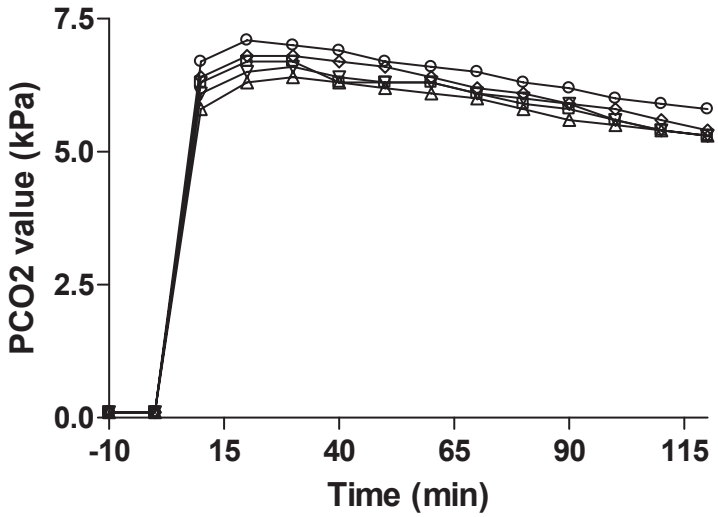

Figure 4.3. In vitro results: absorption of PCO2.
CO2 absorption curves of the different meals; protein-predominant (+), fat-predominant (×), carbohydrate-predominant (◊), compound solution (○) and control (□). On the horizontal axis time in minutes, on the vertical axis the measured PCO2 in kPa.

CO2 absorption

Adding (gaseous) CO2 to the various test meals resulted in minimal change in PCO2 in all meals; see Figure 4.3. Using the bicarbonate and hydrogen solutions to produce gaseous CO2, a maximum PCO2 between 6 and 7 kPa was reached. During the 120 minutes of the measurement, a slight decrease of PCO2 was seen in all meals. This decrease of CO2 was similar in all meals.

DISCUSSION

In this in vitro study different standard test meals of different composition, were tested for their ability to produce or absorb CO2 in a 'stomach like model'. The ideal test meal to be used in diagnostic tonometry testing has the following characteristics: 1) minimal capacity to absorb and produce CO2, 2) maximal challenge of splanchnic arterial blood flow, and 3) standardized (in contents and quantity).

The results of this study show that all standard meals have an almost zero capacity to absorb CO2. The use of all meals will unlikely influence the regional PCO2 in stomach and / or proximal part of the small bowel if local CO2 is produced by mucosal ischemia. On the contrary have all meals, more or less, the capacity to produce CO2, as exposed to bicarbonate. In the human stomach and proximal small bowel large amounts of bicarbonate are present. In the gastric mucosal layer and in the duodenal bulb large amounts of bicarbonate are produced for protection of the stomach mucosa and buffering of stomach acid and start of the fermentation process[11,12].

The ingestion of fatty and protein rich meals is known to give the most significant raise to splanchnic blood flow in humans. The ingestion of carbohydrate rich meals only gives a minor raise in splanchnic blood flow[9,10].

All test meals are of standardized contents and easy to dosage. The different capacities of the different meals to produce CO2 (in the presence of bicarbonate) and the triggering of splanchnic arterial blood flow distinguishes the meals. Taking these capacities in mind, the fat-predominant and the compound solution meal are in theory the most promising meals. These two meals combine standardization, minimal absorption and production of CO2, and maximal challenge of splanchnic blood flow response. We considered the use of these two meals in further human experiments as provocation of gastrointestinal ischemia, in combination with gastrointestinal tonometry.

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Prolonged gastric and jejunal tonometry: a study in healthy subjects

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Submitted

ABSTRACT

Introduction – Gastrointestinal tonometry (GI) has proven its diagnostic value in patients with GI ischemia. Prolonged gastric (and jejunal) tonometry after meals can be of additional value in the work-up of patients suspected of chronic GI ischemia. Initial studies on prolonged tonometry yielded unreliable results due to large variations in PCO2 as a result of the meals and gastric acid production. We decided to challenge these problems by using in vitro tested meals and a rigid acid suppression regime in a healthy subject group.

Methods – Standard meals were tested in vitro on the ability to produce and buffer CO2. The meals with least CO2 variations were subsequently used in healthy subjects. Tonometry of stomach and jejunum was performed for 24 hours, with optimal and controlled acid suppression.

Results – Ten subjects were enrolled in the study. The acid production was sufficiently suppressed. The gastric PCO2 baseline (fasting) was 6.5 (1.0), and significantly lower, than the jejunum PCO2 baseline of 7.6 (0.9) kPa. The baseline was clearly identifiable in all subjects. The gastric baseline during the day was 6.9 (1.6), and significantly lower, than the gastric baseline during the night of 8.0 (1.8), suggesting a diurnal variation of PCO2.

Conclusions – Increases of PCO2 were seen in all subjects, after meals and in between.

Prolonged gastric and jejunal tonometry is feasible in humans. Normal values before and after (standard) meals could be obtained. Prolonged tonometry may be used in the diagnostic work up of patients suspected for GI ischemia.

INTRODUCTION

Measurement of carbon dioxide (PCO2) in the proximal gastrointestinal tract has been used as an indicator of several (patho-) physiological processes[1-4]. During the last decades PCO2 measurement has been used as a measure of perfusion adequacy of the gastrointestinal mucosa. Gastrointestinal PCO2 measurement proved to be an accurate parameter of (early) splanchnic ischemia[5,6]. The latter was popularized by Fiddian-Green with the introduction of the tonometer, a balloon tipped catheter that allows ex vivo measurement of gastrointestinal PCO2[7]. Tonometry has proven its value in the assessment of intra- and postoperative organ perfusion adequacy. In the intensive care setting an abnormal tonometry has been associated with increased morbidity and adverse outcome[8].

Tonometry has also been used in patients suspected of chronic splanchnic syndrome (CSS). In these cases, a test-meal was administered to provocate splanchnic ischemia. Unfortunately, the diagnostic accuracy of tonometry during meals varied widely in these initial studies. This variation was caused by acid secretion and meal-induced CO2 production[7,9]. This led us to develop an alternative provocative test, the gastric exercise tonometry (GET). We demonstrated an accuracy of 86% for GET in patients suspected of chronic splanchnic ischemia[10]. Still, because postprandial pain is more common than exercise-induced pain in CSS patients, meals as a provocative maneuver can not be completely disregarded[11].

The problems of acid buffering and meal-related CO2 production may be minimized by the use of a combination of high dose proton pump inhibitors together with standardized meals selected for metabolic demand and mimicking of normal every day situations. We aimed to develop an accurate, reproducible meal-provocation tonometry test for the upper gastrointestinal tract. We therefore first tested different standardized meals for in vitro CO2 production and buffer capacity. A selection of optimal test meals, high dose proton pump inhibition and prolonged gastric and small bowel tonometry were applied in a group of healthy subjects.

METHODS

The healthy subjects study was approved by the medical ethics committee of our institution.

Choice of test meals

An 'ideal' standard meal for provocation of splanchnic ischemia would be a high protein and fatty meal, as this is associated with maximal gastrointestinal blood flow demand, and with minimal disturbance of local PCO2[12,13]. Based on this argument and the outcome of the in vitro study, we chose the compound solution and fat-predominant meal to be tested in the healthy subjects study.

Fecal sample

From all subjects a fecal sample was tested for the presence of *Helicobacter pylori* antigen (Premier Platinum HpSa, Meridian Bioscience Europe, the Netherlands).

Duplex ultrasound splanchnic arteries

The splanchnic arteries of all subjects were visualized with a standardized duplex ultrasound examination, after a period of 6 hours of fasting.

Arterial blood gasses

The blood PCO2 was measured 30 minutes after each meal. After the first meal an arterial blood sample from the radial artery was drawn, and after the subsequent meals an arterialized capillary blood sample was taken. Analysis of these samples was performed with a standard blood gas analyzer (ABL 500 Radiometer, Copenhagen, Denmark).

Experiment – 24 hours tonometry

A gastric and jejunal tonometry catheter (8 French, Datex Ohmeda, Helsinki, Finland) together with a gastric pH meter (pHersaflex™, internal reference, Medical Measurement Systems, Enschede, the Netherlands) were placed transnasally after 6 hours of fasting and placement was fluoroscopically controlled. An intravenous catheter was placed in a radial vein and omeprazole was started with a bolus of 80 mg in 30 minutes, followed by 8 mg / hour, using an infusion pump (Perfusor compact®, B Braun Melsungen AG, Melsungen, Germany). The catheters were connected to respectively the Tonocap (Datex Ohmeda, Helsinki, Finland) and the pH recording device (Medical Measurement Systems, Enschede, the Netherlands). The Tonocaps were connected to a computer on which a data collection program automatically registered the gastric and jejunal PCO2 every 10 minutes. The gastric pH was automatically recorded and stored in a datalogger (Medical Measurement Systems, Enschede, the Netherlands), which allows for reading of the gastric pH as well.

As soon as the gastric pH was > 4.0 for ≥ 30 minutes, the first meal was started (t = 0 minutes). Timing of consumption of the meals was as follows: breakfast I (t = 0 minutes), liquid compound meal (t = 3 hours), dinner (t = 7 hours), fatty meal (t = 11 hours), and breakfast II (t = 22 hours). The subjects were instructed to eat their meals within 15 minutes. The consumption of small amounts of liquids (non-gaseous) was allowed and noted; consumption of alcohol-, acid-, and CO2-containing beverages was strictly prohibited. The total study time was 24 hours. Due to the limited length of the catheters, the subjects were only capable of performing very minor exercise and were allowed to lay down in supine position from t = 12 hours on.

METHODS OF ANALYSIS

pH data

The pH data were analysed using a standardized computer software program (Medical Measurements Systems, Enschede, the Netherlands). The mean (SD), minimum and maximum values of every 10 minutes were calculated.

From the pH data a gastric hydrogen ion activity was calculated, using the arithmetic mean of the antilog of the pH data. For every 10 minutes a summation of gastric hydrogen ions was calculated.

PCO2 data

1. *Overall PCO2*. The overall measured gastric and jejunal PCO2 values were compared in time. The different values were studied at the same time, and using a different time frame of respectively 10 and 30 minutes later in the jejunum.
2. *Baseline PCO2*. The baseline PCO2 was calculated as the mean PCO2 in the period from 2 hours after a meal to the next meal. The baseline periods were divided into day- and night-time; day-time was defined from 7.00 am to 22.00 pm, night-time defined from 22.00 pm to 7.00 am the following morning.
3. *PCO2 decreases*. A decrease of the PCO2 (dilution) after a meal was defined as significant if the PCO2 decreased 20% or more below the baseline value. These decreases were categorized into: 1) early decrease (< 30 min after end of the meal), 2) late decrease (> 30 and < 120 min after end of the meal), and 3) non-related decrease (> 120 min after the end of the meal).
4. *PCO2 increases*. An increase of PCO2 (peak) after a meal was defined as significant if the PCO2 increased 20% or more above the baseline value. These increases were categorized into: 1) early peak (< 30 min after end of the meal), 2) late peak (> 30 min and < 120 min after end of the meal), and 3) non-related peak (> 120 min after end of the meal). The time of appearance of non-related peaks was scored using the following time schedule: from 0 – 6 hours (6 to 12 am; morning), 6 – 12 hours (12 to 6 pm; afternoon), 12 – 18 (6 pm to 0 am; evening) and 18 – 24 hours (0 to 6 am; night). The appearance of a significant increase of the PCO2 in both the stomach and jejunum within < 30 minutes of each other was defined as a coupled peak.

The area under the curve (AUC) of each PCO2 peak was calculated, with extraction of the baseline PCO2 area under the curve. The delta-peak was defined as the difference between baseline PCO2 and maximal peak value. The time-to-peak (TTP) was defined as the difference in time between the start of the meal and the time of the maximal PCO2 peak value.

pH and PCO2

The relations between (1) gastric hydrogen ion concentration and gastric PCO2, and (2) gastric hydrogen ion concentration and jejunal PCO2 (2) were studied. The relations were calculated per subject, and for the whole group.

Threshold values

The normal threshold of PCO2 decreases and increases following a meal were calculated from mean plus 2 SD's (mean + 2 * SD).

Statistics

All parameters are expressed as mean (± SD), or median (range) when indicated. The PCO2 data were analyzed using a paired t-test (comparison of baselines), analysis of covariance (comparison of gastric and jejunal CO2 values within each subject). The PCO2 peaks were analyzed using a Wilcoxon's signed rank test (areas under the curve) and an unpaired t-test (peak dynamics). A value of $p < 0.05$ was assumed to be statistically significant.

RESULTS

Ten healthy subjects gave informed consent and were enrolled in the study. Their mean age was 38 years (24-56), 5 males and 5 females, all subjects were healthy and had no gastrointestinal complaints and used no medication.

Helicobacter pylori

All healthy subjects had negative findings on Helicobacter pylori fecal antigen testing.

Duplex-ultrasound scanning of the splanchnic arteries

Duplex-ultrasound indicated normal vessels in 8 subjects, in 2 subjects the splanchnic arteries could not be visualized due to over projection of gastric air. Of the latter two, one subject was later excluded from further evaluation because he could not tolerate the fatty meal.

Blood gasses

The mean arterial blood PCO2 measurement after the first meal was 5.3 kPa (SD 0.3), the mean capillary blood PCO2 measurement after the following meals was 5.1 kPa (SD 0.5). No significant differences were found in the repeated capillary blood measurements after the different meals.

Placement of catheters and tonometry

The placement of gastric and jejunal catheters was well tolerated in all subjects. The average time needed to place the jejunal tonometer was 10 minutes (range 5-25).

The 24 hours tonometry testing was well tolerated in 9 of 10 subjects. One subject (number 5) was nauseated and vomited two hours after the intake of the fat solution meal, with displacement of all catheters. The experiment was therefore stopped and this subject was excluded from further evaluation. Because the first four subjects also complained about the

poor tolerability and palatability of the fatty meal, we decided to abandon the use of this test meal in the last 5 subjects (subjects 6-10).

pH-measurements

Overall acid suppression was good in all subjects. A pH of > 4.0 was seen in 93.1% (SD 2.3) of the time; see Figure 5.1.

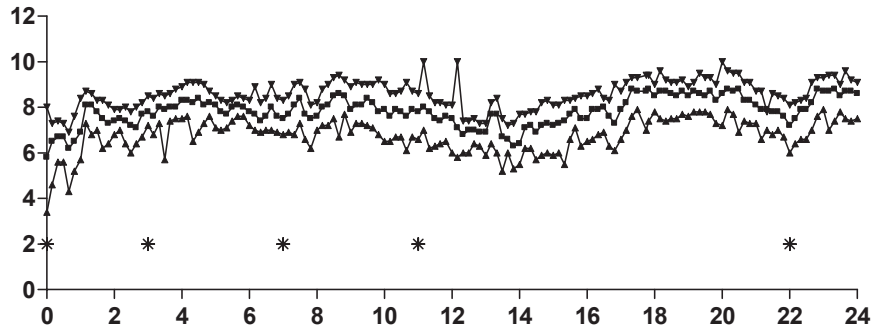

Figure 5.1. pH data of Healthy Subjects.
Median (●), minimum (♦) and maximal (▼) pH curves of all healthy subjects. Horizontal axis time in hours, vertical axis pH. The different meals at scheduled times (∗).

PCO2 measurements

The individual 24 hours PCO2 patterns are depicted in Figure 5.2. In the 9 subjects 31 postprandial periods could be evaluated: 9 after breakfast, 9 after dinner, 9 after compound solution and 4 after fat-predominant meal.

1. *Gastric vs jejunal PCO2 curves.* The overall gastric and jejunal PCO2 were correlated, with a correlation coefficient of 0.29 ($p < 0.0001$).

2. *Baseline.* The overall gastric baseline PCO2 was 6.5 (1.0), and significantly lower ($p < 0.0001$), than the overall jejunum baseline PCO2 of 7.6 (0.9) kPa.

The gastric baseline PCO2 was significantly lower ($p < 0.0001$) during the day compared to the night, respectively 6.9 (1.6) and 8.0 (1.8) kPa. The jejunal day and night baseline PCO2 did not differ significantly, respectively 8.7 (1.9) and 8.6 (1.8) kPa.

3. *PCO2 decreases ('dilutions').* A decrease of PCO2 after meals was seen in all subjects. All, except one in the jejunum, dilutional effects were seen in the stomach. All decreases were 'early decreases', no late or not-meal-related decreases were noticed. In five subjects (56%) a PCO2 decrease was seen after one meal, and in the other four (44%) after more than one meal. The decreases occurred after breakfast in 3 (33%), after diner in two (22%) and after the fatty meal in all (four) subjects.

4. *PCO2 increases ('peaks').* An increase of PCO2 after meals was seen in 8 (89%) subjects. PCO2 peaks were observed in the stomach in 7 (78%) subjects and in the jejunum in 8 (89%) subjects. In the stomach 18 peaks were noticed after 31 meals (58%): 11 early- and 7 late-

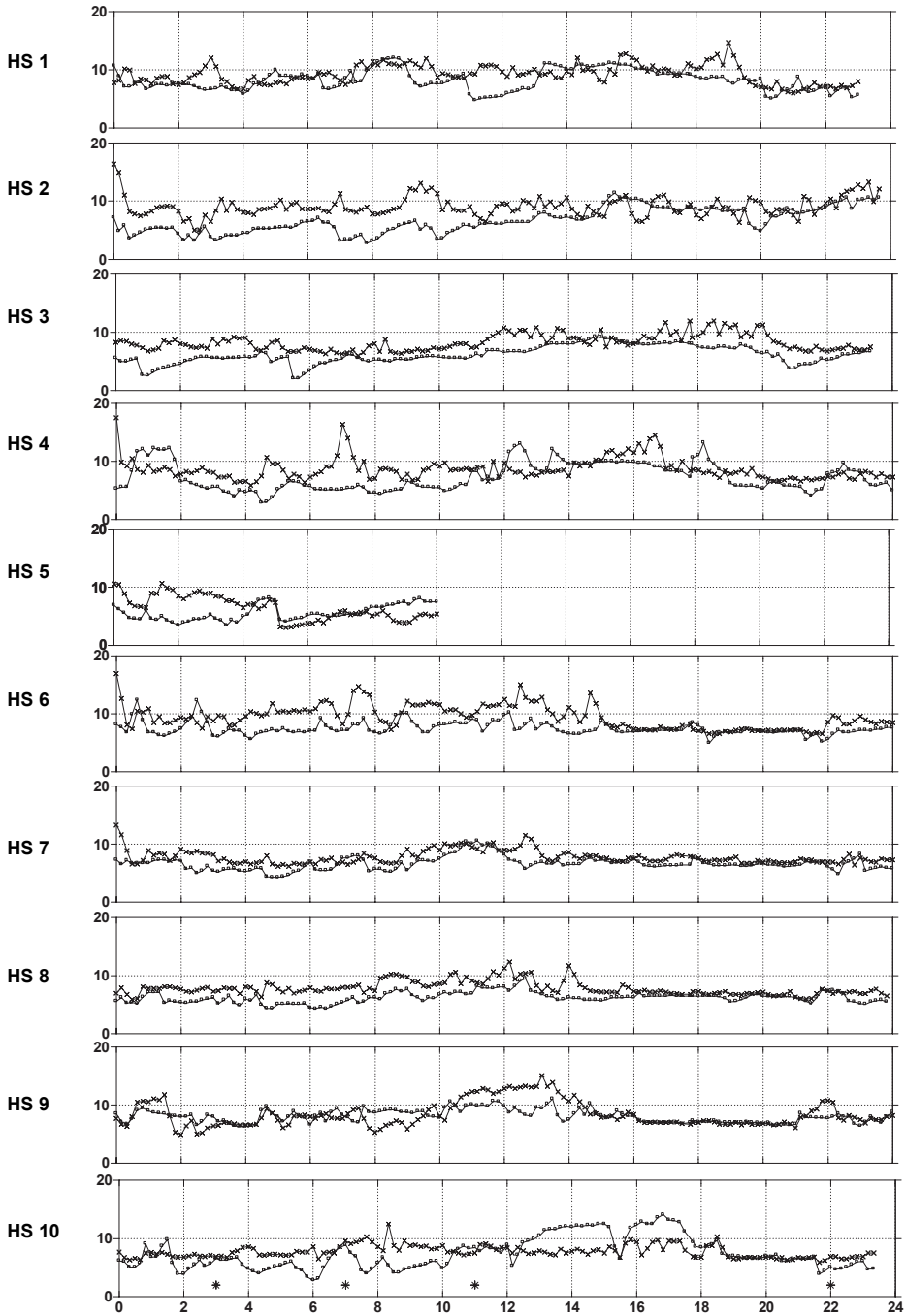

Figure 5.2. Individual PCO2 curves in stomach and jejunum of the healthy subjects.
Healthy subjects (HS) individual curves; on the vertical axis the time from 0 to 24 hours, on the horizontal axis the PCO2 rom 0 to 20 kPa. Curves: PCO2 values measured in stomach (□), jejunum (×) and meals at standard times (∗).

Table 5.1. Peak dynamics of the different meals in the healthy subjects

			Peak	Δ-peak	TTP	Duration	AUC
Stomach	B	Early	9.8 (2.0)	3.5 (1.7)	37 (18)	59 (36)	13.5 (14.3)
	D	Early	10.5 (1.5)	3.4 (1.3)	60 (36)	113 (46)	35.8 (14.7)
	CS	Late	8.6 (1.9)	2.7 (0.9)	53 (15)	87 (38)	20.9 (7.1)
	FM	Early	-	-	-	-	-
	UR		10.4 (1.6)	4.0 (1.7)	131 (111)	238 (162)	60.8 (47.5)
Jejunum	B	Early	10.1 (1.5)	3.6 (1.3)	46 (26)	88 (37)	8.6 (9.4)
	D	Early	11.6 (0.9)	3.5 (0.8)	52 (61)	146 (98)	45.8 (39.9)
	CS	Early	10.2 (1.6)	3.5 (1.3)	53 (59)	93 (60)	20.7 (29.5)
	FM	Early	11.9 (1.1)	3.9 (0.5)	53 (58)	160 (165)	22.0 (19.2)
	UR		12.9 (2.2)	5.0 (1.9)	71 (57)	132 (104)	48.9 (46.2)

All in mean values (SD); Δ-peak = delta-peak, TTP = time to peak, AUC = area under the curve, B = breakfast, D = Dinner, CS = compound solution, FM = fatty meal, UR = unrelated peaks. Peak and Δ-peak in PCO2 in kPa; duration in minutes.

peaks. In the jejunum 22 peaks were noticed after 31 meals (71%): 18 early- and 4 late-peaks. Coupled peaks were noticed 14 times (54% of all peaks).

The meal related peaks were all early peaks, with exception of the compound solution meals, which gave significant late meal-related peaks. The maximal meal-related PCO2 peaks (early and late) did not differ significantly between the different meals. The delta-peak, time-to-peak and duration of the peaks did not differ significantly comparing the different meals, in both the stomach and jejunum.

The areas under the curve in the stomach did not differ significantly for the different meals. The difference between breakfast and dinner was borderline significant ($p = 0.068$). The areas under the curve in the jejunum did also not differ significantly, with again a borderline significant difference between breakfast and dinner and compound solution meal and dinner (both $p = 0.068$); see Table 5.1.

All subjects showed non-meal-related ('isolated') peaks; 8 subjects (89%), both in stomach and jejunum. In total 12 non-meal-related peaks were seen in the stomach, and 14 in the jejunum. These non-meal-related peaks showed high peaks and long duration of peaks, especially in the stomach; see Table 5.2. The majority of the non-meal-related peaks occurred during (late-) evening and night; 2 peaks in the first 6 hours ('morning'), 4 in the 6-12 hours period ('day time'), and 10 in both the 12-18 and 18-24 hours periods ('evening' and 'night time'), equally divided in stomach and jejunum.

The maximum non-meal-related peaks were significantly lower in the stomach compared to the jejunum ($p = 0.005$), respectively 10.4 (1.6) and 12.9 (2.2) kPa.

pH and CO2 measurements

Overall, no significant relation between the gastric hydrogen concentration and gastric and jejunal PCO2 was found.

Thresholds

The calculated PCO2 threshold values after meals are in the stomach 12.1, 11.4, 11.3 and 6.7 kPa for breakfast, dinner, compound solution and fat meal respectively; in the jejunum these threshold values are respectively 12.0, 13.6, 10.6 and 12.3 kPa.

DISCUSSION

This is the first human study evaluating prolonged gastric and jejunal PCO2 measurements using potent acid suppression and standardized, in vitro validated, meals. The differences in baseline PCO2 between stomach and small bowel, and the diurnal variation in the stomach, were not related to gastric acid or meals. The cause of the unrelated peaks (mainly during evening and night) and the observed variations need to be clarified.

Test meals have been used to detect gastrointestinal ischemia, but results were often disappointing due to both CO2 production and CO2 dilution after a meal. In this study we have evaluated both aspects and found the highest CO2 production with protein meals in vitro. This CO2 production is probably caused by buffering of bicarbonate with the amino acids of the proteins of the meal ($NH_3^+ + HCO_3^- \rightarrow NH_3OH + CO_2$). A dinner as provocation meal gives most disturbance of CO2 measurements which can be explained by the fact, that dinner is the most 'uncontrolled' meal, due to different factors: 1) chewing of the meal which adds bicarbonate to the gastric contents by the saliva[14], 2) relatively large amount of proteins, and 3) differences in temperature after ingestion of this meal[15,16]. Although theoretically a perfect test meal, with minimal in vitro production and absorption of CO2, the fat-predominant meal was practically intolerable for most subjects, and is therefore clinically useless. The compound solution meal combined modest variation of PCO2 after meals, palatability and standardization. We therefore consider the compound solution meal to be the best standard test meal to be used for prolonged tonometry in patients suspected of chronic splanchnic ischemia.

A significant correlation between gastric and jejunal PCO2 curves was noted. Overall, the jejunal PCO2 is significantly higher compared to the stomach PCO2. In the fasting state the intraluminal duodenal pH ranges between 2 and 6. These fluctuations in duodenal bulb pH are reduced (or even completely buffered) further on into the mid-duodenum and the duodeno-jejunal junction[17,18]. The PCO2 peaks measured in the proximal jejunum might be the propulsion of (proximal duodenal produced) intraluminal gas by the peristalsis, in other words, CO2 produced in the duodenal bulb is measured in the proximal jejunum.

After a meal the PCO2 in the gastrointestinal tract gradually changes, following the food boluses and secretory processes. The meal related acid production is the major cause of the postprandial pH decrease in the duodenal bulb[17]. This effect of postprandial acidity, and consequently higher PCO2 in the duodenal bulb, was minimized in our experiments by the strict

acid suppression regime. The postprandial peaks are probably due to a higher bicarbonate content caused by increased postprandial pancreatic secretion or local mucosal production[19,20].

The significant different baseline in gastric PCO2 during day and night, suggesting a circadian rhythm, cannot be explained by intraluminal production of CO2. This almost constant raise in stomach PCO2 might reflect minor, reversible, mucosal ischemia caused by the significant lower body and organ perfusion during the night and / or sleep[21,22]. This minor (but significant) change in PCO2 might reflect early ischemia as gastric tonometry is known to detect early local mucosal ischemia.

All subjects showed PCO2 peaks unrelated to ingestion of meals, mostly in the (late) evening and / or (early) night. These peaks can not be explained by gastric acid production, which was almost eliminated by the acid suppression as proven by the intragastric pH registration. The analysis of the relation between remaining acid concentration (and hydrogen ion amount) and the PCO2 profiles of both stomach and jejunum, showed a poor correlation in both per-subject and group analysis. Other possible explanations of these peaks such as the presence of gastric *Helicobacter pylori* infection[23] and actual gastric ischemia by vascular stenosis were excluded. Other explanations could be bicarbonate production by the salivary glands or esophagus and (duodenogastric) reflux.

The addition of saliva (pH range from 5.3 to 7.8) to the meals will undoubtedly influence the intragastric PCO2 as mentioned before. The production of saliva in between meals (during the day) and during the night might also influence the intragastric PCO2. The salivary (unstimulated) rest flow during the day is 0.3 ml/min (for 16 awaken hours a total amount of 300 ml). The production of saliva during the night is nearly zero[14]. Because of the minimal amount of bicarbonate and the fact that most unrelated peaks occur during the evening / night, this seems an unlikely explanation. In the esophagus the median secretion of bicarbonate ranges from 160 - 490 µmol / hour / 10 cm, no data on circadian rhythm of this production exists[24,25]. The peaks in between meals are also unlikely to be explained by production of bicarbonate by the esophagus. Due to our limited knowledge of the circadian production of bicarbonate by the esophagus, this factor cannot be excluded, but seems theoretically an unattractive explanation.

Duodenogastric reflux is a common physiologic phenomenon found in 50 to 65% of healthy subjects[26]. Periods of reflux are often occurring during the early hours of the morning and in the postprandial period. The motor activity in the antroduodenal region seems to be involved in the regulation of duodenogastric reflux[27,28]. The contents of this reflux may vary from pure bile or pancreatic juice or combinations of both[29]. Intraluminal gastric CO2 can be formed during these refluxes, either from buffering of the refluxate with (minimal) residual gastric acid, or as a consequence of the high bicarbonate content itself. The Severinghaus principle does dictate that with similar pH, an increase in bicarbonate content results in 2-fold increase in PCO2 [30].

The results of this healthy subjects study are promising for the use of tonometry after meals in patients suspected of CSS. In this patient group initial experience with simple meal-provocation provided variable results. In retrospect, Fiddian-Green's choice of a milkshake and hamburger meal was not a bad choice, mimicking our compound solution meal[7]. In our own previous healthy subjects study we had a more protein rich solution with PCO2 peaks despite optimal acid suppression. Based on our current study, this must have been caused by buffering of mucosal bicarbonate by the amino acid-containing liquid meal. Our more recently introduced gastric exercise test has its benefits, but is clearly less physiological than measurement after meals, the main provoker for abdominal ischemic pain[11]. The current study provides the background for future patient studies as it identifies the potential meals, as well as the normal 24 hour patterns to be studied. The calculated normal values should be tested in patient studies to establish their value.

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6

One vessel chronic splanchnic syndrome; from myth to reality

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ABSTRACT

Introduction – Isolated stenoses of the splanchnic arteries occur frequently, and are caused by atherosclerosis or celiac axis compression. It is unclear if these isolated stenoses can become symptomatic; therefore treatment is not routinely advised. The gastric exercise tonometry test (GET) is functional test that can identify patients with ischemic complaints. We prospectively studied the use of GET as key criterion for vascular treatment in patients with isolated stenosis of the celiac artery.

Methods – Patients referred for possible chronic splanchnic syndrome (CSS) underwent duplex ultrasound, angiography of the splanchic arteries, and gastric exercise tonometry. Patients with a significant isolated celiac artery stenosis, typical complaints, and abnormal GET were considered for revascularization.

Results – From 1997 – 2003, 320 patients were evaluated; 79 patients had an isolated celiac artery stenosis, 50 of these were diagnosed as CSS. Forty-six of 50 patients had revascularization (35 surgical, 11 endovascular). After a mean follow-up of 37 months, 80% of patients were free of symptoms. The repeated GET improved in 88% of patients free of symptoms and in 29% in patients with persistent complaints after revascularization ($p = 0.0005$).

Conclusions – Isolated celiac artery stenosis can cause ischemic complaints and can be treated safely and with durable results. Using gastric exercise tonometry we could distinguish between patients who would likely benefit from treatment, or not. In our opinion, this test should be included in the analysis and decision making process of patients with CA stenosis suspected of CSS.

INTRODUCTION

The incidence of splanchnic artery stenotic disease (chronic splanchnic disease or CSD) ranges between 20 to 70% in autopsy and angiographic studies. Of these CSD patients, 49-82% have a stenosis of a single splanchnic artery and 18-51% of two or three splanchnic arteries[1-4]. In the normal population an isolated celiac artery stenosis has been found in 7-21% of subjects. These isolated celiac artery stenoses are caused by atherosclerosis or compression by the median arcuate ligament of the diaphragm[5]. It is generally assumed that the vast majority of these individuals with single vessel stenosis remain asymptomatic, because the abundant collaterals of the splanchnic circulation prevent ischemia. Most experts therefore assume that ischemic complaints or the chronic splanchnic syndrome (CSS), defined as CSD causing ischemic symptoms, only occurs in patients with 2 or 3 splanchnic vessel stenosis.

Even more unclear is the potential of the celiac artery compression syndrome (CACS), to cause significant blood flow impairment and ischemia. CACS is defined as external compression of the celiac artery by the arcuate ligament, which varies with respiration. Studies, which failed to show durable symptom relief after revascularization in CACS patients[6-9], coincide with several small series reporting that some patients benefited from revascularisation[10-16]. The lack of an accurate diagnostic test to demonstrate, or rule out, ischemia in patients with solitary celiac artery stenosis may explain the variable, often disappointing, results of treatment in these patients. With the introduction of gastrointestinal tonometry detection of actual ischemia has come within the reach of the clinician[17-20]. In a first clinical study we have shown that gastric exercise tonometry (GET) has an 86% accuracy for detection of ischemia, and may therefore be used to discriminate between patients with CSD or CSS[21].

In this study we prospectively assessed the results of revascularization in patients suspected of ischemia based on an isolated celiac artery stenosis, using an abnormal GET as one of the key indication criteria for treatment.

METHODS

Patients with unexplained chronic abdominal symptoms who were referred for suspected CSS were included in this study. Intra-arterial digital substraction multiplane abdominal angiography (DSA), duplex ultrasound scanning of the splanchnic arteries and GET was performed in all patients. Patients who had been treated previously for CSS where excluded from this study.

Duplex ultrasound

Transabdominal duplex ultrasound scanning of the CA and the SMA was performed using a standardized protocol, after 6 hours fasting. Duplex ultrasound probes of 3.5 to 5.0 MHz with

steerable linear array or convex sector probes were used. The definition of normal or stenotic artery origins was based on the criteria published by Moneta et al[22].

Angiography

The DSA consisted of an anterior-posterior and two or more lateral abdominal aortic injections to visualize the origin of the splanchnic vessels in expiration and inspiration. Thereafter, a selective injection of the celiac (CA), the superior mesenteric (SMA) and the inferior mesenteric artery was performed. A significant stenosis was defined as > 70% luminal reduction. A distinction was made between atherosclerosis and compression of the arcuate ligament. The former is characterised by a concentric stenosis independent of the respiratory cycle, the latter is typically excentric and varies with the respiratory cycle. All angiographies were reviewed by two independent investigators (ABH and RHG). In case of discrepancy between both investigators the DSA was re-evaluated by both and a definitive consensus was reached. The patients with a significant solitary CA stenosis in inspiration and / or expiration were selected for the present study.

Gastric Exercise Tonometry (GET)

The GET was performed, using a standardized protocol with measurement of gastric and arterial PCO2, before, during, and after 10 minutes of sub maximal exercise, as described previously[23]. The criteria for a positive test were: a gradient of > 0.8 kPa after exercise, an increase in gastric PCO2 and an arterial lactate < 8 mmol/l[21].

Diagnosis and treatment

The results of all investigations of the patients were discussed in the multidisciplinary team on gastrointestinal ischemia (MT-GI). In this team a gastroenterologist, a vascular surgeon and an interventional radiologist reviewed and discussed the symptoms, medical history, physical examination and all diagnostic evaluations. For each patient a consensus diagnosis was made and advice for treatment, or not, was given. Patients with a significant CA stenosis, a history consistent of CSS and abnormal results on GET were advised to have treatment. We considered surgical treatment as a first choice treatment, because of the superior patency and established long term follow-up, as compared to percutaneous transluminal angiography (PTA) or stent placement therapy[24-27]. The latter treatment was in general reserved for patients with atherosclerotic lesions and risk factors for increased peri-operatively comorbidity[28].

Follow up

All treated patients visited our clinic every 6 months for assessment of clinical status and repeated duplex ultrasound scanning. A post-intervention GET was scheduled between 3 and 6 months after revascularisation of the CA. The complaints were scored as resolved or per-

sistent (e.g. unchanged). The patients who were diagnosed as non-ischemic, and who were therefore not treated, were discharged from follow-up. The clinical status of these subjects was thoroughly assessed and an inquiry was sent to the referring physician and / or primary care physician.

Statistics

Data were expressed as mean and standard deviation, or median and range when appropriate. The various group comparisons were performed using (Un-) Paired t test, Fisher's exact test or Wilcoxon rank sum testing, p values < 0.05 were considered significant. The results after revascularization were presented in a Kaplan-Meier curve.

RESULTS

Patients

Between July 1996 and July 2003, 320 patients were evaluated for possible CSS. Of these, 85 patients had a significant isolated splanchnic artery stenosis; 81 patients had stenosis of the CA, and 4 patients of the SMA. Two patients were previously treated for single-vessel disease and consequently excluded. The remaining 79 patients with an isolated CA stenosis were enrolled in the present study. The mean age was 47 (range 14 – 83) years, 23 males and 56 females; see Table 6.1.

Table 6.1. Patient characteristics and clinical presentations

	All patients	CSD patients	CSS patients
Number	79	29 (37%)	50 (63%)
Age (years)	46.5 (14-83)	49.2 (14-78)	45.0 (18-83)
Male / female	23 / 56	11 / 18	12 / 38
Duration of complaints (months)	32 (3-192)	24 (4-192)	36 (3-120)
BMI	22.4 (14-33.6)	22.9 (14-33.6)	21.9 (15.7-33)
BMI < 20	27 (34%)	8 (28%)	19 (38%)
Reporting weight loss (nr)	48 (61%)	12 (41%)	36 (72%) *
Weight loss (kg / month)	0.8 (0.1-9)	1.6 (0.7-7.3)	0.5 (0.1-9)
Post prandial pain	59 (75%)	19 (66%)	40 (80%)
Exercise induced pain	33 (42%)	14 (48%)	19 (38%)
Abdominal bruit	26 (33%)	12 (41%)	14 (28%)
Triad 'abominal angine'	13 (17%)	5 (17%)	8 (16%)
Cardiovascular history	20 (25%)	8 (28%)	12 (24%)
Smoking	43 (54%)	7 (24%)	36 (72%) **

BMI = Body Mass Index; * $p = 0.007$; ** $p < 0.001$; all data in numbers (with %) or as mean (with range).

Complaints and physical examination

All 79 patients had chronic abdominal pain, with a mean duration of almost 3 years (range 2 – 192 months). In 59 (75%) patients the pain was meal-related, in 33 (42%) patients pain typically occurred during or after exercise. In 34 (43%) patients a significant weight loss (> 10% of body weight / 1 year) was seen, with a mean of 11 kgs (range 5 – 34). A normal body mass index (BMI > 20) was found in 52 (66%) patients. The 'classical triad' of CSS, consisting of postprandial pain, weight loss and an abdominal bruit, was present in 13 (17%) patients; see Table 6.1.

Duplex ultrasound scanning and DSA of the splanchnic arteries

In 74 patients (94%) the CA and the SMA were assessable for duplex ultrasound investigation. On DSA the stenoses of 42 patients (53%) were compatible with compression by the median arcuate ligament and of 24 (31%) patients with atherosclerotic stenosis. In 5 (6%) patients the concentric stenosis varied with respiration, indicating compression complicated by atherosclerosis. In 8 (10%) patients a differentiation between both types could not be made.

Gastric Exercise Tonometry

In 76 (96%) of patients GET could be performed, no complications occurred. GET could not be performed due to patients' physical inability in 3 patients: poor physical condition due to progressive weight loss and / or complications (n = 2) and history of leg amputation (n = 1).

Consensus diagnosis of the multidisciplinary team on gastrointestinal ischemia

According to the MT-GI, CSS was diagnosed in 50 / 79 (63%) patients, including 45 patients with abnormal results on GET. In 3 patients diagnosed with CSS the GET was normal, but the clinical history was extremely typical for CSS, and they were therefore considered ischemic (and false-negative GET). In 2 patients CSS was diagnosed in the absence of an interpretable GET (physical inability to perform GET). The remaining 29 patients were considered non-ischemic, and thus as CSD alone; see Figure 6.1.

Patient characteristics and clinical presentations

Comparing the CSD and CSS patient groups, we found that significantly more CSS patients reported weight loss ($p = 0.007$) and smoking ($p < 0.001$). None of the other patient characteristics or presenting symptoms differed between the CSD and CSS patient groups.

The patient characteristics of patients with atherosclerotic stenosis and those with CACS differed significantly. The CACS patients had a lower age ($p = 0.003$) and a cardiovascular history was rare ($p = 0.013$), compared to the atherosclerotic stenosis patients; see Table 6.2.

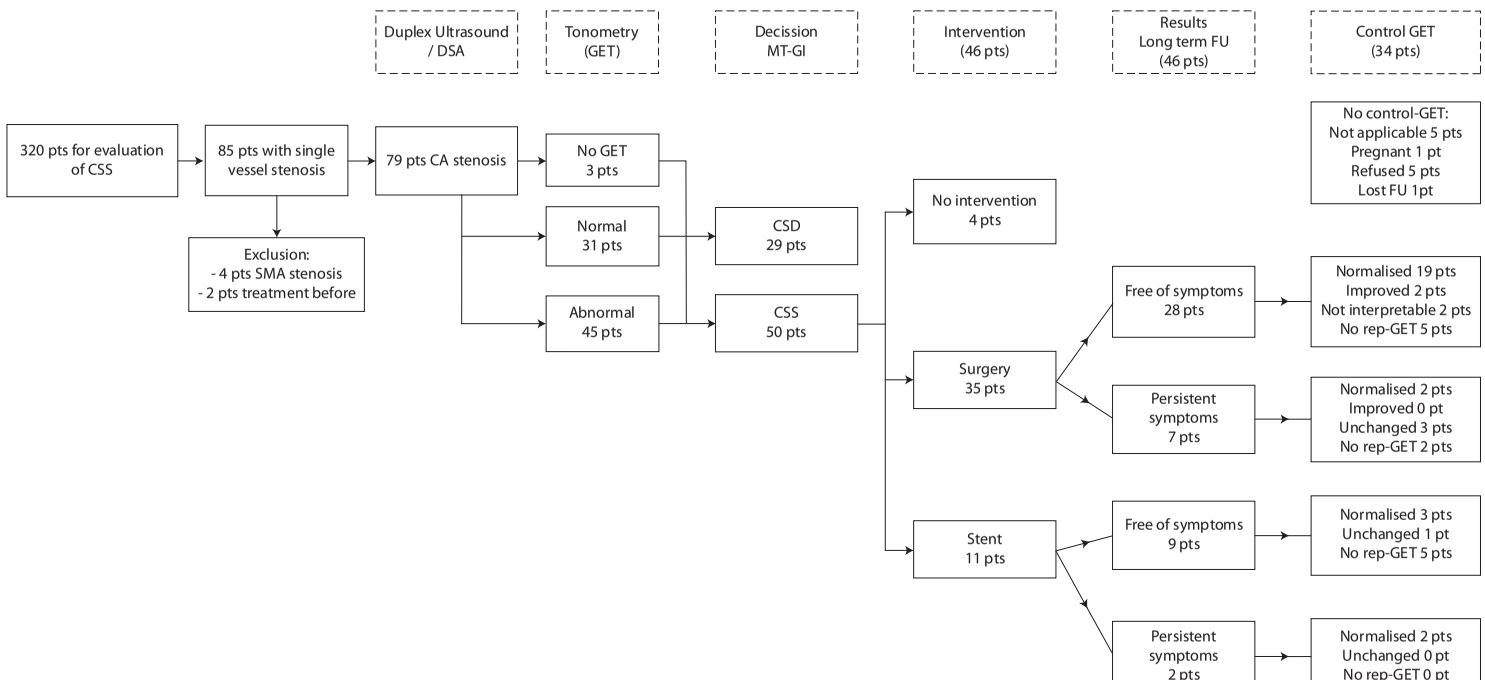

Figure 6.1. Flowchart decision making and results of treatment.

Table 6.2. Patient characteristics and clinical presentations of CACS and atherosclerotic stenosis patients.

	CACS	Atherosclerotic stenosis
Number[#]	30	11
Age (years)	39.8 (18-72)	58.8 (32-83) *
Male / female	7 / 23	4 / 7
Duration of complaints (months)	37 (4-192)	43 (12-120)
BMI	22.1 (17.0-30.9)	22.3 (15.7-33.0)
BMI < 20	10 (33%)	4 (36%)
Reporting weight loss	21 (70%)	8 (73%)
Weight loss (kg/month)	1.9 (0.1-9.0)	0.6 (0.2-1.0)
Post prandial pain	25 (83%)	9 (82%)
Exercise induced pain	12 (40%)	4 (36%)
Abdominal bruit	7 (23%)	4 (36%)
Triad 'abdominal angine'	2 (7%)	3 (27%)
Cardiovascular history	4 (13%)	6 (55%) **
Smoking	21 (70%)	8 (73%)

[#] In 9 patients with CSS no differentiation could be made between CACS and atherosclerotic stenosis; not in this table.
BMI = Body Mass Index; * p = 0.003; ** p = 0.013. All data in numbers (with %) or as mean (with range).

Interventions

In 46 patients (92%) with diagnosis CSS an intervention was performed. In 1 patient who was considered having CSD by the MT-GI, a revascularisation procedure was performed in another hospital. In 4 patients with the diagnosis CSS no intervention was performed because of refusal (n = 1), preferring conservative treatment (n = 2) and postponement due to pregnancy (n=1).

In 35 (76%) patients an operative procedure was performed: a celiac trunk release was performed in 24 patients, venous patching of the CA inflow in 6 patients and an antegrade autologous aortic-celiac bypass in 5 patients. The mean hospital stay was 7.9 days (range 3 – 12 days), there was no mortality and no early (< 30 days after operation) major complications occurred.

Three patients developed late complications after surgical treatment. Two patients after a celiac trunk release and 1 patient after an arterial bypass reconstruction developed severe gastro-oesophageal reflux disease (GERD), 3 – 12 months after treatment. Of these 3 patients, 2 responded well on proton-pump inhibition and 1 patient had anti reflux surgery with good results.

Stent placement was performed as primary treatment in 11 (24%) patients. In 3 (38%) patients complications occurred: 1 patient developed longstanding neuropraxia of the median nerve and 1 patient had occlusion of the brachial artery, after brachial artery canulation. In both patients symptoms resolved on conservative treatment. In another patient displacement of the stent from the catheter occurred during placement, resulting in stent migra-

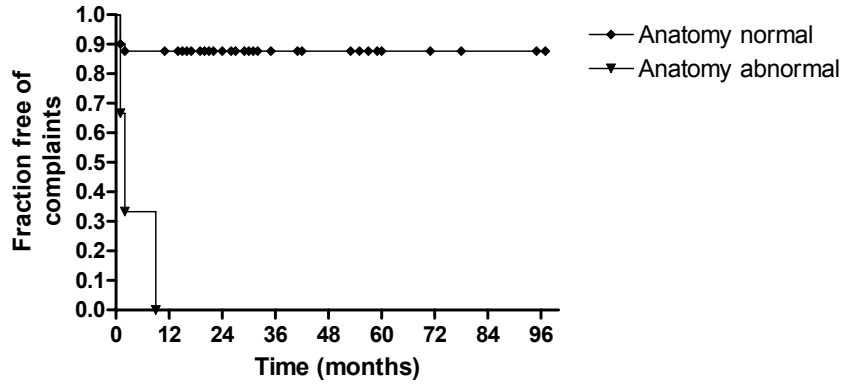

Figure 6.2-A. Symptom free survival after treatment (anatomy after treatment).

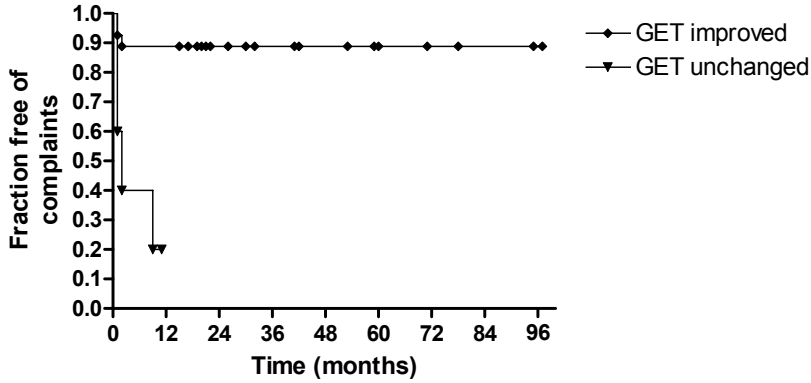

Figure 6.2-B. Symptom free survival after treatment (results of repeated GET).

tion into the common femoral artery, which could be removed operatively without further complications.

Symptoms after treatment

After a median 38 months (range 11 – 104) follow up 37 / 46 (80%) patients were asymptomatic; 35 (97%) of these patients had patent vessels, 1 patient had re-stenosis and in 1 patient the CA could not be visualized on repeated duplex ultrasound. Of the 9 patients with persistent complaints after treatment, 3 (30%) had persistent significant CA stenosis on control duplex ultrasound and / or DSA; a significant difference comparing complaints and vascular anatomy ($p = 0.02$). One patient with a negative MT-GI advice for intervention had persisting complaints after anatomical successful CA release.

Anatomical patency of reconstruction

In 7 / 46 (15%) of all patients with an intervention a significant re-stenosis was diagnosed after the intervention. Of these 7 patients, 3 / 35 (8%) patients had a surgical intervention,

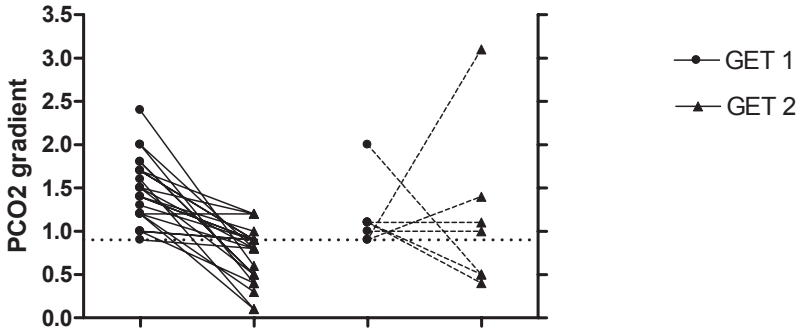

Figure 6.3. Results on GET before and after revascularisation.

and 4 / 11 (36%) had stent placement. In 4 patients a re-treatment was performed, in all 4 patients resulting in normal anatomy; 3 patients had no re-treatment and so persistent abnormal anatomy; see Figure 6.2-A.

Post-intervention GET

In 34 / 46 (74%) of the revascularized patients GET was repeated post-intervention. Of the 12 patients in whom post-intervention GET was not performed, 5 patients were deemed unnecessary because the initial GET was already normal (n = 3) or was not performed pre-intervention (n = 2), 1 patient was pregnant at time of scheduled post-intervention GET (free of symptoms), 5 patients refused repeated GET and 1 patient was lost in follow-up (free of symptoms 2 years after treatment). In 2 patients the results of the post-intervention GET were not interpretable, in 1 patient blood samples proved unreliable and in 1 patient persistent acid production made correct interpretation of the test impossible (both patients free of symptoms).

In 27 / 37 (73%) patients free of symptoms after treatment, a post-intervention GET was performed. In 2 patients the results on repeated GET could not be interpreted. The results of repeated GET showed in 88% normalisation, in 8% improvement and in 4% unchanged results. The maximal PCO2 gradient, measured with GET, in the patients free of symptoms after revascularization was 1.5 (0.4) pre- and 0.7 (0.3) post-intervention ($p < 0.001$). In 7 / 9 (78%) patients with persistent symptoms after treatment, a post-intervention GET was performed. The results of repeated GET showed in 29% normalisation, in 57% unchanged results and in 14% worsened results. The maximal PCO2 gradient, measured with GET, in the patients with persistent symptoms after revascularization was 1.2 (0.4) pre-intervention and 1.1 (0.9) post-intervention (n.s.). Comparing the results of the post-intervention GET between the patients free of symptoms and the patients with persistent symptoms, there was a significant difference ($p < 0.001$) between the 2 groups; see Figures 6.2-B and 6.3.

Follow-up nonischemic group

Follow-up (mean 45 months, range 9-80) was available in 25 / 29 (86%) patients with significant isolated CA stenosis who were diagnosed as non-ischemic. In none of these patients symptoms or signs of worsening of ischemic complaints were seen. Two patients died due to unrelated cause during follow up, 1 patient due to pulmonary carcinoma and 1 patient due to late complications of abdominal radiotherapy for testicular carcinoma.

DISCUSSION

There is of lot of controversy considering the mere existence of single vessel CSS. The opponents argue that abundant collateral circulation prevents ischemia and that positive findings after treatment are mainly due to placebo effect or local pain inhibition by blocking the celiac nerve. They put forward that earlier studies showed no durable positive effect of revascularization on complaints in this patient group[6-9]. In contrary, the proponents argue that many reports show durable effects of revascularization in selected patients[10-16]. One of the shortcomings in earlier research was the non-existence of a diagnostic tool for the assessment of splanchnic ischemia. In this study we have shown that addition of GET in the diagnostic workup of patients with upper abdominal symptoms and an isolated celiac stenosis, the success rate of a reconstruction can be lifted from below the historical 50% to over 80%, as shown in the present study. The mean follow-up of 3 years in this study is relatively short, other studies show relapse of symptoms at 15 years follow-up, so a longer follow-up of these patients is needed, but our mid-term results seem very promising[9]. Moreover, the significant difference in outcome of repeated GET after intervention (normalised in 88% of patients free of symptoms, and only in 29% of patients with persistent complaints) indicates that this test indeed measures gastric mucosal ischemia.

In 4 patients with persistent complaints after (anatomically) successful revascularization, the post-intervention GET remained abnormal. The findings on GET in these patients are considered false-positive results. An explanation of these false-positive findings might be active acid production before and during GET. Persistent stomach acid production is one of the pitfalls of GET: the hydrogen (H^+) in the stomach acid reacts with the bicarbonate ($HCO3^-$) in the stomach mucosal layer, producing CO2, irrespective of the presence of ischemia.

The results of this study give strong evidence for positive added value of GET in this patient group. The significant reduction of complaints, the relation with a normalized functional test after intervention all adds strongly to this notion. This warrants a randomized trial in this patients group in future. Because we only treated the patients in whom the diagnosis ischemia (CSS) was made, a possible beneficial effect of revascularisation in the "non-ischemic" group cannot be excluded.

This study indicates that an isolated stenosis of the celiac artery can give rise to ischemic complaints. The availability of gastric exercise tonometry, a physiological test that detects gastric ischemia, enabled identification of these patients. In these patients the stenosis can be treated safely with durable results.

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The clinical significance of splanchnic artery stenosis; experience in 157 patients

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Submitted

ABSTRACT

Introduction – Splanchnic artery stenosis are not uncommon, and with the increasing use of "screening" CT and MRI scanning more patients will present with (incidental) splanchnic stenosis. The clinical relevance of these stenoses is still unclear, especially the single vessel splanchnic stenosis. The introduction of gastric exercise tonometry enables us to differentiate between patients with a given splanchnic stenosis and actual gastrointestinal ischemia. We prospectively studied a large group of patients with splanchnic stenosis, using a standardized work up, including GET, treatment and follow up.

Methods – Patients referred for possible chronic splanchnic syndrome (CSS) were prospectively analysed, using duplex ultrasound, conventional abdominal angiography and GET. The results of all patients were discussed in a multidisciplinary team and treatment was advised, or not.

Results – In 6 years time, 316 patients were eligible for evaluation. One or more splanchnic stenosis were found in 157 (50%) of these patients. Of these 95 / 157 (61%) had single-vessel, 54 / 157 (34%) two-vessel and 8 / 157 (5%) 3-vessel stenosis. CSS was diagnosed in 107 (68%) patients, respectively in 57% of single-vessel, 83% of 2-vessel and all of the 3- vessel patients. Treatment was performed in 95 (89%) of all CSS patients. Surgery was performed in 62 and stent placement in 33 patients. After a mean follow up of mean 43 months, 83% of treated patients were free of complaints.

Conclusions – GET is crucial in the diagnostic work up of patients suspected of CSS. It identifies patients with actual gastrointestinal ischemia and consequently which patient will benefit from treatment or. Single- and multi-vessel CSS are two different entities with different morbidity and mortality. In both patient groups surgical and endovascular treatment gives satisfying results on mid-term follow-up.

INTRODUCTION

Splanchnic artery stenoses are quite common and their incidence rises with age, to almost 20% at 80 years[1-6]. It is assumed that most patients with splanchnic stenoses remain asymptomatic, especially those with single vessel stenosis[7]. Still, several reports indicate that some individuals benefited from treatment[8,9]. The clinical presentation in literature was variable, and the classical 'abdominal angine' was present in only a minority of patients[9]. The clinician is therefore challenged to differentiate between patients with asymptomatic stenoses, or chronic splanchnic disease (CSD), and patients in whom abdominal complaints are caused by gastrointestinal ischemia, the chronic splanchnic syndrome (CSS). The differentiation is notoriously difficult, and clinical data supporting the clinician in either choice is sparse, often incomplete and gathered over several decades. The growing popularity and increased use of CT and MRI angiography as a 'screening tool' will undoubtedly add to this problem[10,11]. Thus, in a growing number of patients with "incidental stenoses" clinicians will have to decide on treatment or not. The first option is supported by "believers" with more conviction than proof, the latter by those conservative in nature, in line with the *primum no nocere* of our profession. As a result, treatment is often based purely on local expertise, authority or even belief[8,9,12,13].

In recent years with the introduction of gastrointestinal tonometry, the diagnostic evaluation of these patients has changed[14-16]. We have shown that gastric exercise tonometry (GET) enabled detection of ischemia and delineated the precise exercise test environment[17,18]. For several years, patients suspected of CSS were evaluated using a standard workup, including GET, and discussion in a multidisciplinary team (consisting of a gastroenterologist, vascular surgeon and an interventional radiologist) in a prospective manner. In a first paper with 33 patients with CSS, gastric exercise tonometry (GET) proved to be of major importance in the process of distinguishing patients with or without gastrointestinal ischemia[19].

In this study we present a prospectively evaluated cohort of patients with splanchnic stenoses, based on a systematic work up, treatment and follow up. Our aim was to determine the clinical relevance, the benefit and complications of treatment of these splanchnic stenoses.

METHODS

Patients with unexplained chronic abdominal symptoms who were referred for suspected CSS were prospectively included in this study. All patients had intra-arterial digital substraction multiplane abdominal angiography (DSA) and / or duplex ultrasound scanning of the splanchnic arteries, and GET. A subset of the patients with single vessel splanchnic stenosis, have been described in another report (79 patients)[20]. An interim analysis of this patient group has been published before (102 patients, 33 patients with CSS)[19].

Angiography

The DSA consisted of an anterior-posterior and lateral abdominal aortic injections to visualize the origin of the splanchnic vessels in expiration and inspiration. Thereafter, a selective injection of the celiac (CA), the superior mesenteric (SMA) and the inferior mesenteric artery (IMA) was performed. A significant stenosis was defined as more than 70% luminal reduction. The angiographies were scored for pathological collaterals between the different splanchnic arteries. A pathological collateral was defined as a collateral vessel between two main branches, with retrograde filling of one of these branches through this collateral on aselective (aortic) injection.

In the patients with a single CA stenosis, a distinction was made between atherosclerosis and compression of the arcuate ligament. The former is characterised by a concentric stenosis independent of the respiratory cycle; the latter is typically excentric and varies with the respiratory cycle. All angiographies were reviewed by two independent investigators (ABH and RHG). In case of discrepancy between both investigators the DSA was re-evaluated by both, and a definitive consensus was reached.

Duplex ultrasound

Transabdominal duplex ultrasound scanning of the CA and the SMA was performed using a standardized protocol, after 6 hours fasting. Duplex ultrasound probes of 3.5 to 5.0 MHz with steerable linear array or convex sector probes were used. The definition of normal or stenotic artery origins was based on the criteria published by Moneta et al[21].

Gastric Exercise Tonometry (GET)

The GET was performed, using a standardized protocol, before, during, and after 10 minutes of sub maximal exercise, as described previously[18]. The criteria for a positive test, or ischemia, were a gradient of > 0.8 kPa after exercise, an increase in gastric PCO2, and an arterial lactate < 8 mmol/l[19].

Diagnosis and treatment

The results of all patients were discussed in the multidisciplinary team on gastrointestinal ischemia (MT-GI). In this team a gastroenterologist (JJK), a vascular surgeon (RHG) and an interventional radiologist (ABH) discussed the symptoms, medical history, physical examination and all diagnostic evaluations. For every patient a consensus diagnosis was made and advice for treatment, or not, was reported. Thus, the multidisciplinary team approach resulted in a decision on whether or not the symptoms were ascribed to the splanchnic stenosis. Patients with CSS (significant splanchnic stenosis, history compatible with CSS and abnormal results on GET) were considered for revascularization.

We considered operative release or bypass grafting as a first choice treatment, because of the superior patency and established long term follow-up, as compared to percutane-

ous transluminal angiography (PTA) or stent placement therapy. The latter treatment was in general reserved for patients with atherosclerotic lesions and risk factors for increased perioperatively comorbidity[22-26]. In case of stenting we used a balloon expandable short stent with a strong radial force (Bridge® stent; AVE-Medtronic, Santa Rosa, Ca, USA or Express® stent; Boston Scientific, Natick, Ma, USA).

Follow up

All treated patients visited our clinic every 6 months, for the first 2 years, for assessment of clinical status and repeated duplex ultrasound scanning of the splanchnic arteries. The complaints were scored as completely resolved or persistent (e.g. unchanged). After 2 years of follow up, screening was performed every year.

The patients from the non-treatment group were not regularly screened, for patients of this group who did not attend our clinic for > 1 year, a structured inquiry was made by the referring specialist and / or primary physician.

Statistics

The patient data were compared using Students' T-test or Chi-square testing. Data were expressed as mean (standard deviation) or median (range) when appropriate. The results after revascularization were presented in a Kaplan-Meier curve; p values < 0.05 were considered significant.

RESULTS

Patients

Between July 1996 and December 2003, 354 patients were referred to our hospital for evaluation of possible CSS; 38 / 354 (11%) patients were excluded, 17 patients had incomplete diagnostic work-up, 6 patients were evaluated for ischemic colitis, 5 patients presented with another disease, 4 patients were athletes with complaints during and / or after heavy exercise and 6 patients had previous treatment of possible CSS. Thus, 316 patients were eligible for evaluation. The mean age of was 54 (range 14 – 85) years, 108 were males and 208 females.

Splanchnic artery stenosis

A significant stenosis of one or more splanchnic arteries was found in 157 / 316 (50%) patients. A single vessel splanchnic stenosis was found in 95 / 157 (60%) patients (87 patients CA- and 8 patients SMA-stenosis). The stenoses of the CA were excentric in 45 / 87 (52%) patients, concentric in 26 / 87 (30%) patients, concentric varying with respiration in 5 / 87 (6%) patients (indicating both compression and secondary atherosclerosis), and in 11 / 87 (12%) patients the nature of the stenosis remained unclear. A significant stenosis of two splanchnic

arteries was found in 54 patients: in 49 patients of the CA and the SMA and in 5 patients of the CA and inferior mesenteric artery (IMA). A significant stenosis of all three splanchnic arteries (CA, SMA and IMA) was found in 8 patients. A pathologic collateral circulation was found in 74 / 157 (47%) patients.

Gastric Exercise Tonometry

In 139 / 157 (89%) patients with a splanchnic artery stenosis, a GET could be performed. In 18 patients GET could not be performed because of physical inability to perform exercise (n = 15), refusal to perform exercise test (n = 1), intolerability of nasal intubation of catheters (n = 1), and pregnancy (n = 1). In 4 (3%) patients complications occurred during or after GET. In all 4 patients a haematoma followed canulation of the brachial artery, causing long-standing pain in all 4 patients and neuropraxia in 3 patients. These complaints resolved in all 3 of 4 patients on conservative treatment within 6 months. In one patient medial nerve damage caused permanent motoric dysfunction.

In 98 / 139 (71%) patients a gradient of > 0.8 as result on GET was found. In 89 / 98 (91%) patients this increased gradient was defined abnormal, using the criteria aforementioned. In 9 patients with a gradient > 0.8 kPa on GET, an atypical pattern was seen: compatible with persistent acid production (n = 6), or the abnormal gradient was merely due to decreasing arterial PCO2 without increase of gastric PCO2 (n = 3).

Consensus diagnosis

According to the multidisciplinary team, CSS was diagnosed in 107 / 157 (68%) patients. Of these 107 patients, 54 patients had single stenosis, 45 patients had 2-vessel stenosis (44 patients CA and SMA and 1 patient CA and IMA), and 8 patients had 3-vessel stenosis. Stratified to the number of vessels involved, ischemia was diagnosed in 57% of the single vessel, 83% of the 2-vessel and 100% 3-vessel stenoses patients.

In 50 / 157 (32%) patients the multidisciplinary team concluded that the history and data of these patients did not support the diagnosis CSS; 41 single vessel stenosis patients and 9 two vessel stenosis patients, see flow-chart, Figure 7.1.

Characteristics and clinical presentations: CSS vs. non-CSS and single- vs. multi-vessel patients

The mean age of the entire group of splanchnic stenosis patients was 53 (14 – 85) years, 46 males and 111 females, with a mean duration of complains of 28 (1 – 192) months, see Table 7.1.

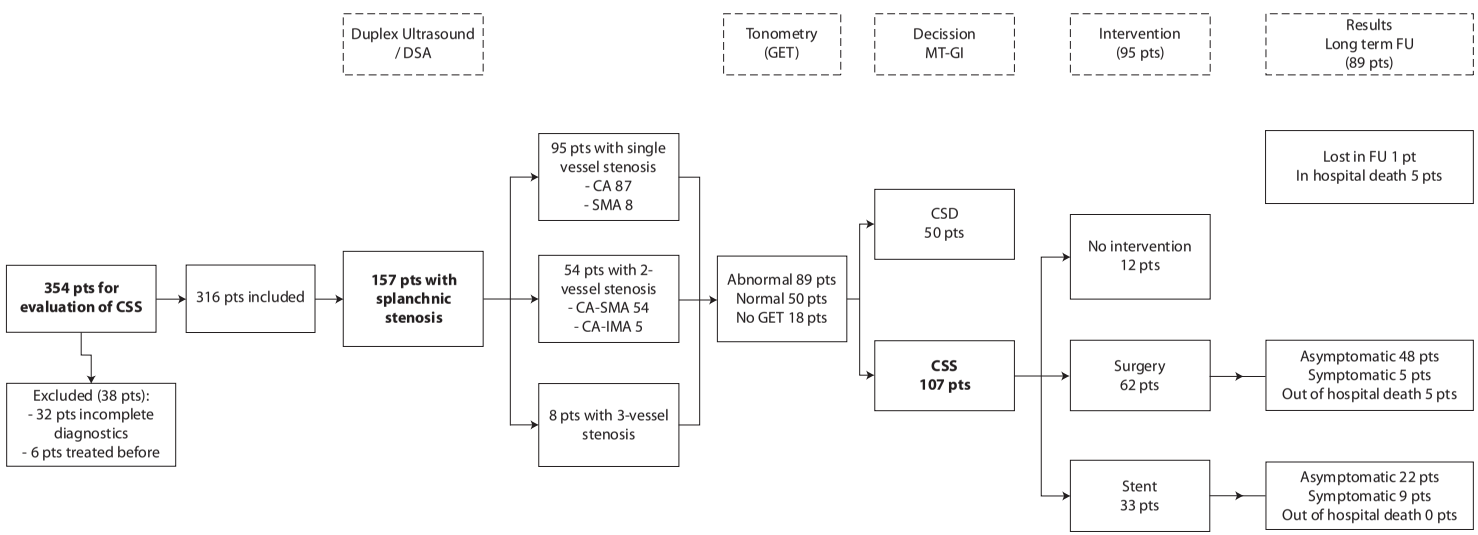

Figure 7.1. Flowchart decision making and results of treatment.

CSS = chronic splanchnic syndrome, CSD = chronic splanchnic disease, DSA = digital substraction multiplane abdominal angiography, GET = gastric exercise tonometry, CA = celiac artery, SMA = superior mesenteric artery, IMA = inferior mesenteric artery, MT-GI = multidisciplinary team on gastrointestinal ischemia.

Table 7.1. Patient characteristics, total group, CSS and non-CSS patients

	Stenosis patients	CSS patients	CSD patients
Number	157	107 (68%)	50 (32%)
Age (years)	53 (14 – 85)	54 (18 – 85)	51 (14 – 83)
Male / female	46 / 111	28 / 79	18 / 32
Duration of complaints (months)	28 (1 – 192)	26 (3 – 192)	30 (1 – 144)
BMI	21.8 (12.0 – 33.6)	21.6 (12.0 – 33.2)	22.4 (13.6 – 33.6)
BMI < 20	49 (31%)	37 (35%)	13 (26%)
Reporting weight loss (nr)	107 (68%)	83 (78%)	24 (48%)*
Weight loss (kg / month)	2.3 (0.1 – 15.0)	1.9 (0.1 – 7.7)	3.5 (0.7 – 15.0)**
Post prandial pain	128 (82%)	92 (86%)	36 (72%)**
Exercise induced pain	67 (43%)	46 (43%)	21 (42%)
Abdominal bruit	30 (19%)	26 (24%)	4 (8%)***
Triad 'abominal angine'	27 (17%)	23 (21%)	4 (8%)
Cardiovascular history	55 (35%)	43 (40%)	12 (24%)
Smoking	70 (45%)	49 (46%)	21 (42%)
Collaterals on DSA	74 (47%)	49 (46%)	25 (50%)
Results on GET	1.2 (0.0 – 2.8)	1.4 (0.3 – 2.8)	0.9 (0.0 – 2.6)

BMI = Body Mass Index; * p = 0.0003; ** p = 0.01; *** p = 0.03; all data in numbers (with %) or as mean (with range).

Table 7.2. Characteristics and clinical presentations of single and multi vessel CSS patients.

	Single-vessel CSS	Multi-vessel CSS
Number	54	53
Age (years)	48 (18 – 83)	61 (35 – 85)*
Male / female	17 / 37	12 / 41
Duration of complaints (months)	29 (3 – 192)	22 (3 – 120)
BMI	22.5 (15.7 – 33.2)	20.6 (12.0 – 30.0)**
BMI < 20	17 (31%)	20 (38%)
Reporting weight loss (nr)	38 (70%)	44 (83%)
Weight loss (kg / month)	1.4 (0.1 – 7.0)	2.6 (0.1 – 7.7)***
Post prandial pain	47 (87%)	45 (85%)
Exercise induced pain	26 (48%)	21 (40%)
Abdominal bruit	15 (26%)	10 (19%)
Triad 'abominal angine'	11 (20%)	10 (20%)
Cardiovascular history	17 (31%)	27 (50%)
Smoking	29 (54%)	23 (43%)
Collaterals on DSA	23 (43%)	24 (45%)

BMI = Body Mass Index, GET = gastric exercise tonometry; * p < 0.0001; ** p = 0.05; *** p = 0.002; all data in numbers (with %) or as mean (with range).

Comparing the CSS and CSD patients groups, the CSS patients reported significantly more weight loss, 78 and 48% respectively (p = 0.0003) and post prandial pain, 86 and 72% respec-

Table 7.3. Morbidity and mortality in all CSS patients

		Morbidity	Mortality	
			In hospital	Out of hospital
Single vessel CSS pts	55	6 (11%)	0*	0
– surgical treatment	35 (64%)	3 (8%)	–	–
– endovascular treatment	15 (27%)	3 (20%)	–	–
– no treatment	5 (9%)	–	–	–
Multi vessel CSS pts	52	2 (4%)	8 (15%)*	5 (9%)
– surgical treatment	27 (52%)	0	5 (19%)	4 (15%)
– endovascular treatment	18 (37%)	2 (11%)	0	1 (6%)
– no treatment	7 (13%)	–	3 (6%)**	–

CSS = chronic splanchnic syndrome; pts = patients; * p = 0.0005; ** 3 patients who died of acute splanchnic disease before complete diagnostic work-up and treatment.

tively (p = 0.01), and on physical examination an abdominal bruit was more frequent in the CSS patients group, 24 and 8% respectively (p = 0.03). Comparing the single and multi vessel patient groups, the multi vessel patients were significantly older, 48 (18 – 83) and 61 (35 – 85) respectively (p < 0.0001), had a significant lower BMI, 22.5 (15.7 – 33.2) and 20.6 (12.0 – 30.0) respectively (p = 0.05) and had significant more weight loss per period, 1.4 (0.1 – 7.0) and 2.6 (0.1 – 7.7) (p = 0.002), see Table 7.2.

In the single vessel patient group there was no mortality, and only one patient presented with major morbidity. This was a 66-year old male in whom the initial presentation was an infarction of 40 cm of the jejunum. This was preceded by a period of severe diarrhoea causing dehydration. Later a significant CA stenosis was demonstrated. He underwent urgent surgical resection of the infracted bowel loop and recovered without symptoms.

In the multi-vessel patient group, 3 / 62 (5%) patients died before an intervention could be performed, all from a bowel infarction. All three patients had signs of "end-stage" disease, characterised by abdominal pain that had developed from "classic" post prandial pain, to almost continuous pain, even without any oral intake. All these three patients had lost over 15 kgs weight in the last year.

Interventions

In 95 / 107 (89%) patients with consensus diagnosis CSS an intervention was performed. In 12 patients (11%) no intervention was performed: in 9 patients an intervention was contraindicated due to comorbidity and / or (technical) inabilities. Three other patients preferred conservative treatment, consisting of small meals, divided over the day and proton pump inhibition. A surgical revascularisation was performed in 62 / 95 (65%) patients, while an intravascular stent was placed in 33 / 95 (35%) patients. In one patient surgery was performed following unsuccessful initial stent placement.

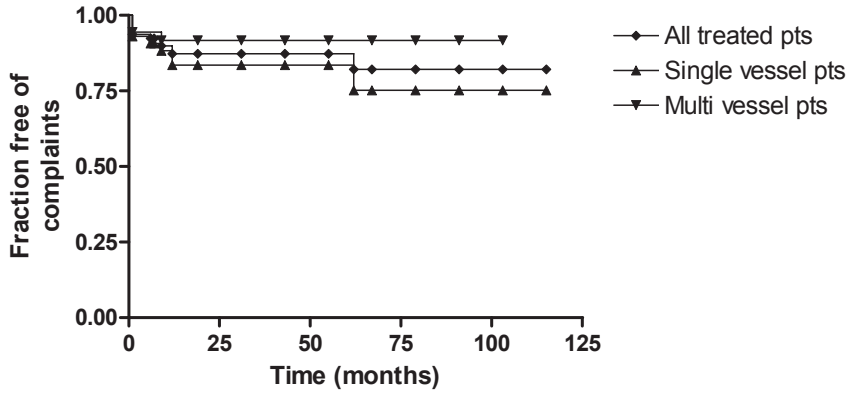

Figure 7.2-A. Symptom free survival after treatment; all, single and multi vessel patients.
Kaplan-Meier survival curve of treated patients, divided into all treated patients, single vessel treated patients and multi vessel treated patient; no significant differences between the curves.

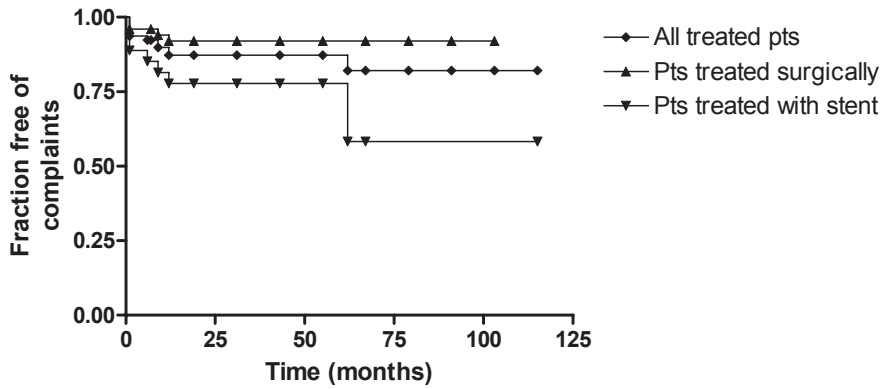

Figure 7.2-B. Symptom free survival after treatment; all, surgical and stent placement treated patients.
Kaplan-Meier survival curve of treated patients, divided into all treated patients, patients treated surgically and patients treated with stent placement; $p = 0.03$ comparing the surgically and stent placement treated patients.

Treatment-related complications and mortality

In the single vessel patients there was no mortality. Complications were seen in 6 / 50 (12%) patients. One patient developed longstanding neuropraxia of the median nerve and one patient had occlusion of the brachial artery, after brachial artery canulation. In the latter patient symptoms resolved on conservative treatment. In another patient displacement of the stent from the catheter occurred during placement, resulting in stent migration into the common femoral artery, which could be removed operatively without further complications. Three patients developed severe gastro-oesophageal reflux disease (GERD), 3 – 12 months after treatment. Of these three patients, two responded well on proton-pump inhibition and one patient had anti reflux surgery with good results.

In the multi vessel patients group, 10 / 45 (22%) patients died, all after surgical treatment. Five patients had signs of multiple organ failure postoperatively and died 15 days (range

5 – 22 days) after the procedure. The BMI of these non-surviving patients was significant lower (p = 0.02) compared to the BMI of the surviving patients, respectively 17.5 (12.0 – 24.7) and 21.0 (17.9 – 30.0). The other 5 patients died more than 30 days after the intervention, two patients due to related cause (one patient due to persistent cachexia and one patient with recurrent ischemia) and three patients due to unrelated causes of death (all three due to fatal cardiac events). Two other complications in the multi-vessel patients group were related to stent placement. In one patient a hematoma developed after canulation of the brachial artery, resolving on conservative treatment; the other patient had displacement of the stent during placement, which had to be removed operatively, followed by successfully placement of another stent ; see Table 7.3.

Symptoms after treatment

The follow up was available for 89 / 90 (99%) patients who left hospital after treatment. The median follow up was 43 months (range 5 – 115). Seventy of 89 (79%) patients were asymptomatic, 4 / 89 (5%) patients had partial improvement of complaints, 10 / 89 (11%) had persistent complaints, 1 / 89 (1%) patient was lost in follow-up. Of the single vessel patients 38 / 50 (76%) were free of complaints after treatment, compared to 32 / 35 (91%) of the surviving multi vessel patients (n.s.), see Figure 7.2-A.

Of the patients treated with stent placement, 22 / 31 (71%) were free of complaints after treatment, compared to 48 / 53 (91%) of the patients who had a surgical revascularization (p = 0.03), see Figure 7.2-B.

Follow-up non-intervention group

Follow-up was available in 41 / 50 (82%) patients with significant single or multi vessel stenosis, considered non-ischemic or asymptomatic. In none of these patients symptoms or signs of developing or worsening splanchnic ischemia were seen. Three patients died due to unrelated causes (pulmonary carcinoma, late complications of radiotherapy treatment after testicular carcinoma and myocardial infarction) during follow-up, all three more than 12 months after diagnostic evaluation for CSS.

DISCUSSION

This is the first prospectively analysed, large cohort of patients with splanchnic stenosis, collected in a relatively short time period, using standard diagnostic work up and decision making. It emerges that almost 70% of these patients have symptomatic stenoses. Of those patients who were diagnosed as having CSS, the vast majority had durable relief of symptoms after treatment. A large difference between single- and multi-vessel stenoses was observed, which may result in different work-up and treatment. The study underscores the value of

gastric exercise tonometry (GET), as a physiologic test, allowing for detection of ischemia in this patients group, and thereby enabling us to distinguish between CSD and CSS.

The role of gastric exercise tonometry seems crucial in both single and multi vessel patients. In the single vessel patients group, the result on GET determinates if patients have CSS (or CSD with a negative GET) and will benefit from revascularization or not. As demonstrated in a separate paper, the normalization of the GET was the principle indicator of successful revascularization[19]. In the 2-vessel patients group the potential of GET decreases, but still almost 20% of patients do not have (gastric) ischemia with GET and on follow-up. In the 3-vessel patients group GET seems to play a minor role for decision making of treatment. However, in several patients of the latter group, we have observed a pattern of (pathologic) PCO2 profiles before or after GET, in combination with abdominal pain in between meals. This combination might indicate persisting ischemia and suggests that these patient are at risk for "acute on chronic" splanchnic infarction. These findings set the indications for "urgent" diagnostic work up and treatment, for the prevention of ischemic morbidity, and possible mortality, in near future.

A standard work up of patients suspected of CSS, together with a discussion of complaints, medical history and diagnostic results of all patients in a multidisciplinary team, proves worth wile. The follow-up of almost 4 years is relatively short, but most failures of therapy might be expected in the first years after treatment. The fact that our institution is a tertiary reference centre for patients with suspected CSS, and therefore "end-stage" patients have been included in this cohort, a bias of patient-selection has to be taken in mind. For patients with 'incidental' splanchnic stenosis the assumptions and conclusions drawn from study should be applied with great caution.

From the analysis of this cohort it may be concluded that CSS actually consists of two different entities: single and multi vessel disease. The results of this study evidently show that these two entities have different morbidity and mortality. The single vessel patients had minor morbidity and no mortality. In multi vessel patients major morbidity and mortality occurred, directly disease- and treatment-related. The goal of treatment of single-vessel patients is primarily symptom relief and for multi vessel patients, besides symptom relief, is primarily preventing major morbidity and / or mortality in future.

The outcome of treatment of the CSS patients is overall good: almost 80% of treated patients are free of symptoms after successful revascularisation. The surgical treatment proved to have a significantly better outcome on complaints, compared to endovascular treatment, being in line with earlier reports[21-24]. The significant higher mortality rate in the multi-vessel patients group can be explained by the (significant) differences between age, BMI and quantitative weight loss. The significant difference between BMI's of the surviving and the non-surviving multi-vessel patient after surgical treatment, indirect add to this notion. In general, taken aforementioned into consideration, surgical treatment should be considered as the first choice treatment in patients with single or multi vessel CSS. Our experience with

complicated surgical treatment was especially in the first period (1996-2000). Four out of five patients, who died in the post-operative period, had an adverse outcome in that period. The one patient that died in the second period (2000-2003), was a patient in which primary stent placement failed, which was followed by an operative procedure, with an adverse outcome. From the year 2000 on we decided to put endovascular stent placement as a first choice therapy in patients with a general poor performance status, either due to advanced age, a lower BMI or co-morbidity.

In conclusion, using a standard work up including gastric exercise tonometry, we were able to identify patients with the chronic splanchnic syndrome, based on single or multi vessel splanchnic stenosis. Gastric exercise tonometry proved to be of crucial importance in all patients groups. Surgical and endovascular treatment proved to have excellent results on mid-term follow-up. It emerges that single and multi vessel splanchnic stenosis patients are quite different entities, which deserve different approaches based on, both disease and treatment related, morbidity and mortality. We suggest a patient tailored approach of treatment, leading to reduction of morbidity and mortality in especially the multi vessel ischemia patients group.

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First results of prolonged tonometry in patients suspected of the chronic splanchnic syndrome

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Submitted

ABSTRACT

Introduction – Gastrointestinal tonometry is used to define patients with or without gastrointestinal ischemia. The majority of patients with the chronic splanchnic syndrome have complaints after meals and less during or after exercise. Earlier studies have proven to give unreliable results using (gastric) tonometry after meals, related to carbon dioxide disturbances by the meal and gastric acid production. Recently we have conducted a healthy subjects study using standard meals and continuous proton pump inhibition, providing normal values. In this retrospective study we (re-)challenged the use of tonometry after meals in patients suspected of gastrointestinal ischemia, providing a maximal controlled environment.

Methods – Patients referred for suspected chronic splanchnic syndrome had standard diagnostic work up, including abdominal angiography, duplex ultrasound of the splanchnic arteries and gastric exercise tonometry. The latter was followed by prolonged, 24 hours, tonometry after standard meals and continuous intravenously proton pump inhibition. Gastric and jejunal tonometric and gastric pH measurements were performed. Results of all patients were discussed in our multidisciplinary team.

Results – Thirty-three patients were enrolled in the study. Significant splanchnic stenosis were found in 23 / 33 (69%) patients. CSS was diagnosed in 17 (52%) patients. Applying the cut off values conducted from the healthy subjects study, prolonged tonometry predicted correctly ischemia in 14 / 17 patients, and correctly no ischemia in 11 / 16 patients. Representing a sensitivity of 82% and a specificity of 69%.

Conclusions – The use of prolonged tonometry after meals in patients suspected for gastrointestinal ischemia seems feasible and gives promising results for detection of ischemia. A prospective study is necessary to define its additional diagnostic value in this particular patient group.

INTRODUCTION

In patients presenting with unexplained postprandial pain, especially when associated with weight loss and a positive history for cardiovascular diseases, the chronic splanchnic syndrome (CSS) should be among the differential diagnosis[1-3]. Vascular anatomic abnormalities can be clearly demonstrated with angiography, or more recently MRI and CT scanning. Still, a stenosis does not necessarily imply ischemia. We have recently demonstrated the value of the gastric exercise tonometry (GET) to allow differentiation between patients with and without gastrointestinal ischemia. This is a physiological test that shows actual ischemia. The GET proved to have an accuracy of 87% in the detection of gastrointestinal ischemia. Using GET, patients with actual ischemia can be selected, and these patients are consequently the ones who are most likely to benefit from revascularization techniques[4-8].

The accuracy of tonometry might further improve from prolonged measurements, especially following meals. Over 90% of CSS patients report postprandial pain, while about 60% has post-exercise complaints[8,9]. In the latter, ischemia is caused by a steal phenomenon of blood shunted to the muscles and away from the splanchnic circulation. The ischemic pain after meals in CSS is caused by insufficient increase of postprandial blood flow, to balance the increased metabolic demand of the gastrointestinal tract. The measurement of intragastric CO2 directly after meals would therefore be the most physiologic approach of measuring the ischemia in these patients. However, earlier studies showed unreliable results using tonometry after meals, related to insufficient gastric acid secretion and dilution effects[10-12]. We therefore started with testing standard meals in vitro and in healthy subjects, together with high dose proton pump inhibition as optimal gastric acid suppressant[13]. In this study we evaluate retrospectively the additional value of prolonged gastrointestinal tonometry in a group of patients suspected for possible CSS.

METHODS

Patients with unexplained chronic abdominal symptoms who were referred for suspected CSS were included in this study. More common causes of chronic abdominal symptoms such as gallstone disease, stomach or duodenal ulcerations, inflammatory bowel disease, chronic pancreatitis and irritable bowel syndrome had been excluded previously by appropriate diagnostic evaluation. All patients had imaging of the splanchnic arteries (intra-arterial digital substraction multiplane abdominal angiography (DSA) and / or duplex ultrasound scanning) and GET. Next to this standard diagnostic work up, patients had a prolonged tonometry test, directly following GET.

Angiography

The DSA consisted of an anterior-posterior and two or more lateral abdominal aortic injections to visualize the origin of the splanchnic vessels in expiration and inspiration. Thereafter, a selective injection of the celiac (CA), the superior mesenteric (SMA) and the inferior mesenteric artery is performed. A significant stenosis was defined as more than 70% luminal reduction. All angiographies were reviewed by two independent investigators (ABH and RHG). In case of discrepancy between both investigators the DSA was re-evaluated by both and a definitive consensus was reached.

Duplex ultrasound

The transabdominal duplex ultrasound scanning of the CA and the SMA was performed using a standardized protocol, after 6 hours fast, as described previously. Duplex ultrasound probes of 3.5 to 5.0 MHz with steerable linear array or convex sector probes were used[14]. The definition of normal or stenotic artery origins was based on the criteria published by Moneta et al[15].

Gastric Exercise Tonometry (GET)

The GET was performed, using a standardized protocol, before, during, and after 10 minutes of sub maximal exercise, as described previously with both gastric and jejunal catheters[16]. The criteria for a positive GET, established in healthy volunteers and a patient cohort were a gradient of > 0.8 kPa in the stomach after exercise, an increase in gastric PCO2, and an arterial lactate < 8 mmol/l[8,16].

Prolonged tonometry

A gastric and jejunal tonometer catheter (8 French, Datex Ohmeda, Helsinki, Finland) were inserted transnasally, using fluoroscopy. A gastric pH meter (pHersaflexTM, internal reference, Medical Measurement Systems, Enschede, the Netherlands) was placed nasogastrically. Intravenous infusion of omeprazole was started with a bolus of 80 mg in 30 minutes, followed by 8 mg / hour, using an infusion pump (Perfusor compact®, B Braun Melsungen AG, Melsungen, Germany). The catheters were connected to respectively the Tonocap (Datex Ohmeda, Helsinki, Finland) and the pH recording device (Medical Measurement Systems, Enschede, the Netherlands). The Tonocaps were connected to a computer on which a data collection program automatically registered the gastric and jejunal PCO2 every 10 minutes. The gastric pH was automatically recorded and stored in a datalogger (Medical Measurement Systems, Enschede, the Netherlands), which allows for real-time reading of the gastric pH as well.

As soon as the gastric pH was > 4.0 for ≥ 30 minutes, the first meal was started (t = 0 minutes). All patients had the meals at standard times: breakfast I (8.00 am), dinner (12.00 pm), liquid compound meal II (15.00 pm), bread meal (18.00 pm), liquid compound meal II (21.00 pm), and breakfast II (8.00 am the next day). The breakfast, bread and dinner meals

were standardized. The liquid compound meal consisted of 2 packages of 200 ml each meal. The patients were instructed to eat their meals within 15 minutes. The consumption of small amounts of liquids (non-gaseous) was allowed and noted, consumption of alcohol-, acid-, and CO2-containing beverages was strictly prohibited. Due to the limited length of the catheters, the subjects were only capable of performing very minor exercise and were allowed to lay down in supine position from 22.00 pm on.

The criteria for a positive 24 hours tonometry testing were a pathologic response after one, or more, (standard) meals, using the criteria established in a healthy subjects study[9]. These criteria consisted of maximal peak after meals (breakfast, dinner and compound solution meal), maximal non-meal related peaks and basal PCO2 (in between meals). All criteria for both stomach and jejunum measurements, when appropriate.

Diagnosis and treatment

The results of all diagnostic procedures of all patients were discussed in the multidisciplinary team. In this team a gastroenterologist, a vascular surgeon and an interventional radiologist discussed the symptoms, medical history, physical examination and all diagnostic evaluations, with exception of the results on prolonged tonometry. For every patient a consensus diagnosis was made and advice for treatment, or not, was reported. The multidisciplinary team decided: 1) no splanchnic stenosis and no ischemia, 2) splanchnic stenosis and no ischemia (CSD) or 3) splanchnic stenosis and ischemia (CSS). The outcome of the GET, the outcome of the consensus of the multidisciplinary team and the definitive outcome were compared to the results of the prolonged tonometry testing.

Statistics

Data were expressed as mean (standard deviation) or median (range) when appropriate. The data of the ischemic and non-ischemic patients were compared using Students' T-test or Chi-square testing.

RESULTS

Patients

Thirty-three patients were included in this study; mean age 54 (22 – 82) years, 8 males and 25 females. Significant splanchnic stenoses were found in 23 / 33 (69%) patients. A significant single vessel splanchnic stenosis was found in 14 / 33 (42%) patients (13 CA and 1 SMA). A significant stenosis of 2 splanchnic arteries was found in 9 / 33 (27%) patients (all both CA and SMA stenosis); see Table 8.1.

Table 8.1. Patient characteristics, results of diagnostic tests and conclusion.

Nr	Age	Sex	Stenosis	GET	Conclusion	PT
1	61	F	None	0.5	No stenosis	N
2	36	M	CA	0.4	CSD	N
3	55	F	CA	0.7*	CSS	ABN
4	76	M	None	0.6	No stenosis	N
5	47	M	None	1.6#	No stenosis	N
6	42	F	CA+SMA	1.5	CSS	ABN
7	65	F	CA+SMA	2.0	CSS	ABN
8	77	F	CA+SMA	2.2	CSS	ABN
9	72	F	SMA	1.8	CSS	ABN
10	41	M	None	2.8**	No stenosis	N
11	72	F	CA	–	CSS	ABN
12	67	F	CA	0.9	No stenosis	N
13	40	F	CA	1.1**	No stenosis	N
14	82	M	CA+SMA	1.0	CSS	*N*
15	54	F	CA	0.9	CSS	ABN
16	26	M	CA	–	CSS	ABN
17	58	M	None	2.2**	No stenosis	N
18	22	F	CA	0.7	CSD	*ABN*
19	42	F	None	1.1†	CSD	N
20	48	F	CA	1.7	CSS	*N*
21	51	F	CA	–	CSD	N
22	43	F	CA+SMA	0.5‡	CSS	ABN
23	54	F	CA+SMA	1.5	CSS	*N*
24	76	F	CA+SMA	0.6##	CSS	ABN
25	53	M	None	–	No stenosis	*ABN*
26	53	F	CA	1.1	CSS	ABN
27	50	F	CA	1.3	CSS	ABN
28	61	F	CA+SMA	–	CSS	ABN
29	63	F	None	0.8	No stenosis	*ABN*
30	24	F	CA	1.3	CSS	ABN
31	74	F	CA+SMA	0.8	CSD	N
32	41	F	None	1.2†	No stenosis	*ABN*
33	63	F	None	0.0	No stenosis	*ABN*

M = male, F = female; CA = celiac artery, SMA = superior mesenteric artery; GET = gastric exercise tonometry; CSD = chronic splanchnic disease, CSS = chronic splanchnic syndrome; PT = prolonged tonometry, N = normal results on PT, ABN = abnormal results on PT.
* = false negative GET, # = acid production during GET, ** = false positive GET, † = no CO2 raise during GET, ‡ = abnormal jejunum gradient during GET, ## = minor exercise during GET.

Complaints and physical examination

All 33 patients had chronic abdominal pain for mean 35 months (range 3 – 120); 24 / 33 (73%) patients had pain following meals, 11 / 33 (33%) patients reported pain during or after exercise, and 23 / 33 (70%) patients reported weight loss. The mean weight loss was 11 kgs (range 3 – 28 kgs) in 17 months (range 2 – 120 months).

Gastric Exercise Tonometry

In 2 patients the results of GET could not be interpreted because the patients were physically unable to perform submaximal exercise. In 18 / 31 (58%) patients a gradient of > 0.8 as result on GET was found. In 14 / 18 (78%) patients this increased gradient was defined abnormal, using the criteria as previously defined. In 4 patients with a gradient > 0.8 kPa on GET, an atypical pattern was seen: 3 patients showed a pattern compatible with persistent acid production, and 1 patient performed excessive exercise during GET.

Consensus diagnosis of the MT-CSS

According to the MT-CSS, the diagnosis no stenosis or ischemia, CSD and CSS were diagnosed in respectively 12 (36%), 4 (12%) and 17 (52%) patients.

Acid suppression during prolonged tonometry

The overall gastric acid suppression was good, with a gastric pH > 4 of mean 94.8% (range 71% – 100%) of time.

Prolonged tonometry

The prolonged tonometry was well tolerated in all patients; no medical or technical problems occurred. In 28 / 33 (85%) patients tonometric measurements were performed in both stomach and jejunum, in the other 5 / 33 (15%) patients only stomach measurements were performed; see Figure 8.1. In 8 / 33 (24%) patients a dose reduction down to 200 ml compound solution at one meal time had to be done, due to patients inability to consume the normal dosage.

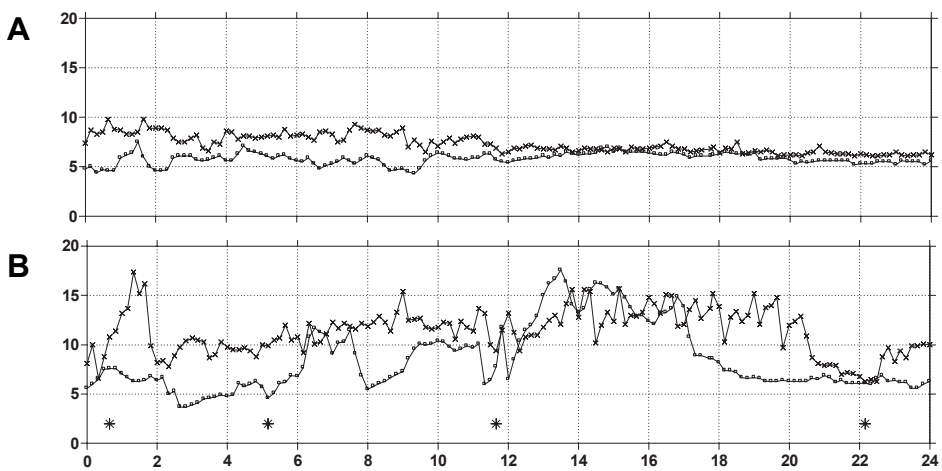

Figure 8.1. Two individual curves of results of prolonged tonometry in a non-ischemic (A) and an ischemic patient (B).
Individual curves of a non-ischemic patient (A) and an ischemic patient (B); on the horizontal axis the time from 0 to 24 hours, on the vertical axis the PCO2 from 0 to 20 in kPa; curves: PCO2 values measured in stomach (□) and jejunum (×) and meals at different times (∗).

Table 8.2. Results of prolonged tonometry in ischemic and non-ischemic patients.

	Ischemic pts			**Non-ischemic pts**		
STOMACH	*Peak*	*Δ-peak*	*Mean CO2*	*Peak*	*Δ-peak*	*Mean CO2*
B	10.6 (3.9)	4.0 (3.4)	–	8.5 (2.7)	2.6 (2.0)	–
D	9.9 (1.9)	3.7 (1.5)	–	8.5 (2.3)	3.3 (2.5)	–
CS	10.4 (3.0)	3.3 (2.2)	–	8.1 (2.6)	1.8 (1.2)	–
Fasting	–	–	7.7 (1.4)*	–	–	6.8 (0.7)
– day	–	–	6.9 (1.1)	–	–	6.5 (0.7)
– night	–	–	8.2 (1.8)	–	–	6.9 (0.8)
JEJUNUM	*Peak*	*Δ–peak*	*Mean CO2*	*Peak*	*Δ–peak*	*Mean CO2*
B	11.6 (3.2)**	3.2 (1.5)	–	8.8 (1.4)	2.1 (0.8)	–
D	12.2 (3.4)$^{\#}$	3.7 (2.0)	–	9.0 (1.7)	2.2 (0.7)	–
CS	10.6 (2.2)	2.5 (1.6)	–	9.0 (1.9)	1.5 (1.0)	–
Fasting	–	–	8.9 (1.6)†	–	–	7.4 (0.7)
– day	–	–	8.8 (1.3)	–	–	7.5 (0.9)
– night	–	–	8.9 (1.9)	–	–	7.5 (0.8)

CO2 = carbon dioxide in kPa; B = breakfast, D = dinner, CS = compound solution meal; * p = 0.02, ** p = 0.005, $^{\#}$ p = 0.04, † p = 0.03.

The fasting baseline of stomach and jejunal PCO2 measurements were significantly higher in the ischemic patients compared to the non-ischemic patients group, respectively 7.7 (1.4) and 6.8 (0.7) in the stomach and 8.9 (1.6) and 7.4 (0.7) in the jejunum (p = 0.02 and p = 0.005). Also the jejunal PCO2 peaks after breakfast and dinner were significantly higher in the ischemic patients compared to the non-ischemic patients, respectively 11.6 (3.2) and 8.8 (1.4) for breakfast and 12.2 (3.4) and 9.0 (1.7) (p = 0.04 and p = 0.03); see Table 8.2.

Using the cut off values from the healthy subjects study for the different standard meals and the baseline periods (PT-1), the result of prolonged tonometry had to be defined as abnormal in 14 / 17 of the ischemic patients and in 5 / 16 of non-ischemic patients. This representing a sensitivity of 82% and a specificity of 69%; see Table 8.1.

DISCUSSION

As in the previous performed healthy subjects study, prolonged tonometry seems feasible in patients suspected of gastrointestinal ischemia. The measurements were easy to perform, generally well tolerated and no complications occurred. In this retrospective study, the results of prolonged tonometry seem very promising, and a useful additional diagnostic test in this particular patient group. It may even replace gastric exercise tonometry as a diagnostic tool [8].

The usage of standard meals with a large metabolic demand, like the compound solution meal, caused a dose reduction in some patients. This dose reduction did not influence the

reading of the data and results of the prolonged tonometry. In all patients the 24 hours period could be completed. The patients tolerated the three transnasally placed catheters well.

The results of the prolonged tonometry were significant different comparing the ischemic and the non-ischemic patient groups (overall) during baseline periods in stomach and jejunum. This might be explained by the continuous compromised arterial blood flow of the mucosa of the stomach (and / or jejunum) in the ischemic patients group. The significant higher maximum peak after the breakfast and dinner meal in the ischemic patients group, compared to the non-ischemic, might be expected. Surprisingly the maximum peak after the compound solution meal did not differ significantly between both patient groups (borderline significant, $p = 0.07$ and $p = 0.052$ respectively for stomach and jejunum). The delta-peak (stomach) after the compound solution was significant higher for the ischemic patients group, compared to the non-ischemic patients.

Using the cut off values accounted from the previously performed healthy subjects study, the sensitivity (and specificity) of the prolonged tonometry for the detection of gastrointestinal ischemia is slightly lower, compared to the GET[8]. Comparing the results of GET and prolonged tonometry, prolonged tonometry predicted correctly in 3 patients no gastrointestinal ischemia and in 1 patients ischemia, where as GET concluded otherwise.

The results of this retrospective study show that prolonged tonometry is feasible and can be used safely in patients suspected of gastrointestinal ischemia. Using the cut off values from the healthy subjects study, a reasonable sensitivity and specificity for detection of gastrointestinal ischemia was noted. A prospective study has to define the exact place of prolonged tonometry with standard meals, in the diagnostic pathway of patients suspected of the chronic splanchnic syndrome.

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9

Summary and conclusions
Samenvatting en conclusies

General discussion and future perspectives

SUMMARY AND CONCLUSIONS

This thesis focuses on two issues: 1) the clinical value of gastric exercise tonometry (GET), and 2) the development of reliable prolonged tonometry, including postprandial measurement, and its potential in patients suspected of gastrointestinal ischemia.

Including GET in the analysis of patients with solitary celiac artery stenosis had major clinical impact. The GET results enabled us to distinguish between patients with and without gastric ischemia. The clinical improvement after vascular treatment in ischemic patients was sustained for up to 4 years, and compares favorably to earlier reports. These results put the single vessel splanchnic syndrome on the map as a clinical entity.

The ability of GET to separate ischemic form non-ischemic patients proved beneficial in the large cohort of patients with both single- and multi-vessel splanchnic stenoses as well. Similar to the single-vessel patients, GET identified patients with gastrointestinal ischemia, subsequent treatment resulted in good results on mid-term follow-up. The single- and multi- vessel patients differed significantly in patient characteristics, clinical presentation, morbidity and mortality (before and after treatment). This leads to the notion that the chronic splanchnic syndrome (CSS) has to be divided into two different entities, with different diagnostic and therapeutic approach, urgency, and goals of treatment.

Prolonged tonometry, including postprandial measurements, proved feasible in healthy subjects when in vitro tested standard meals were taken and high dose acid suppression was administered. From this study 'normal' values were obtained. Using these normal values in a cohort of patients, the accuracy for ischemia detection of prolonged tonometry showed acceptable results. Careful and prospective studies are clearly needed to confirm these first results before prolonged tonometry can be advocated in patients suspected for CSS.

The introduction presents gastrointestinal ischemia in a broader perspective. In **chapter 2** non-occlusive mesenteric ischemia is reviewed. The main focus is on the gradual transitions between normal, physiological adaptation of splanchnic vessel tone and mucosal ischemia, or NOMI. Interestingly, NOMI is well-known and acceptably common, and hardly disputed among intensivists, while it is usually considered very rare among gastroenterologists. In this chapter we tried to make our own, very small, version of a "universal field theory".

In **chapter 3** our current view on the up-to-date clinical approach in patients with suspected CSS is presented. The clinical presentation, current diagnostic tools with a focus on gastrointestinal tonometry and results of treatment are outlined.

The second part of this thesis consists of 2 studies which focus on the methodology of prolonged gastrointestinal tonometry.

In **chapter 4** the results of in vitro testing of different meals are presented. Four standard meals, a carbohydrate-, a protein-, a fat-predominant and a compound solution meal, were compared for their ability to produce and absorb carbon dioxide. The hypothesized ideal test meal should not produce nor absorb carbon dioxide, and would not influence with the intraluminal carbon dioxide level in gastrointestinal ischemia. The two most promising meals were the fat-predominant and compound solution meals.

In **chapter 5** the findings of prolonged tonometry in a group of 10 healthy subjects are depicted. Prolonged tonometry was performed during continuous high-dose intravenous proton pump inhibition, and two of the in **chapter 4** tested standard meals. Prolonged tonometry was generally well tolerated, meaningful patterns were identified, and normal values could be obtained.

The third part of the thesis contains of three clinical studies using GET (gastric exercise tonometry) and prolonged tonometry in patients suspected of CSS.

In **chapter 6** the results of a prospective study of patients with single celiac artery stenosis are presented. Much debate is going on about the mere existence of this disease entity: opponents put forward that the abundant collateral blood supply of the splanchnic circulation protects against the development of gastrointestinal ischemia in patients with single celiac artery stenosis. Proponents put forward that many case reports and small series patients with single celiac artery stenosis demonstrated pain relief following revascularization. In the current study 79 patients with single celiac artery stenosis were included; 46 were treated for the largest part based on the GET results. After successful treatment, 80% of patients remained free of symptoms for over 3 years. Moreover, normalization of the post-treatment proved to be the strongest predictor of treatment success defined as disappearance of pain. Thus, the results of this study show that patients with single celiac artery stenosis can indeed suffer from chronic ischemic complaints, which can be diagnosed with tonometry and can be treated safely and successfully.

In **chapter 7** a large cohort of CSS patients with one or more splanchnic stenoses is presented. To our knowledge, this is the largest patient cohort study in patients with splanchnic stenosis. It is the first study in which patients suspected of gastrointestinal ischemia were prospectively investigated, using a strict diagnostic work-up protocol in a multidisciplinary approach. The diagnosis ischemia was always made by the multidisciplinary team. The follow-up was used to assess long-term results, as well as to adjust the diagnosis when indicated. One of the major conclusions of this study is that CSS consists of two different entities: single-vessel and multi-vessel splanchnic ischemia. The first patients group has minor morbidity and no mortality, thereby justifying a complaints based approach. The second patients group has a high morbidity and mortality rate, both disease and treatment related. Patients with two- or three-vessel splanchnic stenoses have a high risk of having actual CSS and are at high risk for bowel infarction. The end-stage of these multi-vessel CSS patients is rapidly progressive, and

diagnosis and treatment should not be delayed. The treatment of CSS consists of surgical revascularization or endovascular stent placement. The surgical treatment has a significant better result on follow up, but also a higher risk of post-treatment death. Post-operative mortality was related to a significant lower body-mass-index for non-survivors compared to survivors. Stent placement therapy has minor or no mortality but some morbidity, especially neuropraxis after arterial canulation.

In **chapter 8** the first results of the diagnostic potential of prolonged tonometry in patients suspected of CSS are presented. A retrospective analysis in the first 33 patients who underwent prolonged gastric and jejunal tonometry for suspected CSS was performed. Prolonged tonometry was well tolerated and no complications occurred. Using the normal values obtained from the healthy subjects study (**chapter 5**), the accuracy seemed acceptable. Further, prospective, studies are needed to clarify the patterns seen in patients and to evaluate the diagnostic potential of prolonged tonometry in patients suspected of CSS.

SAMENVATTING EN CONCLUSIES

Dit proefschrift behandelt twee hoofdpunten: 1) het klinische belang van inspanningstonometrie en 2) de ontwikkeling van betrouwbare 24 uurs tonometrie, inclusief metingen na maaltijden, en de bepaling van de (aanvullende) waarde van deze 24 uurs tonometrie bij patiënten verdacht voor chronische maagdarmischemie.

De toevoeging van inspanningstonometrie in de diagnostische work-up van patiënten met een solitaire arteria coeliaca stenose blijkt van essentieel klinisch belang. De resultaten gevonden bij inspanningstonometrie stellen ons in staat onderscheid te maken tussen patiënten met en zonder maagischemie. Na succesvolle revascularisatie, met een follow-up van bijna 4 jaar, blijft een meerderheid van de patiënten klachtenvrij; een evidente verbetering vergeleken met eerdere studies. Tevens zetten de resultaten van deze studie zetten het één-vats chronisch splanchnisch syndroom op de kaart als klinische entiteit.

Inspanningstonometrie blijkt ook van additionele waarde in een groot cohort van patiënten met één- en meer-vats splanchnische stenosen. Evenals bij de één-vats patiënten kon met behulp van inspanningstonometrie patiënten met gastro-intestinale ischemie worden geïdentificeerd, resulterend in goede resultaten na behandeling bij middellange termijn follow-up. De één- en meer-vats patiënten bleken significant te verschillen met betrekking tot patiënt karakteristieken, klinische presentatie, morbiditeit en mortaliteit (voor en na behandeling). Dit ondersteunt de gedachte dat het chronisch splanchnisch syndroom bestaat uit twee verschillende ziektebeelden, die beide een verschillende diagnostiek, behandeling, urgentie en doel van behandeling behoeven.

In een groep van gezonde proefpersonen blijkt 24 uurs tonometrie, voor en na maaltijden, goed uitvoerbaar met gebruik van in vitro geteste standaard maaltijden en maximale zuurremming. 'Normaalwaarden' konden met behulp van deze studie worden bepaald. Bij de (retrospectieve) toepassing van deze normaalwaarden in een groep patiënten, bleek de sensitiviteit voor aantonen voor ischemie acceptabel. Zorgvuldige en prospectieve studies zijn nodig om deze eerste resultaten te bevestigen, voordat 24 uurs tonometrie routinematig kan worden toegepast bij patiënten verdacht voor chronische maagdarmischemie.

In de introductie van dit proefschrift wordt een overzicht gegeven over maagdarmischemie in bredere zin. In **hoofdstuk 2** wordt een review gepresenteerd betreffende niet-occlusieve mesenteriale ischemie (NOMI). De graduele overgang van normaal, fysiologische adaptatie van mesenteriale vaattonus naar mucosale ischemie of NOMI wordt belicht. Opvallend is het feit dat NOMI een bekend en algemeen geaccepteerd verschijnsel is voor de intensivist en een relatief weinig erkend probleem voor de maag-darm-lever arts. **Hoofdstuk 3** beschrijft onze kijk op de huidige klinische benadering van patiënten verdacht van chronische maag-

darmischemie. De klinische presentatie, huidige diagnostische mogelijkheden met een centrale rol voor tonometrie en resultaten van behandeling worden uiteengezet.

Het tweede deel van dit proefschrift bestaat uit 2 studies aangaande de methodologie van de 24 uurs tonometrie.

In **hoofdstuk 4** worden de resultaten gepresenteerd van een in vitro studie van standaard maaltijden. Vier standaard maaltijden, een koolhydraat- , eiwit-, vet- en combinatie-maaltijd werden vergeleken op het vermogen om kooldioxide te produceren of absorberen. De hypothetisch ideale test-maaltijd absorbeert en produceert geen kooldioxide, om op deze manier het intraluminale kooldioxide gehalte niet te beïnvloeden, in geval van gastrointestinale ischemie. De vet- en combinatie-maaltijd bleken de meest geschikte standaard maaltijden.

De resultaten van 24 uurs tonometrie bij 10 gezonde proefpersonen worden gepresenteerd in **hoofdstuk 5**. De 24 uurs tonometrie werd uitgevoerd met behulp van continue hoge dosering intraveneuze zuurremming en de twee 'beste' standaard maaltijden uit *hoofdstuk 4*. De 24 uurs tonometrie werd over het algemeen goed verdragen, patronen werden geïdentificeerd en normaalwaarden verkregen.

Het derde deel van dit proefschrift bevat drie klinische studies waarbij inspanningstonometrie en 24 uurs tonometrie worden toegepast bij patiënten verdacht voor chronische maagdarmischemie.

De resultaten van een prospectieve studie bij patiënten met een solitaire arteria coeliaca stenose worden gepresenteerd in **hoofdstuk 6**. Controversie bestaat over het bestaan van het één-vats chronisch splanchnisch syndroom (met het arteria coeliaca compressie syndroom als onderdeel hiervan): 'tegenstanders' bepleiten dat de overvloedig aanwezige collaterale bloedvoorziening van de splanchnische circulatie beschermt tegen ischemie bij patiënten met een één-vats stenose. Medestanders beweren dat in (meerdere) case reports en kleine patiënten series, patiënten met een solitaire arteria coeliaca stenose wel degelijk profiteerden van behandeling. In deze studie worden 79 patiënten met een solitaire arteria coeliaca stenose gepresenteerd; 46 patiënten worden behandeld, voornamelijk gebaseerd op de uitslag van de inspanningstonometrie. Na succesvolle revascularisatie blijft 80% van deze patiënten klachtenvrij bij een follow-up van langer dan 3 jaar. De normalisering van de inspanningstonometrie na behandeling blijkt een belangrijke voorspeller voor succesvolle revascularisatie, gedefinieerd als verdwijnen van pijnklachten. De resultaten van deze studie bewijzen onomstotelijk dat het één-vats chronisch splanchnisch syndroom bestaat en op een adequate manier gediagnosticeerd en (veilig) behandeld kan worden.

In **hoofdstuk 7** wordt een groot cohort patiënten met één- of meer-vats splanchnische stenoses gepresenteerd. Voor zover ons bekend de grootste cohort studie met patiënten met splanchnische stenoses. Het is ook de eerste studie waarin patiënten verdacht voor chronische maagdarmischemie op een prospectieve manier, volgens een strikt diagnostisch traject

en met een multidisciplinaire benadering worden geanalyseerd en (eventueel) behandeld. De diagnose wel of geen ischemie wordt altijd gesteld middels multidisciplinair overleg. De follow-up wordt gebruikt als gebruikelijke manier van controle van resultaat, maar tevens als controle van de initiële diagnose. Eén van de belangrijkste conclusies van deze studie is dat chronische maagdarmischemie bestaat uit 2 verschillende ziektebeelden: één- en meer-vats stenoses chronische splanchnische ischemie. De eerste groep patiënten vertoont minimale morbiditeit en geen mortaliteit, waarmee een klachten-gerichte behandeling gerechtvaardigd lijkt. De tweede groep patiënten heeft hoge morbiditeit en mortaliteit, beide gerelateerd aan de ziekte zelf en de behandeling. Patiënten met twee- of drie-vats splanchnische stenoses hebben een hoge kans op het chronisch splanchnisch syndroom en daardoor een verhoogd risico op darminfarcering. Het eindstadium van het meer-vats stenoses splanchnisch syndroom is vaak snel progressief, wat een spoedige diagnose en behandeling vereist. De behandeling van het chronische splanchnisch syndroom bestaat uit chirurgische revascularisatie of endovasculaire stent plaatsing. De chirurgische behandeling heeft significant betere resultaten op langere termijn, maar ook een hogere mortaliteit in de post-operatieve periode. Deze post-operatieve mortaliteit is significant gerelateerd aan een lagere body mass index bij de non-survivors, vergeleken met de survivors. Endovasculaire stent plaatsing heeft een minimale of geen mortaliteit, maar wel enige morbiditeit vooral bestaande uit neuropraxie na arteriële canulatie.

In **hoofdstuk 8** worden de eerste resultaten van 24 uurs tonometrie bij patiënten verdacht voor chronische maagdarmischemie gepresenteerd. Retrospectief werden bij 33 patiënten de resultaten van maag- en/of jejunum 24 uurs tonometrie geanalyseerd. De 24 uurs tonometrie werd in het algemeen goed verdragen, zonder complicaties. Met behulp van de verkregen normaalwaarden van de gezonde proefpersonen (*hoofdstuk 5*) werd een acceptabele sensitiviteit voor aantonen van ischemie gevonden. Aanvullend, prospectief, onderzoek is nodig om de precieze waarde van 24 uurs tonometrie en verklaring voor de bevindingen bij deze specifieke patiënten groep, te bepalen.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Gastrointestinal tonometry is an accurate tool to detect early mucosal ischemia by measuring intraluminal PCO2. In the intensive care unit, it has been shown repeatedly that early gastrointestinal ischemia can be detected with tonometry. Mucosal ischemia proved a frequent finding, has been associated with morbidity and mortality. However, because the results of tonometry had no significant impact on patient the outcome, it is used sparsely. . The results of the studies presented in this thesis in single vessel CSS as well as the entire CSS group point to a crucial role of gastric exercise tonometry (GET). GET proved to be an accurate tool to identify patients with ischemia, and treatment of these patients resulted in long-term improvement in the vast majority. Still, GET has its disadvantages including the relative complex setting and, more importantly, the well-known fact that more CSS patients have postprandial pain than exercise-induced pain.

This postprandial pain is caused by a mismatch between meal triggered increased metabolic demand and restricted blood flow over the stenosis. The principle of postprandial ischemia is used by prolonged tonometry: measuring the gastric (and jejunal) PCO2 before and after meals. Using a maximally controlled environment with acid potent suppression and standard meals, prolonged tonometry proved feasible and interpretable in healthy subjects and patients. The first results in patients seem promising. These results of a retrospective study using prolonged tonometry in patients suspected of CSS, warrant a prospective study to detect the actual diagnostic value of prolonged tonometry in this particular patients group. Currently a prospective study to answer this question is going on in the Medisch Spectrum Twente.

Air-automated tonometry has shown its benefits and given answers (as described in this thesis), but also give rise to (new) questions. The current air-automated tonometry technique measures the intraluminal PCO2 every 10 minutes, the equilibrium of PCO2 in that time. The actual PCO2 peak dynamics in that same time period might be quite different. A faster CO2 sensor with a response time of less than a minute could provide more insight in the precise relation between intraluminal CO2 and systemic (haemo-)dynamics. This, more or less, continuous PCO2 measurement might especially be of importance in short 'GET-like' measurements, probable less in prolonged tonometry settings. Last year Sebastiaan Herber (University of Twente, Enschede) presented a hydrogel-based CO2 sensor, which is able to measure almost continuously intraluminal CO2. The use of this sensor might give substantially more insights on the CO2 dynamics in the human stomach and proximal small bowel. Currently plans are made to test this newly developed sensor in healthy subjects. Even more interesting are combined measurements of intraluminal CO2, intraluminal pressure and mucosal bloodflow, for example in patients with the irritable bowel syndrome.

10

Nawoord

Curriculum vitae

NAWOORD

Het begint in januari 1998 met een afstudeerscriptie over één van de eerste chronische maag-darm ischemie patiënten in het Medisch Spectrum Twente en het 'eindigt' met een promotie in januari 2006 aan de Erasmus Universiteit in Rotterdam. Daartussen liggen 8 jaren van samenwerking met een groot aantal personen, waar ik veel dank aan verschuldigd ben.

Allereerst wil ik natuurlijk Jeroen Kolkman bedanken! Jeroen, je tomeloze enthousiasme en begeleiding waren geweldig. Ik heb veel van je geleerd en mis de gesprekken tijdens de verschillende autoritten heen en terug van Münster en/of Steinfurt. Je hebt me laten inzien dat het doen van onderzoek méér is dan het verzamelen van gegevens en over de resultaten een 'stuk' schrijven. Dat de zorg voor de patiënten, bij al deze wetenschap, altijd toch op de eerste plaats is gebleven en blijft, is iets wat erg heb leren waarderen.

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Mijn collega's op de Interne Geneeskunde en afdeling MDL van het Medisch Spectrum Twente en later op de afdeling MDL van het Erasmus MC wil ik bedanken voor de leuke tijd en ondersteuning waar nodig. De laatste maanden heb ik veel gehad aan mijn kamer genoten in de 'bovenbouw': Joyce Kuiper en Monique van Leerdam. Joyce bedankt voor de koffie (je bent een fantastische 'secretaresse') en gezelligheid en Monique voor de praktische tips (ervaring telt!).

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Peter

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 31 december 1969 te Almelo. Na het behalen van het V.W.O. eindexamen aan het 'Pius X' college in Almelo werd in 1988, ten gevolge van uitloting, gestart met de studie Biologie in Utrecht. Na 1 jaar, na opnieuw uitgeloot te zijn, werd besloten tot een 'interne' opleiding tot autoradiateuren-specialist in de zaak van pa Mensink. Na 3 jaar uitloting volgde uiteindelijk in 1991 naplaatsing voor de studie Geneeskunde aan de Universiteit van Groningen. Het doctoraal examen werd behaald in april 1996 en het arts examen in mei 1998, na de co-schappen te hebben doorlopen in het Medisch Spectrum Twente te Enschede. In juni 1998 tot 1 oktober werkte hij als arts-assistent op de afdeling Longziekten (opleider dr. J.Klein) van het Medisch Spectrum Twente en aansluitend tot 1 januari 2005 als arts-assistent op de afdeling Interne Geneeskunde van hetzelfde ziekenhuis. In de periode van 1 september 1999 tot 1 januari 2003 als arts-assistent in opleiding tot Internist (opleider dr. D. Richel, later dr. B. Hylkema) en vervolgens van 1 januari 2003 tot 1 januari 2005 als arts-assistent in opleiding tot Maag-darm-lever arts (opleider dr. J. Kolkman). Tijdens het keuze-coschap werd de belangstelling gewekt voor de patiënt met maag-darm-ischemie. Dit leidde uiteindelijk in 2001 tot aktieve deelname in de werkgroep maag-darm-ischemie van het Medisch Spectrum Twente en participatie in de lopende onderzoeken bij dit patiënten cohort. Vanaf september 2002 tot september 2004 werkte hij mee aan een Euregio onderzoek naar de behandeling van maag-darm ischemie, dit in samen werking met de Universiteit van Münster en de Technische Hogeschool te Steinfurt (Duitsland).

Sinds 1 januari is hij werkzaam als Maag-darm-lever arts in opleiding in het Erasmus Medisch Centrum te Rotterdam (opleider Prof.dr. E. Kuipers). Met Linda Molenkamp woont hij in Rotterdam en zij hebben samen een (prachtige!) zoon, Tomas.