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TOPIC HIGHLIGHT

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Diagnosis and management of splanchnic ischemia

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Abstract

Splanchnic or gastrointestinal ischemia is rare and randomized studies are absent. This review focuses on new developments in clinical presentation, diagnostic approaches, and treatments. Splanchnic ischemia can be caused by occlusions of arteries or veins and by physiological vasoconstriction during low-flow states. The prevalence of significant splanchnic arterial stenoses is high, but it remains mostly asymptomatic due to abundant collateral circulation. This is known as chronic splanchnic disease (CSD). Chronic splanchnic syndrome (CSS) occurs when ischemic symptoms develop. Ischemic symptoms are characterized by postprandial pain, fear of eating and weight loss. CSS is diagnosed by a test for actual ischemia. Recently, gastro-intestinal tonometry has been validated as a diagnostic test to detect splanchnic ischemia and to guide treatment. In single-vessel CSD, the complication rate is very low, but some patients have ischemic complaints, and can be treated successfully. In multi-vessel stenoses, the complication rate is considerable, while most have CSS and treatment should be strongly considered. CT and MR-based angiographic reconstruction techniques have emerged as alternatives for digital subtraction angiography for imaging of splanchnic vessels. Duplex ultrasound is still the first choice for screening purposes. The strengths and weaknesses of each modality will be discussed. CSS may be treated by minimally invasive endoscopic treatment of the celiac axis compression syndrome, endovascular antegrade stenting, or laparotomy-assisted retrograde endovascular recanalization and stenting. The treatment plan is highly individualized and is mainly based on precise vessel anatomy, body weight, co-morbidity and severity of ischemia.

Key words: Splanchnic ischemia; Mesenteric ischemia; Tonometry; Blood flow; Chronic splanchnic syndrome; Chronic splanchnic disease; Chronic mesenteric ischemia; Celiac artery compression syndrome; Ischemic colitis

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INTRODUCTION

In this review we will cover the current insights in splanchnic or gastrointestinal ischemia. This disorder is still rarely seen in daily practice, and randomized controlled trials are absent, therefore the view of this paper is highly personal and partly authority-based in its conclusions. The spectrum of ischemic bowel disease is broad, ranging from transient left-sided ischemic colitis (with a good prognosis) to full blown intestinal infarction, with a high death rate. We will focus on new developments in clinical presentation, diagnostic approaches, and treatment options. Splanchnic ischemia can develop during low-flow states in patients with patent vessels, and in subjects with varying degree of splanchnic artery stenoses or splanchnic venous thrombosis. The prevalence of significant splanchnic arterial stenoses, or chronic splanchnic disease (CSD) is high, ranging from 30% to 50%[1,2]. Chronic splanchnic syndrome (CSS) occurs when ischemic symptoms develop. The most characteristic ischemic symptoms consist of postprandial pain, with resultant fear of eating and weight loss. When epigastric bruit is included, these are the so-called classical triad of CSS. In most patients

with CSS, this triad is incomplete. The true incidence of CSS is currently unclear, but is rare compared to CSD due to abundant collateral circulation.

Two important developments occurred in the last decade. Firstly, validation of the gastric exercise tonometry, which is currently the only clinically available and validated diagnostic test to ascertain the presence of splanchnic ischemia[3,4]. Using an ischemia-specific test it should be possible (1) to identify patients with symptomatic vessel stenoses, or CSS, which can be treated, and (2) to make this diagnosis in time and thus prevent the disaster of acute intestinal infarction. Secondly, the increasing evidence that one vessel CSD may cause splanchnic ischemia resulting in one vessel CSS, and can be successfully treated with appropriate selection procedures[5]. An important difference in presentation, treatment and outcome has been shown to exist between single and multi-vessel disease[6]. In the latter group, the clinical presentation is often less typical, with diarrhea, unexplained gastric ulcers, or dyspepsia-like symptoms. These insights stem mainly from our work with tonometry.

An entirely different entity consists of patients suffering from splanchnic ischemia without splanchnic stenoses; the so-called non-occlusive mesenteric ischemia (NOMI). It can be seen as a consequence of physiological adaptation mechanisms during low-flow states were blood is dispersed from the gastrointestinal region to more vital organs[7]. This situation is very common in intensive care and operative units, but can also be seen in outpatients. Treatment consists of aggressive fluid resuscitation and medication. However, bowel infarction can still occur.

In the last decade a change in imaging of the splanchnic vessels occurred. Duplex ultrasound, although operator dependent and suitable for 80% of patients, is still the first choice. Visceral angiography has increasingly been replaced by CT and MR-based angiographic reconstruction techniques. The clinically important advantages and disadvantages of these techniques will be discussed. Whichever technique is used, it leaves the clinician with only anatomical information. To decide whether a given stenosis has caused the symptoms, information on actual ischemia is required. This information can be obtained using tonometry, which has a proven accuracy of 80%-90%. Other tests including, serological iFABP, endothelial progenitor cell measurement, or MR angiography (MRA)-based saturation measurements, may serve that purpose in the near future.

Treatment options have changed considerably over the last decade. Apart from the classical transabdominal vascular reconstructive surgery techniques, minimally invasive endoscopic treatment of the celiac axis compression syndrome, endovascular antegrade stenting, or laparotomy-assisted retrograde endovascular recanalization and stenting have broadened our therapeutic "armory" considerably. The main patient characteristics to guide therapy choice, which include anatomical considerations, as well as body weight, co-morbidity and severity of ischemia, will be discussed.

EPIDEMIOLOGY

The prevalence of CSD is not insignificant, and rises with increasing age. In a 30-year-old angiographic study of 713 patients, 5% of the splanchnic arteries were occluded and in 70% of these occlusions the IMA was involved[8]. In a retrospective study including 980 patients with a mean age of 68 years who underwent angiography for various indications, 8% had significant stenoses of at least one splanchnic artery[9]. In a screening study with duplex ultrasonography in 553 healthy elderly subjects with a mean age of 84 years, stenoses in the celiac artery (CA) or superior mesenteric artery (SMA) were found in 18%[10]. In patients with atherosclerotic disorders of aorta, iliac and femoral vessels the incidence ranged from 25% to 40%[11,12].

A minority of patients with CSD will develop CSS or acute splanchnic syndrome (ASS). A follow-up of the study in elderly subjects in whom duplex had shown CSD, revealed no CSD-related mortality after 6 years of follow-up[13]. This risk is increased in subjects with 2 and 3 vessel CSD. In the study by Thomas *et al* 4.5% of patients with three-vessel CSD developed CSS and another 1.5% died of ASS after a follow-up of an average of 2.6 years[9]. In the Detroit experience, of the 23 patients with severe acute intestinal ischemia studied between 1963 and 2000, 12 (52%) patients had undetected CSS symptoms well before presentation[14].

ANATOMY AND (PATHO)-PHYSIOLOGY

Anatomy

Three major arteries supply blood to the stomach, small intestine and colon. The first branch, the celiac artery (CA) supplies the stomach, proximal duodenum, liver and spleen. The second, the superior mesenteric artery (SMA) supplies the distal duodenum, small intestine and proximal colon. The third branch supplies the distal colon and the rectum. There is an abundance of collateral vessels to protect the gastrointestinal tract from ischemia. Branches of these arteries enter the serosa of the gut on the mesenteric side and form a vascular plexus around the gut. After penetration of the bowel wall, a dense submucosal plexus is formed. From this plexus, arterioles penetrate the muscularis mucosa to the superficial mucosal layers. At the mucosal tip they branch into an intense capillary network of capillaries and venules. Each villus has a single, central arteriole. This arteriole travels to the tip of the villus, then splits into a network of capillaries, which form a central venule at the base of the villus. This is why countercurrent exchange can take place[15]. The tip of the villus is quite susceptible to ischemia[16].

Blood flow

Under normal conditions, approximately 20% of the cardiac output goes through the splanchnic vessels. This splanchnic blood flow doubles after a meal to approximately 2000 mL/min. Blood draining from the bowel enters the splanchnic veins and finally drains into

the portal vein. The liver, therefore, receives its blood supply from two sources: venous blood from the portal vein and arterial blood from the hepatic artery, which branches from the CA in 75% and from the SMA in remaining 25%. This dual blood supply renders the liver relatively protected against ischemia. When the blood flow to the bowel decreases below a certain level (the critical O2 delivery level), the cells will switch to anaerobic glycolysis, resulting in lactate production[17]. In the gastrointestinal system this occurs when blood flow is reduced below 50% of the basal rate[18,19]. In most cases of splanchnic ischemia, the arterial lactate levels will remain normal despite increased lactate production by the gut. The reason for this discrepancy is the large lactate metabolizing capacity of the liver. Thus, systemic lactic acidosis is a late phenomenon in these patients, indicating severe transmural ischemia and probably liver involvement as well.

The regulation of the splanchnic blood flow involves both vasoconstrictive and vasodilating substances. The main vasoconstricting substances are the catecholamines and endothelin, especially endothelin-1[20,21]. The main splanchnic vasodilators are nitric oxide (NO) and prostaglandins. It is assumed that part of the gastrointestinal toxicity of NSAIDs can be attributed to vasoconstriction because of reduced mucosal prosta-glandin concentration[22].

During low-flow states, splanchnic vasoconstriction is an early and profound phenomenon[23], which may lead to blood flow reduction below the 50% threshold. Splanchnic ischemia develops well before systemic hemodynamic instability arises[24]. This splanchnic vasoconstriction may be triggered by shock states, including hemorrhage, sepsis, dehydration or cardiac failure, from vasoactive medications, nicotine and cocaine abuse, or even in strenuous exercise[19,25-27] or severe psychological stress[28]. This combination of ischemia despite normal vessel anatomy, has given rise to the term non-occlusive mesenteric ischemia (NOMI).

Ischemic and reperfusion damage

After the onset of ischemia, an ischemic and reperfusion phase can be distinguished. When this ischemia lasts for less than 6-8 h all processes are reversible; thereafter, transmural gangrene may be the result of completely interrupted blood flow. The ischemic phase starts when the energy-containing ATP is depleted due to lack of oxygen, leading to disruptions of the tight junctions. Also, membrane-bound enzymatic pumps stop functioning, leading to inflow of luminal electrolytes and water into epithelial cells resulting in cell death. Both effects lead to reduced intestinal epithelial barrier function, with bacteria and other luminal contents entering the blood stream[29]. At the same time, the mucosal enzyme xanthine dehydrogenase is converted to xanthine oxidase (XO), which at this stage is harmless. These early effects of the ischemic phase alone are localized and can remain clinically undetected for many hours. The reperfusion phase starts when oxygen-enriched blood re-enters the ischemic tissue. This reperfusion may begin after partial dissolution of an embolus or thrombus or after revascularization. This oxygen is transformed into reactive oxygen species (ROS) by the abundantly present XO. ROS are toxic to proteins and DNA[30], and diffuse into tissues, leading to intensification and spreading of the damaged area. This so-called ischemia-reperfusion cascade initiates an inflammatory and thrombotic response in the submucosal layer of the villus. In the future, antagonists of leukocyte vessel wall adhesions, an early event in the ischemia-reperfusion cascade, could attenuate these inflammatory and thrombotic responses[31]. Successful restoration of splanchnic blood flow, containing toxic products, from the ischemic area into the systemic circulation might trigger multiple organ failure.

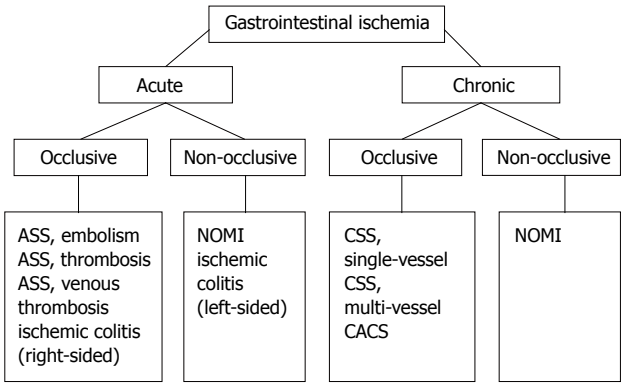

Figure 1 Classification of splanchnic, or gastrointestinal ischemia. ASS: Acute splanchnic syndrome; CSS: Chronic splanchnic syndrome; CACS, Celiac artery compression syndrome; NOMI: Non-occlusive mesenteric ischemia.

CLINICAL PRESENTATION

The naming of gastrointestinal ischemic syndromes is often confusing and requires a brief introduction. We will divide the different syndromes based on duration of complaints and vessel abnormalities (Figure 1). Acute splanchnic syndrome (ASS; synonym: acute mesenteric ischemia, acute bowel infarction) is characterized by a sudden onset of abdominal pain due to interrupted splanchnic circulation. It consists of occlusive disorders: acute splanchnic emboli, venous thromboses and end-stage arterial thrombotic occlusions, and the non-occlusive disorder, NOMI. Chronic splanchnic syndrome (CSS) is defined by a combination of chronic splanchnic disease (CSD) with ischemic symptoms. Celiac artery compression syndrome (CACS) is defined by the combination of eccentric celiac artery compression by the arcuate ligament of the diaphragm and chronic abdominal symptoms caused by ischemia. NOMI may be diagnosed with chronic or remittent splanchnic hypoperfusion, for example in heart failure[32] or in dialysis patients[33]. Finally, ischemic colitis is a separate entity and will be discussed separately.

Acute splanchnic syndrome

Acute splanchnic ischemia can result from arterial thrombosis, acute embolism, venous thrombosis or non-occlusive ischemia[34-39]. Most often the superior mesenteric

artery is involved. Clinically, it is recognized by an acute onset of abdominal pain, which might be accompanied by nausea, vomiting and hypotension. On physical examination and laboratory testing there are usually minimal abnormalities at first[40]. If left untreated, the pain often disappears. Without restoration of blood flow and depending on the collateral circulation, a full blown peritonitis follows within hours or days, with translocation of bacteria and SIRS, or systemic inflammatory response syndrome, and multiple organ failure. Mortality is high, ranging from 32%-80% depending on the etiology. In the last four decades a reduced mortality rate was observed for venous thrombosis and arterial embolism (now 32% and 51%), while the mortality of NOMI and arterial thrombosis remained unchanged at 73% and 77%[39]. Therefore, the most important factors for improvement of survival should be a high index suspicion, a proper diagnosis of CSS before ASS develops and an immediate restoration of blood flow.

Chronic splanchnic syndrome

Chronic splanchnic syndrome (CSS), a synonym for chronic mesenteric ischemia, gastrointestinal ischemia or intestinal angina, is a relatively rare disorder and may be under-diagnosed. After institution of a multidisciplinary approach team for the evaluation of insufficiently explained abdominal pain in the Medisch Spectrum Twente Hospital, the recognition of CSS increased from seven to 23 persons per million per year[41]. The major symptoms of CSS are outlined in Table 1. The most characteristic is postprandial pain, starting 15-30 min after a meal, and persisting for 1-3 h. Patients often report fear of eating, and take smaller meals, with less fat and proteins. Weight loss, the second characteristic finding in CSS, is almost always caused by reduced intake due to this fear of eating and not to malabsorption. Diarrhea, unexplained gastric ulcers or even gastroparesis can also be presenting symptoms.

This multidisciplinary team, with nationwide referrals, also found a differentiation between single- and multi-vessel disease[6]. Although the clinical presentation is quite similar, the course and outcome justifies separate discussion of both groups[42].

Single-vessel disease

The etiology of isolated stenoses of the splanchnic arteries, most often the celiac artery, is caused in most cases by splanchnic arteriosclerosis or external compression by the crux of the diaphragm[5]. Due to the presence of abundant collateral vessels, it was generally assumed that a single stenotic lesion rarely, if ever, causes complaints[43]. In 1972, Szilagyi *et al*[44] reviewed the entire literature on CA compression syndrome and found no proof of any abnormality of intestinal structure or function that could be attributed to this compression, nor proof that treatment had more than a placebo effect. However, several papers were published with good results for CA decompression operations[45-47]. These opinions were challenged recently by our group. We have shown that by using tonometry as a functional test, we could successfully distinguish patients that benefited from surgery from those who did not, and that the disappearance of symptoms after successful revascularization was associated with normalization of this functional test[5]. The prognosis of single-vessel CSS seems rather benign. In 50 patients with an isolated stenosis, no mortality and low post-operative morbidity were seen on follow-up, which contrasts sharply with multi-vessel CSS[6]. No difference in short-term outcome between patients with CACS or atherosclerotic lesions was observed. In our view, single-vessel CSS can be diagnosed when (1) there is a significant stenosis on duplex ultrasound or angiography (> 70%), (2) the clinical history fits CSS and (3) the functional test (gastric exercise tonometry) indicates splanchnic ischemia.

Table 1 Clinical picture in 107 CSS patients[6]

Patient characteristics in 107 CSS patients	
Age	Mean 55 years, range 18-85
Male:Female	26%:74%
Duration of symptoms	Mean 18 mo, range 3-192
Reported weight loss	78%
BMI	Mean 20.8 kg/m^2, range 12.0-33.2
BMI < 20 kg/m^2	35%
Weight loss (kg/mo)	Mean 1.3 kg/mo, range 0-8
Pain after meal	86%
Pain after exercise	43%
Abdominal buit	24%
Classical abdominal angina	22%
Cardiovascular history	40.20%
Nicotine use	45.80%

Multi-vessel disease

When 2 or 3 of the main splanchnic arteries have significant stenoses the ratio of CSS versus CSD increases to almost 90% in patients referred to our unit (unpublished data). Although the clinical presentation is in essence not very different from patients with single vessel disease, (postprandial pain and weight loss as the main symptoms) sometimes quite atypical presentations can be seen. Even experienced clinicians can miss an adapted lifestyle that masks a case of slowly progressive CSS. In multi-vessel CSS the clinical presentation can mimic simple dyspepsia with bloating and fullness, gastroparesis, unexplained diarrhea or simply lack of energy. When the disease progresses, the pain may be provoked by small triggers such as a simple drink, or even during rest. Abdominal vascular resting pain, persisting abdominal pain not related to a meal, are important prognostic indicators, and often indicate imminent or ongoing bowel infarction, or ASS. It should be remembered that the time to develop irreversible ischemic changes is about 6-8 h in end-stage 2- or 3-vessel CSS.

Ischemic colitis

There are two types of ischemic colitis: left-sided and right-sided ischemic colitis. Left-sided ischemic colitis usually presents with abrupt onset abdominal pain, followed by bloody diarrhea, which may persist for days

to weeks. It is often associated with low-flow states[48], coagulation disorders[49], cardiac abnormalities or after abdominal aortal surgery. Low-flow states may be induced by arrhythmias or cardiac dysfunction, drugs, dehydration or (aortic) surgery. Isolated right-sided ischemic colitis usually presents with abdominal pain, but rarely with bloody diarrhea[50]. Right-sided ischemic colitis is usually associated with SMA stenosis or occlusion. It should therefore be considered as part of CSS or ASS.

The late stages of ischemic colitis can be a clinical challenge, with clinical presentation and endoscopic findings mimicking both Crohn's disease and ulcerative colitis. In most cases isolated ischemic colitis will be transient, although persistent colitis, stricture formation and even gangrenous colitis have been seen to develop[48].

NOMI

NOMI has already been mentioned as cause of ASS in 20%-30% of patients. Most NOMI patients however, never develop ASS, and this condition is quite common due to the early splanchnic vasoconstriction with reduced circulating blood volume of any cause. Moreover, the bowel has limited capacity to preserve aerobic metabolism. NOMI is very common and widely recognized in intensive care and peri-operative medicine, where it is referred to as intramucosal acidosis or mucosal ischemia[7]. Here, the clinical signs of NOMI may range from abdominal tenderness, nausea, diarrhea, ulceration, bleeding and full thickness ischemia, and may lead to bowel wall necrosis and even death. In critically ill patients, this process can easily lead to translocation of bacteria and endotoxins, causing SIRS and multi organ failure[51].

We also distinguished a group of patients with 'abdominal migraine' characterized by symptoms compatible with splanchnic ischemia, abnormal functional tests (tonometry) indicating ischemia, splanchnic angiography without relevant pathology, and good response to vasodilators[4,52].

DIAGNOSTIC METHODS

Duplex ultrasound

Duplex-ultrasound is widely used as screening tool for detection of splanchnic stenosis. In experienced hands the CA and the SMA can be visualized in 80%-90% of patients. Proper visualization can be difficult because of the location behind the, often air-filled, stomach. First, vessel anatomy is established using the B-mode. 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. Retrograde flow in the common hepatic artery may indicate proximal CA stenosis or occlusion. The SMA normally has a triphasic signal. A biphasic signal in the SMA is normal after a meal or when the right, or rarely the common hepatic artery, comes from the SMA as an anatomic variant; it may indicate a proximal stenosis if it occurs in the fasting state. Blood-flow measurement is performed using a measurement angle of less than 60 degrees. A significant stenosis is characterized by areas of high velocity jets (small streaks of very high, sometimes turbulent flow) within the artery, and overall increased flow velocity. The widely accepted cut-off values, published by Moneta in 1993, are: for the CA a Peak Systolic Velocity (PSV) and End Diastolic Velocity (EDV) of 200 m/s and 55 m/s; and for the SMA, PSV and EDV of 275 and 45 m/s, respectively[53]. Using these threshold values, 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. One criticism of the "Moneta criteria" has been that he used a cohort from the general population with atherosclerotic disease, who did not necessarily suffer from chronic abdominal symptoms. In daily practice, duplex ultrasound is performed under fasting conditions. Some studies suggested measurement after test meals, because patients with ischemia had suppressed augmentation of blood-flow following a meal compared to subjects with normal vessels[54-58]. Until recently, post-test meal splanchnic duplex made no headway in daily practice. Duplex-derived flow velocities after splanchnic artery bypass grafting may be affected by graft diameter or type of reconstruction and are not equal to the preoperative criteria[59].

MRA

By using contrast, so-called contrast enhanced (ce)-MRA it is possible to identify splanchnic artery stenoses and even collaterals, for example Riolan's artery[60-62]. Surprisingly, we could identify only two studies that compared digital subtraction angiography (DSA) with MRA in 19[63] and 23 patients[61] with good correlation. In our own experience, with 25 patients in whom DSA and MRA were performed within 2 mo, the MRA had a 95% sensitivity and 90% specificity, compared to DSA as the "gold standard". We observed a significant inter and intra observer variation in grading of stenoses in 45% of the cases[64]. Although widely used, it can therefore not be considered a gold standard investigation for assessment of vessel anatomy. A potential advantage of MRA is its ability to measure actual flow through the splanchnic and portal circulation. The arterial flow is harder to measure than in veins, because of the smaller caliber and the pulsatile character of arterial flow[56]. However, a consistent relationship between flow in the arteries and veins was observed[65,66]. Several studies with healthy volunteers and patients have shown augmentation of flow after a meal and significant differences between patients with vessel stenoses and healthy volunteers[54,58]. These results may be promising for future use in diagnosing CSS.

CT angiography

With the introduction of the multi-slice CT scan, CT angiography of the abdominal arteries has become possible. There are several studies showing that CT angiography is an accurate way to image the splanchnic arteries, veins, and collaterals[67-70]. Surprisingly, studies focusing on CSD and comparing this technique to the gold

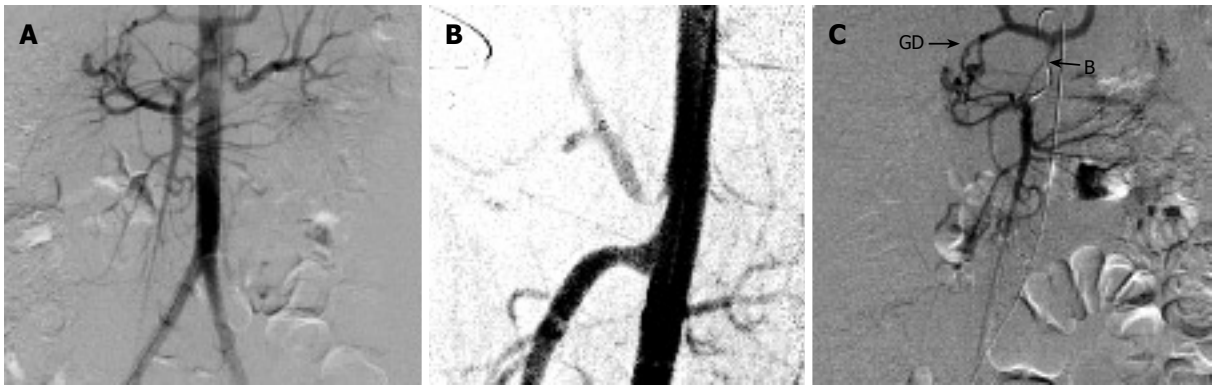

Figure 2 Collateral vessels: gastroduodenal (GD) artery and Buehlers artery (B). A: The gastroduodenal (GD) artery and Buehlers artery (B) are visible on non-selective aortography indicating stenosis of the origin of either the CA or SMA. The late filling of the CA points to a stenosis in its origin; B: Lateral aortography showing an asymmetrical stenosis of the CA; C: On selective cannulation of the SMA, both collaterals are more clearly visible.

standard (DSA) in a representative group of patients, are lacking to our knowledge. It is essential to use multi-slice scanners with slice thicknesses of 2 mm at most (preferably 1 mm) to allow accurate visualization of the arteries. With the state-of-the-art technology, CT-scanning in inspiration and expiration is possible and is a prerequisite when there is suspicion of celiac artery compression syndrome. The advantages of CT angiography are clear: in a patient with acute abdominal complaints it can show or exclude arterial and venous obstruction, bowel involvement (wall distention and thickening, presence or absence of contrast enhancement, pneumatics), as well as alternative diagnoses. Among these are perforations, pancreatitis, and abscesses. Similarly, in the setting of chronic unexplained postprandial pain, CT angiography may also show alternative diagnoses. In our experience, these include pancreatitis, pancreatic cancer, and retroperitoneal tumors. Adding the advantages of minimal invasiveness and lower costs, CT angiography can be a serious competition for conventional angiography[67,69,71,72].

Angiography

Intra-arterial digital subtraction angiography (DSA) of the splanchnic vessels can be used to perform endovascular therapeutic procedures in the same session, including infusion of papaverine and angioplasty or stenting of stenoses. The combination of high diagnostic accuracy and the possibility for intervention makes angiography the procedure of choice in patients suspected of symptomatic splanchnic stenoses, especially with imminent or ongoing infarction. In acute splanchnic infarction, angiography serves as guideline for endovascular or operative revascularization.

A state-of-the art visceral angiography involves three steps: (1) a non-selective anterior-posterior abdominal aortic angiography. When collaterals show in this stage, they indicate significant splanchnic artery stenosis and are considered pathological (Figure 2A and B); (2) a lateral aortography during maximal inspiration and expiration, for detection of external compression of the CA and/or, rarely, the SMA; and (3) selective angiography of all three splanchnic vessels to obtain a detailed view of the vascular anatomy, stenoses and anatomical variations[42]. Although CT and MR angiography are gaining ground as the principal investigative tools for splanchnic vessel anatomy, detailed angiographic information of anatomy, stenosis, collaterals and anatomical variations is, in our view, essential in the preparation of an optimal revascularization strategy.

Endoscopy

Although almost all patients with CSS underwent upper GI endoscopy during the work-up of their complaints, abnormalities were rarely noted. Reports on gastroparesis and gastric gangrene have been published, but are also rare. In our experience, 7% of patients with CSS presented with unexplained gastroduodenal ulcers (Helicobacter negative, no NSAID-use). In colonic ischemia endoscopy is the mainstay of diagnosis. The typical picture consists of superficial ulceration, mucosal friability, edema, and patchy areas of either bleached or cyanotic mucosa[73,74]. Colonic ischemia of longer duration may mimic ulcerative colitis or even Crohn's disease. Some papers have focused on endoluminal light spectroscopy oximetry. With this technique, mucosal hemoglobin oxygen saturation can be measured[75-80]. In a recent study it was shown that mucosal saturations are low in patients with chronic splanchnic ischemia, compared to healthy subjects. After successful treatment in these patients, mucosal oxygen saturations increased substantially[76]. There are a several potential limitations to this technique. Firstly, ischemia is patchy in nature, and can therefore be missed. Secondly, ischemia might be present in parts of the small bowel that are difficult to reach endoscopically. Thirdly, ischemia might only be present in a situation of increased oxygen demand (after a meal, or during exercise), especially earlier in the course of the disease.

Tonometry

Tonometry of the gastrointestinal tract has the unique potential to the detect ischemia, irrespective of flow or metabolism. Tonometry is based on a general physiological principle that during ischemia, anaerobic metabolism leads to increased production of acids, which are buffered locally by bicarbonate ions, leading to increased carbon dioxide tension (PCO_2) in the tissue. This relation between

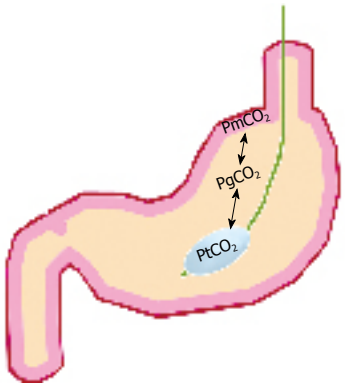

Figure 3 Tonometer balloon placed in the stomach nasogastrically. CO_2 diffuses rapidly over different membranes, therefore the tonometer PCO_2 ($PtCO_2$) will be in equilibrium with gastric luminal PCO_2 ($PgCO_2$) and mucosal PCO_2 ($PmCO_2$). The PCO_2 can be measured from the catheter either from injected saline using blood gas analyzers or by connection to a semi-automated Tonocap device. The underlying physiological principle is that ischemia is always associated with PCO_2 increase. Therefore, focal measurement of ischemia is possible for long periods *via* a minimally invasive technique.

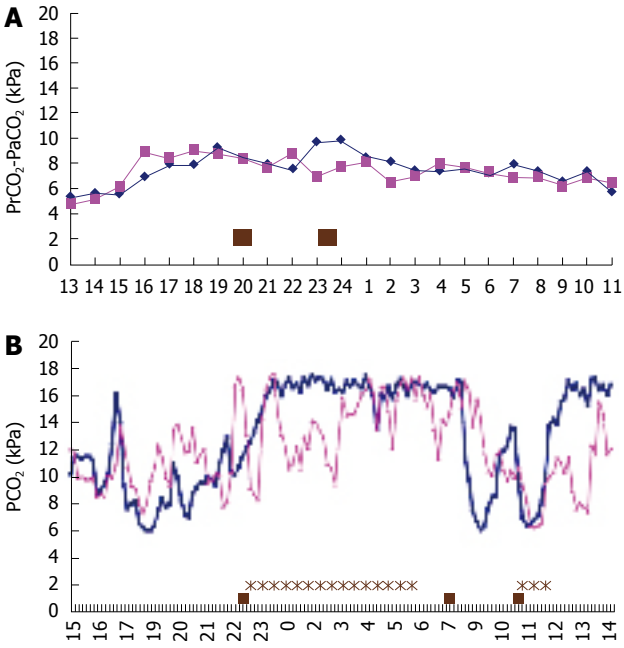

Figure 4 Imminent ASS and normal gastric and jejunal PCO_2 pattern. A: Normal 24 h PCO_2 pattern in the stomach (squares) and jejunum (diamonds) with variation in PCO_2, but no peaks above 11 kPa following meals; B: Imminent bowel infarction in a patient with severe 3 vessel CSS. After her evening meal she had pain for almost 6 h, and extreme ischemia with PCO_2 > 16 kPa for 7 h. She was treated with endovascular stent placement the day after this measurement, with immediate relief of complaints. She is still doing well, over 3 years later.

ischemia and increased PCO_2 has been observed in all ischemic models and animals studied. The most specific marker of ischemia is an increased difference between luminal and arterial CO2, the PCO_2 gradient, which is barely influenced by other systemic factors, including hyper- or hypoventilation. The luminal PCO2 can be measured conveniently using a nasogastric tonometry catheter and air tonometry (Figure 3). The unique property of tonometry in measuring ischemia *per se*[3] sets it apart from all other diagnostic methods. Indeed, when blood flow is gradually reduced, the PCO2 gradient remains normal until the blood flow decreases to < 50% of the basal flow and then increases sharply[18,19].

In patients with suspected chronic ischemia, gastric tonometry has been used initially using a test meal with variable, but overall disappointing, results[81-83]. The main methodological problems involved buffering effects by gastric acid and dilution effects of the ingested test meals[84]. We therefore developed a tonometric test involving 10 min of submaximal exercise, in order to provoke GI ischemia[19]. The diagnostic accuracy of the gastric exercise tonometry test (GET) was evaluated in a cohort of patients referred for suspected CSS. GET had a 78% sensitivity and 92% specificity for ischemia detection[4]. We have used GET to guide treatment in patients with single vessel stenoses. The main finding in this study was the tight relationship between normalization of GET and disappearance of symptoms after anatomically successful revascularization[5]. We also re-examined the potential use of a 24-h tonometry test, including test meals, with standardization of the test circumstances, including potent acid suppression and standard test meals[85]. In a pilot study in 33 patients referred for suspected CSS, the 24 h tonometry showed promising results, with a sensitivity of 76% and a specificity of 94%, comparable to those of exercise testing[86]. We are now analyzing a study comparing GET and 24-h tonometry. The preliminary data suggest that 24-h tonometry permits accurate measurement of postprandial and fasting PCO_2 levels; following meals, gastric and small bowel PCO_2 gradients may physiologically increase up to 10 kPa. During ischemia, gradients exceed 11 kPa (60 mmHg)[87]. Also, prolonged PCO2 increases for several hours (up to 7 h in one subject, Figure 4), especially in combination with abdominal pain during fasting, indicate imminent infarction, and thereby provide invaluable extra information.

Serological markers

Currently, there is no reliable marker to diagnose gastrointestinal ischemia. Studies have been performed using several markers, including (L and D)-lactate, LDH, D-dimer; however, none of these was proven to be sensitive or specific. In contrast, various animal models have successfully used markers like D-lactate and i-FABP (intestinal Fatty Acid Binding Protein) as an early marker of intestinal ischemia. This enzyme is present in the mature enterocytes of the small intestine, in the highest concentration at the villi[88,89], the region most susceptible to ischemia, and is released early after an ischemic insult. Therefore it seems a good candidate marker for early ischemia detection[90]. There are a few patient studies indicating its potential as marker for ASS[89,91], but also during pancreatitis[92] or inflammatory bowel disease[93]. We performed a pilot study comparing tonometric responses to a test meal and indeed found increased i-FABP in these subjects[94]. More studies are needed before the role of this and other promising plasma markers can be established.

WORK-UP AND TREATMENT

In the work-up of patients in whom splanchnic ischemia is suspected four questions should be addressed: (1) is the history compatible with splanchnic ischemia, (2) which of the three vessels are narrowed, to what degree and are pathological collaterals present, (3) is there (functional) evidence of actual ischemia, and (4) is the impairment of the splanchnic blood flow in the short-term threatening for the bowel.

Endovascular techniques have emerged allowing for stent placement in CA and SMA in most patients. The choice is between dilation or stent placement. Dilation alone has a low short-term success rate, and we currently use it only as diagnostic tool to distinguish between CSS and CSD. Although some vessels can be treated *via* the femoral artery; the sharp downward angulation (60 degrees) of the AMS and CA often necessitates brachial artery cannulation in many cases. In our center, both techniques are often combined, using the femoral catheter as a guide for the stent placed *via* the brachial catheter. Compared to operative revascularization, the main disadvantage of stent placement is the shorter long-term patency. The latter was shown in three recent studies, of which two compared endovascular and open repair. Atkins *et al* reported in a cohort of 80 patients with CSS primary patency at 1 year of 58% after endovascular and 90% after open repair and a primary assisted patency of 65% *vs* 96% respectively[95]. Bieble *et al* reported that in a cohort of 49 patients with CSS, 75% after endovascular and 89% after open repair were symptom free after 2 years[96]. The main difference in this study was the restenosis rate of 8% after open versus 25% after endovascular treated patients, with lower complication rates in the latter. Sarac *et al*[97] reported a primary, primary assisted and secondary patency of 65%, 97% and 99% in a cohort of 87 endovascular treated splanchnic arteries. The low short-term morbidity makes it an excellent choice in patients with limited life expectancy or those too weak or underweight for operative revascularization.

A variety of surgical techniques have been advocated for open repair of the splanchnic arteries, including reimplantation, transarterial and transaortic endarterectomy, antegrade and retrograde aortovisceral bypass using vein or arterial autograft bypasses and prosthetic bypass, with early success rates between 91% and 96% and late success rates between 80% and 90%[98]. The choice of technique is usually based on the preference and experience of the surgeon. However, the majority of centers with wide experience believe that antegrade autogenous revascularization techniques of both the CA and the SMA in selected cases offers the best long-term results. The disadvantage of major aortic surgery is the not inconsiderable burden for the patient. In general, we prefer antegrade two-vessel reconstruction for young patients with CSS and a body mass index above 19.5 kg/m^2, and endovascular or minimal invasive retrograde single or multi-vessel reconstructions for patients with relevant comorbidity or reduced life expectancy. Also endovascular repair could act as bridge to open repair after full recovery and weight gain in selected young patients with end stage CSS.

Acute splanchnic syndrome

The diagnosis of ASS begins with a high index of suspicion. Any patient with acute onset of abdominal pain that remains unexplained after proper investigation for two hours should be suspected to have ASS. An urgent investigation of vessel patency should be ordered. The choice is between an acute angiography and a CT scan. Simultaneously with the CT scan or DSA, the volume status should be aggressively restored to counterbalance the splanchnic vasoconstriction, which is almost always present in these patients. All necrotic bowel should be removed and blood flow restored as soon as possible. The latter will involve intravenous heparin in venous ASS, revascularization or embolectomy in arterial ASS, and in selected cases, intra-arterial vasodilation in ASS-NOMI[73]. In arterial ASS, the choice of revascularization, and whether it should be done before or after bowel resection, depends on local expertise. Bowel vitality can be hard to assess initially, therefore second- and third look operations to ascertain bowel vitality are often advised and seem prudent. It has been shown that aggressive treatment might be responsible for the modest improvement in outcome of ASS[39]. In cases of limited extent of severe bowel ischemia we advise immediate retrograde endovascular revascularization[99,100] and resection of the ischemic bowel to diminish the detrimental cascade of ischemia-reperfusion resulting in multi organ failure and high mortality.

Acute ischemic colitis

Isolated acute left-sided ischemia can usually be treated conservatively, as it is almost always non-occlusive in nature. Right-sided ischemic colitis should be considered as ASS and treated accordingly. Patients with left-sided ischemic colitis should be treated with intravenous fluid and bowel rest. Broad spectrum antibiotics are advised, which might reduce bowel damage[48,101], but there is no evidence to back this up. Left-sided ischemic colitis subsides in 2 wk[48] in most patients. About 20% of patients with acute ischemic colitis ultimately need surgery, either because the ischemic colitis persists or complications occur. A non-responsive left-sided ischemic colitis can manifest as ongoing sepsis refractory to medical treatment, persistent diarrhea, bleeding, or protein-losing enteropathy for more than 14 d. In some patients progressive peritonitis or gangrene of the colon develops, with a mortality rate of 30%-60%[48,102].

CHRONIC SPLANCHNIC SYNDROME

Single-vessel CSS and CACS

Patient selection is crucial in these patients. When single-vessel CSS is diagnosed by history, vessel anatomy and functional tests, treatment may help to relieve the symptoms. The prognosis quod vitam is good; therefore

treatment is aimed at relief of symptoms only. Some patients prefer conservative measures including small meals and proton pump inhibitors. When a revascularization is indicated, the choice of technique depends on vessel abnormalities as well as local experience.

In CACS patients primary stent placement is not an option because the repeated force by the diaphragm with each respiration will fracture the stent in the short-term. Different techniques are currently used to release the CA from compression by the diaphragm's crux. One potential complication is the development of reflux disease[5], which is related to the damage to the crux, which also plays an important role in the physiological anti-reflux barrier. Recently, we have performed the release by an endoscopic retroperitoneal technique with equally good results compared to the open approach in the short-term[103]. The problem of reflux seems to be reduced, although more studies with longer follow-up times are needed.

Multi-vessel CSS

Most patients with abdominal symptoms and multi-vessel stenoses have, in our experience, CSS. The risk of developing ASS is considerable[6], therefore the treatment goal is aimed at symptom relief as well as prevention of ASS. There are no prospective studies on the conservative treatment of CSS, but advice on diet and lifestyle have been described. Most patients have already changed their eating pattern, with smaller and more frequent meals that contain less fat and protein. It should be strongly advised to stop smoking because it causes strong splanchnic vasoconstriction. The use of proton pump inhibition is not evidence based, however, it makes sense as these drugs reduce the secretion of gastric acid, and thus gastric metabolic demand, while increasing the gastric blood flow[104]. Atherosclerosis is a generalized disorder; therefore the usual measures should be initiated including treatment of hypertension, hyperlipidemia, and diabetes.

Most multi-vessel CSS patients have an indication for revascularization. Whether patients with multi-vessel (asymptomatic) CSD should be treated to prevent ASS is uncertain. It may be considered in young patients in good health, but firm evidence is lacking. The choice of revascularization in multi-vessel CSS again depends on anatomy, experience, and comorbidity as discussed before.

NOMI

Chronic splanchnic ischemia due to NOMI comes in two different patient groups. The first group has severe underlying medical conditions, with reduced effective circulating volume and splanchnic vasoconstriction and ischemia. These include dialysis patients[33] and chronic heart failure[32] patients. Treatment is difficult because the treatment of their underlying disease requires reduction of intravascular volume, which may worsen their abdominal complaints. In our experience the use of nitrates, ketanserin and alpha-inhibitors may have a positive effect on the abdominal symptoms, whereas calcium channel blockers seemed to worsen these. A second group we encountered are patients with a clinical presentation similar to CSS, with normal microvasculature but functional tests indicating ischemia. As discussed earlier, in some of these we have observed vascular spasms during angiography, with onset of pain within minutes thereafter[4]. In a pilot study, we treated them with vasodilators, nitrates, ketanserin or nicorandil. Over 50% of patients show a reduction of abdominal pain of at least 50% on a visual analog scale, which is sustained for years in most cases[52]. Further studies are needed to assess the prevalence, precise mechanism and the best treatment options of this disorder.

Post-intervention care

After revascularization, severe reperfusion injury can occur. The exact risk factors for its development are unknown. In our experience it is more common in patients with serious and long-standing multi-vessel disease. The following pattern in reperfusion damage after revascularization is typical. The first 1-2 d after revascularization the patient has good clinical recovery. Most could start eating again without pain or special discomfort. After 2-3 d symptoms develop, in hours to days, consisting of nausea, abdominal pain, similar or even worse than before treatment, diarrhea and in extreme cases, protein-losing enteropathy with very low serum albumin levels. Massive ascites may develop during reperfusion.

It is crucial to distinguish reperfusion injury from vessel occlusion; therefore vessel patency has to be ascertained with CTA or DSA. This bowel reperfusion syndrome can persist for days to weeks. We therefore treat these patients with parenteral nutrition, intravenous fluids, and proton pump inhibitors. The end of the reperfusion syndrome is usually heralded by increased appetite, reduced pain and reduced diarrhea. Patients can restart oral intake, be taken off parenteral nutrition and generally have uneventful recovery within weeks thereafter. No long-term complications have been observed in these patients.

CONCLUSION

Splanchnic ischemia has developed into a broad spectrum of diseases. These are characterized by onset, vessel anatomy, and presence of ischemia. Each syndrome has different characteristics, outcome, and treatment options, therefore a state-of-the art vessel anatomy assessment and accurate functional test are crucial. Tonometry is the only validated test assessing the adequacy of the splanchnic blood-flow and consequently is crucial in proper patient selection. Treatment options, including noninvasive, minimal invasive and classical open vascular reconstructive techniques, are wide and require a multi-disciplinary team-approach for proper selection and follow-up.

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