Diagnosis of Chronic Gastrointestinal Ischemia

Désirée van Noord

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De diagnostiek van chronische gastrointestinale ischemie

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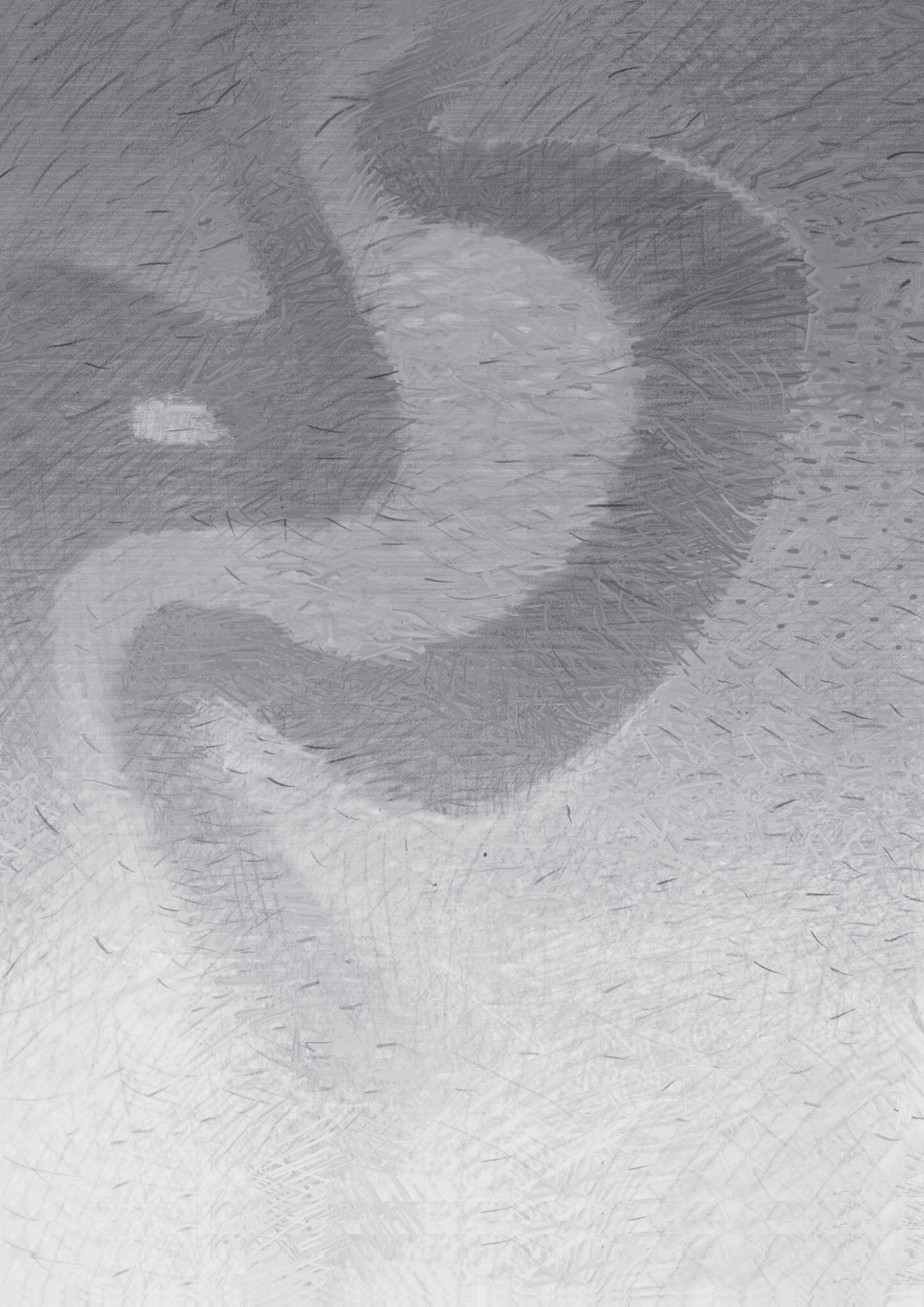


Chapter 1

Aims and outline

INTRODUCTION

Three aortic branches provide the arterial blood supply to the gastrointestinal tract: the celiac artery (CA), superior mesenteric artery (SMA) and inferior mesenteric artery (IMA). The CA supplies stomach, liver, part of the pancreas and proximal part of the duodenum. The SMA supplies the distal part of the duodenum, the entire small bowel and the proximal colon. The IMA is relatively small and supplies the distal colon. The anatomy of these arteries varies largely and gastrointestinal artery stenotic disease is not uncommon. Occlusive gastrointestinal arterial disease often remains asymptomatic, due to the presence of abundant collateral circulation. Only patients with significant arterial stenosis in combination with insufficient collateral circulation develop clinical signs of mesenteric ischemia. In these cases, the diagnosis is often missed due to lack of sensitive diagnostic tests. The diagnostic approach in patients with possible chronic gastrointestinal ischemia (CGI) focuses on identification of gastrointestinal arterial stenosis and demonstration of mucosal ischemia.

AIMS AND OUTLINE

This thesis deals with the diagnosis of chronic gastrointestinal ischemia, which often remains a clinical challenge. This in part explains why CGI was for long considered to be a very rare disease, only presenting in patients with multiple stenotic abdominal arterial disease. The existence of single vessel abdominal arterial disease has long been debated. We therefore firstly reviewed the existence and characteristics of single vessel abdominal arterial disease in **chapter 2**.

The introduction of gastrointestinal tonometry as the first functional test and one of the major keys in diagnosing CGI, has changed the view towards CGI. Several studies with tonometry have shown that CGI is a clearly identifiable disease, which can occur both in the presence of multi-vessel as well as single vessel abdominal arterial stenosis. Currently, the established approach for patients suspected of CGI is the combination of duplex ultrasound and gastric exercise tonometry (GET), followed by a conventional digital subtraction angiography (DSA) of the gastrointestinal arteries. However, GET is cumbersome and impossible to perform in a considerable proportion of patients. DSA is quite invasive and has a considerable complication rate. Alternative diagnostic methods have recently been developed, in particular 24 hour gastrointestinal tonometry (TM) and computed tomography angiography (CTA). TM and CTA seem to be promising, minimally invasive techniques to detect mucosal ischemia and define gastrointestinal artery stenoses, respectively. In **chapter 3** we challenge the use of TM in combination with CTA as an alternative approach to evaluate patients suspected of CGI.

Tonometry is only used in a limited number of centers with a dedicated CGI program, which means that the majority of potential CGI patients are still assessed without functional testing. Unfortunately, the wider use of gastrointestinal tonometry is hampered by its cumbersome and invasive nature. Visible light spectroscopy (VLS) is a relatively new technique that enables non-invasive measurements of mucosal capillary hemoglobin oxygen saturations during endoscopy. This saturation reflects the adequacy of mucosal perfusion and should therefore, in theory, be lowered in CGI. VLS could be of great value as a new and less invasive diagnostic tool in patients suspected of CGI. We therefore prospectively evaluated the diagnostic accuracy of VLS for detection of ischemia in a large cohort of patients clinically suspected for CGI. The results of this evaluation are described in **chapter 4**.

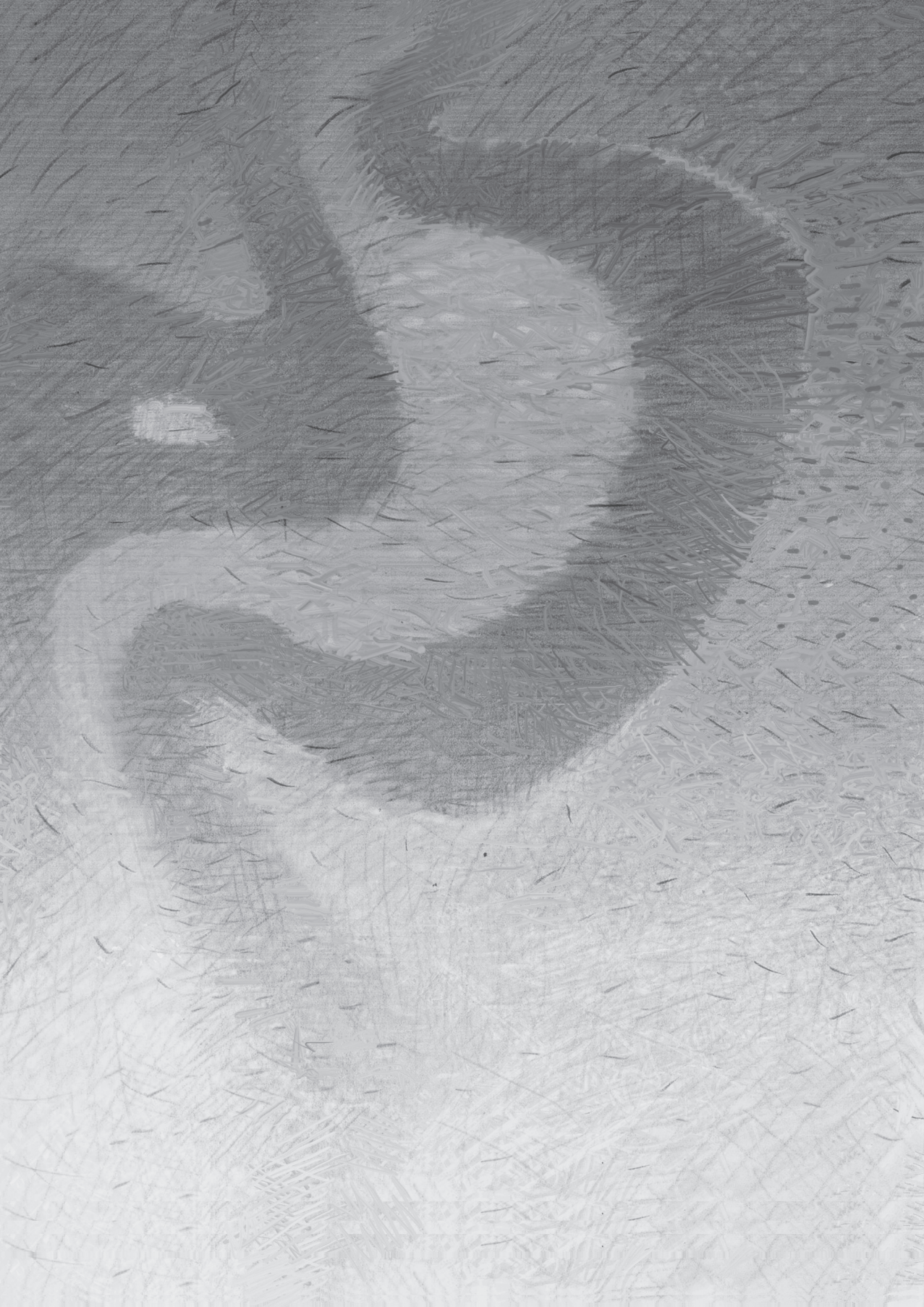
Serum markers for CGI would be of great diagnostic additional value as a non-invasive test method. A recent study suggested a possible relationship between serum intestinal fatty acid binding protein and transient postprandial mucosal ischemia as detected with tonometry in CGI patients. The potential diagnostic role of serum markers in patients with well-defined ischemia was therefore prospectively investigated (**chapter 5**). Furthermore, small bowel function might be altered in CGI patients due to hypoperfusion of this region caused by compromised blood flow in the superior mesenteric artery. Therefore, malabsorption and unexplained diarrhea may be the initial or the pre-dominant feature of the clinical presentation in these patients. In this chapter we also evaluated intestinal mucosal injury in patients suspected of CGI.

Based on the assumption that patients with symptomatic CGI have typical gastroduodenal abnormalities, upper endoscopy is often used for the assessment of patients with suspected CGI. Histological examination of biopsy material currently plays no role in the diagnosis of transient CGI. However, little is known about the true prevalence and characteristics of gastroduodenal endoscopical lesions and histological changes in patients with CGI. The endoscopic findings and corresponding histopathology have only been described sporadically. In **chapter 6** we describe the upper endoscopic findings in patients with well-defined CGI in a prospective cohort study. **Chapter 7** prospectively investigates gastrointestinal histopathology in patients with well-defined CGI.

CGI is most commonly caused by atherosclerotic stenosis of the gastrointestinal arteries. Although CGI is an extracardial manifestation of atherosclerosis, its relationship with classical risk factors of cardiovascular disease is unclear. **Chapter 8** describes whether classical risk factors of cardiovascular disease associate with atherosclerotic CGI. Furthermore, the risk factors for cardiovascular disease were compared between patients with atherosclerotic CGI and non-CGI.

The most common clinical symptoms of CGI are postprandial pain, exercise-related pain, weight loss, diarrhea and an abdominal bruit. In **chapter 9** we discuss the most common presenting symptoms of CGI by two examples of uncommon presenting symptoms of patients finally diagnosed with CGI.

Finally, in **chapter 10** we summarized and discussed the main findings of the studies presented in this thesis. In addition, we presented potential clinical implications and suggestions for future research.



Chapter 2

Single vessel abdominal arterial disease

Désirée van Noord[1], Ernst J. Kuipers[1,2], Peter B.F. Mensink[1]

Departments of Gastroenterology and Hepatology[1], Internal Medicine[2], Erasmus MC - University Medical Center, Rotterdam, The Netherlands

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ABSTRACT

The long-standing discussion concerning the mere existence of single vessel abdominal artery disease can be closed: chronic gastrointestinal ischemia (CGI) due to single vessel abdominal artery stenosis exists, can be treated successfully and in a safe manner. The most common causes of single vessel CGI are the celiac artery compression syndrome (CACS) in younger patients, and atherosclerotic disease in elderly patients. The clinical symptoms of single vessel CGI patients are postprandial and exercise related pain, weight loss, and an abdominal bruit. The current diagnostic approach in patients suspected of single vessel CGI is gastrointestinal tonometry combined with radiological visualisation of the abdominal arteries to define possible arterial stenosis. Especially in single vessel abdominal artery stenosis, gastrointestinal tonometry plays a pivotal role in establishing the diagnosis CGI. First-choice treatment of single vessel CGI remains surgical revascularisation, especially in CACS. In elderly or selected patients endovascular stent placement therapy is an acceptable option.

INTRODUCTION

Three aortic branches provide the arterial blood supply to the gastrointestinal tract: the celiac artery (CA), superior mesenteric artery (SMA) and inferior mesenteric artery (IMA). The CA supplies stomach, liver, part of the pancreas and proximal part of the duodenum. The SMA supplies the distal part of the duodenum, the entire small bowel and the proximal colon. The IMA is relatively small and supplies the distal colon. It is generally assumed that in single vessel abdominal arterial disease the abundant collateral circulation of the arterial mesenteric tract prevents clinically relevant gastrointestinal ischemia. This might be illustrated by the fact that single vessel abdominal arterial stenosis is frequently found in the general population (up to 18%), but the clinical diagnosis chronic gastrointestinal ischemia (CGI) is rarely made (1,2). The aetiology of the majority of stenoses of the abdominal arteries can be divided into concentric and eccentric diseases; see Table 1. In the younger patient the celiac artery compression syndrome (CACS) is the most common cause of abdominal arterial stenosis. Atherosclerotic disease is the major cause of abdominal arterial stenosis in the elderly patient.

Table 1: Single vessel abdominal arterial disease entities

Concentric:
- atherosclerotic stenosis
- vasculitis
- (familial) fibromuscular dysplasia
Eccentric:
- celiac artery compression syndrome (CACS)
Intra-arterial:
- thrombo-embolism
- dissection

Nonconcentric intra-arterial disease causes significant stenoses (i.e. arterial thrombosis or dissection) in a minority of cases. Until recently, controversy existed about the mere existence of single vessel CGI. It was generally thought that CGI is caused by significant stenosis involving at least two of the three main mesenteric arteries. Consequently it was thought that due to the supposedly abundant collateral circulation, single vessel abdominal arterial stenosis (caused by either atherosclerosis or compression by the median arcuate ligament) would not give clinically relevant gastrointestinal ischemia.

EPIDEMIOLOGY

Data about the prevalence of, mostly, asymptomatic abdominal arterial stenosis are available from autopsy studies (3,4) These data show that solitary narrowing of the CA and SMA is frequently found, respectively in 44% and 37% of subjects, and CA stenoses were

significant (>50–70%) in 21% of subjects (5). A more recent autopsy study showed that in 29% of cases stenosis of either CA or SMA was found, with the CA as the most common affected site. The latter study also showed a strong correlation between abdominal arterial stenosis and aging: in subjects younger than 40 years the prevalence of arterial abdominal stenosis was 6%, rising to 67% in subjects aged 80 years or more (6). Recent studies using modern imaging modalities of the abdominal arteries also show a high prevalence of abdominal arterial stenosis. In a cross-sectional study of asymptomatic patients undergoing abdominal angiography for chemo-embolisation of hepatic tumours, 7.3% of patients had a significant stenosis of the CA (7). In a recent study in a cohort of 553 asymptomatic elderly Americans (mean age 77 years), the prevalence of stenosis in the CA and SMA was evaluated using abdominal duplex ultrasound measurements. In 18% of these subjects stenosis of the CA and/or SMA was found. Eighty-six percent of these stenoses affected the CA only. Two percent consisted of isolated CA occlusion, 5% isolated SMA stenosis, and 7% combined CA and SMA stenosis (2). In another report using abdominal duplex ultrasound measurements in asymptomatic subjects, the prevalence of isolated CA stenosis was found in 3% of subjects under 65 years, rising to 18% in subjects above 65 years of age either alone or in combination with lesions in other vessels. Amongst cases with single vessel disease, again stenosis of the CA was most frequently found (81% CA versus 19% SMA stenosis) (8). The exact prevalence of symptomatic single vessel abdominal arterial stenosis is unknown. It was for long thought to be very rare or non-existent, but the wide availability of new diagnostic tools such as CT-angiography have taught that CGI in the presence of single vessel disease is a distinct, not uncommon disorder. In one large clinical series from the Netherlands including 102 patients with CGI assessed by a combination of methods including gastric exercise tonometry, single vessel disease accounted for approximately 60% of CGI cases (9). The most common cause of single vessel abdominal arterial stenosis is compression of the CA by the median arcuate ligament, being the cause in up to 65% of isolated CA stenosis. In virtually all other cases, the primary aetiology is atherosclerosis.

CLINICAL PRESENTATION

The clinical symptoms of CGI caused by single vessel abdominal arterial disease (either due to atherosclerosis or to CACS) are comparable to the symptoms of multivessel abdominal arterial disease patients (10). Postprandial pain, weight loss, exercise-related pain and an abdominal bruit are presenting symptoms found in respectively 84%, 74%, 44% and 26% of patients with single vessel CGI (Table 2) (10,11). The postprandial symptoms occur typically within 15–30 min after the meal and last for 60–120 min. In only a minority of patients the classical triad of 'angine abdominale', namely postprandial pain, weight loss due to fear of eating and an abdominal bruit, is found. In general, isolated SMA stenosis causes more

frequently actual mucosal ischemia (i.e. CGI; 75% of cases), as compared to patients with isolated CA stenosis (55% of cases) (10). The risk factors for atherosclerotic abdominal arterial disease seem to be comparable to the known risk factors for general arterial vascular disease. The Framingham Heart Study and other large-scale epidemiologic studies have identified major cardiovascular risk factors. In atherosclerotic arterial disease the risk factors hypertension, dyslipidaemia, glucose intolerance, obesity, hyperhomocysteinaemia and cigarette smoking are comparable to the known cardiovascular risk factors. Until now, only one study has focused on atherosclerotic risk factors in patients with CGI. In a cohort study of 168 patients with CGI, the risk factors for abdominal arterial atherosclerosis were identical to the general established risk factors for arterial atherosclerotic disease. Striking was the female preponderance and the high prevalence of hyperhomocysteinaemia (45%) (12).

Table 2: Clinical symptoms single and multivessel CGI patients

Complaints	SVID*	MVID
Postprandial pain	84 %	86 %
Weight loss	74 %	78 %
Exercise-related pain	44 %	43 %
Abdominal bruit	26 %	24 %
Diarrhea	4 %	11 %
Risk factors for CVD:		
- smoking	51 %	42 %
- other RF	47 %	82 %

SVID = single vessel ischemic disease (*including both celiac artery compression syndrome and atherosclerotic disease), MVID = multivessel ischemic disease, CVD = cardiovascular disease, RF = risk factors

ARTERIAL OCCLUSIVE DISEASE

Concentric diseases

Abdominal arterial atherosclerosis

In the largest prospective cohort-study in patients with CGI, the CA was the most common affected vessel, compared to the SMA, accounting for respectively 92% and 8% of all single vessel stenosis (10). Other studies report that the SMA was more affected in single vessel atherosclerotic disease than CA stenosis, but these studies were all small and retrospective in design (13,14). The aforementioned cohort study and several case reports have described CGI resulting from solitary CA or SMA stenosis as a result of atherosclerosis, being successfully treated with revascularisation (15,16). An isolated atherosclerotic stenosis of the IMA with accompanying complaints is a very rare entity. The prevalence in studies ranged from 0% to 6% in patients diagnosed with CGI (10,13,14). The clinical consequences of significant stenosis of the IMA are still a point of discussion. In clinical practice, the IMA is often sacrificed during aorta reconstruction surgery procedures without major consequences, but ischemic colitis

has been reported to occur in 5–35% of these cases, which supports the hypothesis that the IMA is pivotal for the circulation of the left colon at least in part of the population (17). Reports of clinical successful revascularisation in two- or three-vessel stenosis CGI patients (including IMA stenosis) without revascularisation of the IMA, underline the minor role of this entity. Collateral circulation seems to prevent symptomatic ischemic complaints in these cases.

Abdominal arterial inflammatory disease

Acute or chronic vascular inflammation can result in significant arterial stenosis or occlusion of the abdominal arteries. Pain is the most common symptom of GI involvement in vasculitis and may be caused by arterial blood flow reduction (i.e. gastrointestinal ischemia) or due to complications of the inflammatory processes such as ulceration, perforation, peritonitis or vascular rupture. Frequencies of gut involvement in vasculitis are highly variable in different series and for different vasculitides. These ranged from 17% to 92% for Churg–Strauss disease, 25–80% for Henoch–Schönlein purpura, 14–60% for polyarteritis nodosa, 11–50% for Behçet's disease, 0–39% for Wegener's granulomatosis, 25–33% for Cogan's syndrome, 11–28% for systemic lupus, 0–19% for Takayasu's arteritis, 0–10% for rheumatoid arthritis, and rare for giant cell arteritis and Kawasaki's disease (18). Due to the nature of the disease, inflammatory abdominal arterial vascular diseases usually affect multiple vessels and present as systemic inflammatory disease. Occurrence of single abdominal arterial inflammatory vessel disease has been reported, but occurs infrequently. In several cases isolated SMA vasculitis, visualised on angiography, in patients presenting with abdominal pain were successfully treated with glucocorticoids (19–21). In all cases no underlying disorder was revealed after extensive laboratory and clinical investigations. Isolated vasculitis has also been reported in the appendix, gallbladder (22,23) and pancreas (22). Polyarteritis nodosum can also present with isolated vasculitis in the coecum (24) or isolated CA aneurysm with splenic artery stenosis (25). An occluded origin of the SMA presented in a patient with abdominal pain and weight loss originating from an abdominal vasculitis as an atypical presentation of Wegener's granulomatosis (26).

Familial fibro-muscular dysplasia

Fibro-muscular dysplasia is an arteriopathy with still an unclear epidemiology. It affects the renal and cerebral arteries most commonly, followed in sequence by the mesenteric, subclavian, iliac, carotid and coronary arteries (27). The occurrence of single vessel abdominal artery fibro-muscular dysplasia has been described in several patients with familial fibro-muscular dysplasia (28,29). Multivessel disease seems to occur in approximately 26% of patients (30). The diagnosis can be made with conventional angiography showing a typical appearance, 'string of beads', or histologically where fibro-muscular proliferation is seen.

Intra-arterial diseases

Isolated thrombo-embolism

Thrombosis of the abdominal arteries has been reported as a cause of acute abdominal pain due to intestinal ischemia or infarction (31). Acute mesenteric thrombo-embolisms can produce massive gangrene of the bowel and the possibility of (isolated) mesenteric thrombo-embolism should be kept in mind (32). Acute thrombo-embolisms have a high morbidity and mortality rate, and account for 1.2% of all causes of death of subjects over 80 years of age (33). Isolated thrombo-embolisms are usually located in the SMA. Isolated CA occlusion due to thrombo-embolism is rare because the CA often branches vertically at the aorta. In more than 75% of cases thrombo-embolisms originate from the heart, mainly due to cardiac rhythm disorders (for example acute or chronic atrial fibrillation). Other possible causes are hereditary clotting dysfunction, (34) cardio-embolic stroke (35) or isolated non-compaction of the left ventricular myocardium (36). Furthermore, solitary thrombo-embolism of an abdominal arterial vessel has been described in combination with the use of oral contraceptive pills (37).

Isolated dissection

Dissection of abdominal arteries is a rare cause of acute abdominal pain. Isolated dissection of an abdominal artery is even more infrequently seen. A few cases concerning isolated CA dissection, without associated aortic dissection, and abdominal trauma have been reported in the literature (38–43). Approximately 50 cases involving isolated dissection of the SMA have been reported in the literature. Isolated dissection of the SMA is mostly associated with aortic dissection and abdominal trauma; a few cases of spontaneous solitary dissection of the SMA have been reported. SMA dissection, solitary or in combination with aortic dissection, has however become a more common diagnosis in the last decade with the widespread use of computed tomography imaging for abdominal pain (44). Isolated dissection of the IMA remains a very rare phenomenon (45,46).

Eccentric diseases

Celiac artery compression syndrome (CACS)

The main cause of single vessel stenosis is by extrinsic compression due to CACS, also known as median arcuate ligament syndrome (MALS). This condition was first described by Lipshutz in 1917 (47). Harjola defined the syndrome in 1963 (48), soon thereafter followed by Dunbar in 1965 (49). Thus CACS is also referred as Dunbar's syndrome. The median arcuate ligament usually passes over the aorta at the level of the first lumbar vertebral body, superior to the origin of the celiac axis. The actual cause of clinical symptoms in the CACS is still a point for discussion. Two main theories are used to explain the pathogenesis of symptoms. In the

first theory, the presence of an anomalous fibrous diaphragmatic band compresses the celiac axis in patients with relatively low insertion of the diaphragm, especially during expiration with partial relief during inspiration. This extensive compression limits the inflow of blood, causing mucosal ischemia. According to the second theory, the pain results from stimulation of the celiac plexus either by mesenteric vasoconstriction or local irritation (50). CACS is typically diagnosed in women under the age of 50 years. A significant compression of the CA by the median arcuate ligament of the diaphragm can give rise to symptoms of CGI. In a recent prospective study concerning CACS patients, the major complaints were postprandial pain (80%), weight loss (77%) and exercise-related pain (40%). An abdominal bruit on physical examination was only found in 23% of patients and smoking seemed to have a correlation with CACS (63% reported smoking), while other cardiovascular risk factors were minimal (6%) (11). In the past 50 years, different studies have shown varying results of treatment of CACS. Especially, in a subset of these studies, the results of long-term follow up after treatment were very disappointing (51–56). More recently, a prospective study has been published using gastric exercise tonometry as the key investigation in patients with suspicion of CACS. In carefully selected cases, surgical release of the CA led to persistent relief of complaints on long-term follow-up. The success rate after this specific diagnostic work-up and treatment was 83%, compared to the 0–50% in earlier studies. The existence of impaired mucosal perfusion in CACS patients was even more underlined by the fact that all successfully treated patients showed improvement or normalisation of gastric exercise tonometry after treatment (11).

DIAGNOSIS

Abdominal arterial stenosis

Non-invasive diagnostic methods to screen for arterial abdominal stenosis are abdominal duplex ultrasound scanning (57), computed tomography angiography (CTA) and magnetic resonance angiography (MRA) (Table 3). Angiography of the mesenteric arteries is still considered to be the 'gold standard' for diagnosing and staging of arterial abdominal stenosis. The advantages of digital subtraction angiography (DSA) are the high sensitivity (and specificity)

Table 3: Diagnostics in single vessel abdominal arterial disease

	Sensitivity	Specificity
Abdominal arterial stenosis		
Duplex ultrasound	88 %	92 %
CTA	82 %	100 %
MRA	100 %	95 %
Mucosal ischemia		
Gastric Exercise Tonometry	82 %	87 %
Prolonged Tonometry	77 %	94 %

Conventional angiography (digital subtraction angiography) considered 'gold standard'

for stenoses in the origin of the abdominal arteries, the good quality of projection of the peripheral mesenteric vasculature, the possibility to project (pathological) collateral circulation, and the ability to perform good quality imaging during in- and expiration, especially of great importance in patients suspected of CACS. The main disadvantages of DSA are its invasive character, the potential complications (i.e. contrast allergy, renal function problems), and the fact that surrounding tissues are not adequately visualised.

Abdominal duplex ultrasound has an acceptable sensitivity and specificity for detection of stenosis in the origins of the abdominal arteries. The sensitivity for significant (>50–70%) stenosis of the CA is 75–100%, with a specificity of 88–89%. The sensitivity for significant stenosis of the SMA is 89%, with a specificity of 92–97% (58). Lateral (conventional) aortography is the primary modality for diagnosing CACS to detect extrinsic compression by the median arcuate ligament. During expiration the compression of the celiac axis typically increases, while during inspiration any compression is less apparent. Duplex ultrasound performed during deep expiration can demonstrate a marked increase in flow velocities at the compressed region of the CA and suggest the diagnosis of CACS (59). In recent years CTA and MRA have evolved as very promising techniques for screening for stenosis of the abdominal arteries and evaluation of patients suspected of CGI. The main advantages of both imaging techniques are the non-invasive approach and the possibility to visualise the other abdominal organs during the same procedure. Only a few studies compared CTA or MRA with DSA as current gold standard in the evaluation of patients suspected for CGI. In a recent Australian study 52 patients had both CTA and DSA, the sensitivity of CTA for abdominal arterial stenosis proved 82%, with a specificity of 100% (60). One study compared MRA and conventional DSA in 65 patients suspected for CGI; in this study the sensitivity of MRA for abdominal arterial stenosis was 100%, with a specificity of 95% (61). The MRA tended to over-rate stenoses in up to 15% of patients, and evaluation of the IMA was only possible in 64% of patients. At this moment no studies are available comparing CTA and MRA in patients suspected of CGI. However, the IMA and the smaller peripheral mesenteric vessels are currently better assessed with CTA than with MRA because of the higher spatial and temporal resolution and faster acquisition times of CTA (62). In addition, CTA allows the identification of calcified plaques. The main advantages of MRA over CTA are its lack of radiation exposure and the possibility to perform flow measurements. MRA measurements have shown a consistent relationship between flow in the portal or superior mesenteric vein and flow in the arteries supplying those veins (63). The assessment of flow velocities of the portal and superior mesenteric vein before and after oral caloric stimulation seems a promising diagnostic tool for CGI.

Mucosal ischemia

Especially in single vessel arterial abdominal stenosis, diagnosing actual mucosal ischemia is of the utmost importance. It is estimated that in patients with (otherwise unexplained, mainly upper) abdominal complaints and a single vessel arterial abdominal stenosis of 50% or more,

60% of patients actually have CGI, and therefore will benefit from revascularisation. At this moment, gastrointestinal tonometry is the only established technique to detect gastrointestinal mucosal ischemia. Gastrointestinal tonometry, in combination with duplex ultrasound of the abdominal arteries, is suggested as currently being the best diagnostic strategy for patients suspected of CGI (64). In two large patient cohorts evaluated for possible CGI including a total of 102 and 354 patients, gastrointestinal tonometry proved to have a sensitivity and specificity of respectively 78–85% and 82–92% for the detection of CGI (Table 3) (9,10). Two types of tonometry are currently used for diagnosing mucosal ischemia in patients analysed for CGI. The first introduced was gastric exercise tonometry (GET) which uses sub-maximal exercise (cycling) as a provocation of gastrointestinal ischemia, in essence very similar to the concept of exercise testing commonly used for the evaluation of cardiac ischemia. Because GET is quite cumbersome and cannot be performed in up to 20% of patients due to patients' inability to perform exercise, an alternative tonometry test was introduced. This test consists of prolonged (24 h) gastric and jejunal tonometry and uses meals as provocation of gastrointestinal ischemia (65). This prolonged tonometry test was found to be as accurate as GET for detection of gastrointestinal ischemia with a sensitivity of 77% and a specificity of 94%, and is easier to perform without patient restrictions, nevertheless it remains an invasive technique which requires 24 h hospital admission.

Despite these considerable improvements in diagnostic tools, diagnosing mucosal ischemia (i.e. CGI) remains challenging. Even with tonometry 15–23% of patients with GI ischemia are missed (9,10,65). At the moment no other single, simple test with a high sensitivity is available to detect mucosal ischemia. The characteristics of mucosal ischemia in CGI patients are one of the main causes for this. Mucosal ischemia can often be present for short periods and fully reversible in between. These periods are also most common during exercise and after a meal, both of which restrict the ease to access the mucosa of the gut. Alternative diagnostic methods are nevertheless being developed, these are likely to replace tonometry in the near future. Diagnosing CGI using visible light spectroscopy during endoscopy is a new promising endoscopic technique in which tissue saturation in patients suspected of CGI is measured (66). Additionally, serum markers for early gastrointestinal ischemia could be of great value in diagnosing CGI and contribute to the diagnostic properties as a non-invasive test method. If these techniques prove their value, their ease of use and general accessibility are likely to lead to a considerable increase in the frequency with which patients with CGI are adequately diagnosed.

TREATMENT

In general, treatment of single vessel abdominal arterial disease involves fewer complications and very low mortality as compared to multivessel disease. The primary goal of treatment in

patients with single vessel disease is relief of symptoms. This is in contrast with patients with multivessel abdominal arterial disease; these patients are at increased risk for complicated disease (i.e. high morbidity and mortality). In the latter group, treatment primarily aims to prevent progression of complaints or morbidity in future (10). For treatment of CGI caused by concentric or occlusive disease there are two therapeutic options: radiological intervention including percutaneous transluminal angioplasty (PTA, with or without stent placement) or surgical revascularisation. The choice of treatment depends on type of lesion (compression or atherosclerosis), the technical options to perform endovascular treatment (presence or absence of complete occlusion, angle of origin of abdominal artery) and patient factors (age, co-morbidity and body mass index (BMI)).

Radiological interventional revascularisation

PTA is a minimally invasive technique as compared to open surgical revascularisation. Currently, endovascular treatment for arterial abdominal stenosis consists of PTA with stent placement therapy, because of the short patency of PTA alone (67). Only in selected cases is PTA as single modality treatment without stent placement sufficient. This is particularly the case in the presence of fibromuscular dysplasia, and in some cases where there remains doubt whether a partial stenosis is associated with clinically relevant CGI. Endovascular therapy is the first choice of treatment in patients with single vessel abdominal arterial atherosclerotic disease and co-morbidity, elderly age and as 'bridge-to-surgery' in patients with a low BMI due to severe weight loss (i.e. cachectic state) because of the increased peri-operative morbidity (10). Furthermore, endovascular treatment is preferable in patients with high peri-operative risks and those with limited life expectancy. The long-term efficacy of stent placement is threatened by stent occlusion and displacement. This has in several series been reported to occur in 28% of cases (68–70). As such, long-term patency of the current generation of stents is still inferior to surgery. There is no known difference in patency of stents placed in the CA versus the SMA (14).

Surgical revascularisation

The main indication for surgical therapy in single vessel abdominal arterial stenosis is CACS. The majority of CACS patients is relatively young and has no co-morbidity. In atherosclerotic stenotic disease, patients unsuited for radiological intervention (occlusion or a pinpoint stenotic vessel) and younger patients (without co-morbidity) are candidates for surgical revascularisation. Surgical bypass procedures or end-arterectomies provide long- term patency, but may be associated with considerable post-operative morbidity (69).

CA release during open surgical treatment is the established approach for patients with CACS, with usually a good prognosis. Additionally, intra-operative duplex ultrasound could document the improvement in CA flow after the decompression procedure, and in this way detect possible rest-stenosis, which can be treated accordingly. This intra-operative reassurance of

improvement (i.e. normalisation) of flow in the CA after decompression has been advocated as one of the factors having a positive influence on long-term outcome. During the release of the CA, the median arcuate ligament and the fibrous celiac plexus overlying the CA may both be transected. Some authors suggest that the symptomatic improvement observed after this surgical intervention may, at least in a proportion of patients, be attributed to the concurrent destruction of the celiac ganglion, rather than to release of the CA. Along this line, it has been hypothesised that recurrence of symptoms may be related to healing of the nervous plexus (56,71,72). A more evident proof of the mere existence of CACS, and that it can be treated successfully, were the results of a study that showed that in patients treated for CACS with clinical and anatomical success, the repeated gastrointestinal tonometry normalised, or at least improved, in majority of patients. This finding underlines the fact that in CACS patients the chronic impairment of gastrointestinal blood flow causes mucosal ischemia, which can be reversed by cleavage of the median arcuate ligament (11).

Recently, laparoscopic cleavage of the median arcuate ligament was introduced. This minimal invasive surgical therapy seems to shorten the duration of hospital admission, improve intraoperative safety and seems at least as successful as conventional open decompression procedures (73–75). Endovascular stent placement is contra-indicated in CACS: repeated pressure from the median arcuate ligament with each respiratory cycle can damage the stent resulting in bending and rupture of stents within 1–2 years after placement (76) or stent displacement (77). Embolectomy with or without a necessary intestinal resection is performed in case of gastrointestinal infarction or acute gastrointestinal ischemia due to an isolated thrombo-embolism (31). Medical treatment is indicated in case of a peripheral or non life-threatening embolism. The most appropriate treatment of isolated dissection of an abdominal artery has not yet been established. Surgical repair, radiological intervention (transcatheter embolisation) (78) and conservative therapy (79,80) have been applied until now. In most cases, dissection of isolated mesenteric arteries is limited, and does not cause clinically significant organ ischemia (43). Therefore, a conservative treatment is advocated, applying a watchful waiting policy. PTA or surgical revascularisation is advocated in symptomatic patients with abdominal artery (familial) fibro-muscular dysplasia (27).

Treatment of vasculitis

Isolated single vessel abdominal artery vasculitis is treated with immunosuppressive therapy. Highdose steroid therapy can result in resolution of complaints and normalisation of angiographic findings (19–21).

ACCIDENTAL FINDINGS OF SINGLE VESSEL ABDOMINAL ARTERIAL STENOSIS

The increased availability of non-invasive diagnostics, such as CTA and MRA, has resulted in an increase of detection of unexpected vascular pathologic changes. Isolated CA and SMA stenosis without accompanying symptoms of CGI are occasionally observed. In the past, evaluation of the vascular abdominal anatomy was performed using conventional angiography in patients who are candidates for transplantation or subjects who are possible candidates for living related donor procedures. In the current work-up of patients evaluated for possible liver transplantation, screening of the hepatic arterial anatomy is now common, as the CA is the only source of arterial blood supply to the transplanted liver. In case of CA or hepatic artery obstruction, graft loss might be expected. Isolated CA stenosis, or aneurysms, without accompanying symptoms of CGI are indications for treatment, aiming at normalisation of mesenteric arterial anatomy to prevent in this way post-transplant complications and potential graft loss. Recently, CTA and MRA have become the first choice diagnostic tools to visualise abdominal arterial (and venous) anatomy. One study showed an incidental significant asymptomatic isolated CA stenosis in 14% of the living donor candidates, without evidence of generalised atherosclerotic disease (81). For possible living-related liver donors, isolated CA stenosis found on preoperative CTA, MRA or angiography is considered an exclusion criterion in some centres. However, other centres have shown that donor hemi-hepatectomies can be performed safely in the presence of significant isolated CA stenosis in asymptomatic living-related donors (81). In these occasions, the vascular anomaly is not to be considered a contraindication because of expected extensive collateral circulation. In these selected cases care should be taken to maintain retrograde collateral perfusion to the main hepatic artery through the pancreatico-duodenal arcade, during the transplantation procedure. Due to the popularity of total body scan screening programs; subjects will be increasingly confronted with incidental findings of abnormalities of the abdominal arterial anatomy. The benefits and risks of this screening method have not been assessed in adequate clinical trials (82,83). In one retrospective study of 1192 subjects, abnormal findings of the abdominal vascular anatomy were detected in 48% of subjects (mean age of 54 years). The most common abdominal vascular abnormality reported was vessel wall calcification (96%) (84).

SUMMARY

The discussion as to whether single vessel abdominal arterial disease can cause CGI is finished. In the past years, different larger cohort studies have shown that this disease entity exists, can be diagnosed correctly and treated with clinical success at long-term follow up.
The most important CA stenosis aetiology is extrinsic compression due to the median arcuate ligament (i.e. CACS). Atherosclerosis is the second most common cause of single vessel

mesenteric disease. In both asymptomatic and symptomatic patients isolated atherosclerotic stenosis is more common in the CA than in the SMA. Arterial atherosclerotic disease is the major cause of abdominal arterial stenosis in the elderly patient, while in the younger patient CACS is the most common cause. The clinical symptoms of CGI caused by single vessel abdominal arterial disease are postprandial pain, weight loss, exercise-related pain and are comparable with the complaints of multivessel abdominal arterial disease patients. Abdominal duplex ultrasound, CTA and MRA can be used as a screening method to diagnose abdominal arterial stenosis. The classical angiography is still considered the 'gold standard' but especially CTA and MRA are evolving rapidly and improving non-invasive techniques. The established diagnostic approach to detect mucosal ischemia in patients suspected of CGI is gastrointestinal tonometry. The use of gastrointestinal tonometry has improved the detection of actual mucosal ischemia, and is especially of importance in patients with single vessel abdominal arterial stenosis. Introduction of gastrointestinal tonometry in the diagnostic work-up of patients suspected of single vessel CGI led to improvement of outcome from 0–50% to over 80% after treatment at long-term follow up. CA release during open surgical treatment is the established approach for CACS. Recently laparoscopic release of the CA has been introduced, with promising results. First-choice treatment of isolated atherosclerotic abdominal arterial stenosis in a relatively young patient without co-morbidity is surgical revascularisation, especially with the known long-term patency of surgical as compared to endovascular therapy. Endovascular stent placement therapy is advised in elderly patients, in patients with co-morbidity and as 'bridge-to-surgery' in patients with severe weight loss.

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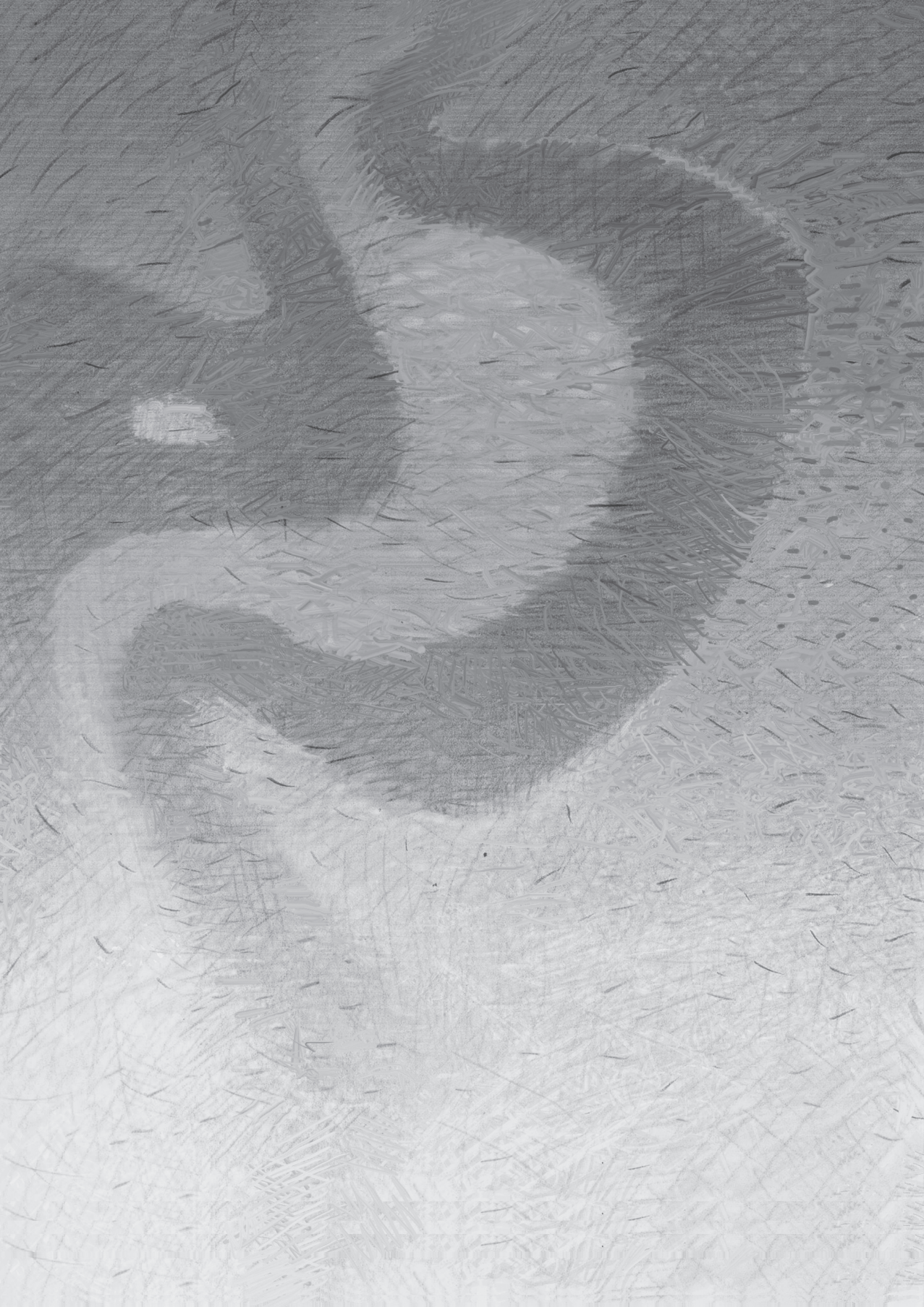

Chapter 3

Combining radiological imaging and gastrointestinal tonometry: a minimal invasive and useful approach for the work-up of chronic gastrointestinal ischemia

Désirée van Noord[1], Aria Sana[1], Leon M.G. Moons[1], Peter M.T. Pattynama[2], Hence J.M. Verhagen[3], Ernst J. Kuipers[1,4], Peter B.F. Mensink[1]

Departments of Gastroenterology and Hepatology[1], Intervention Radiology[2], Vascular Surgery[3], Internal Medicine[4], Erasmus MC - University Medical Center, Rotterdam, The Netherlands

Submitted

ABSTRACT

Introduction The combination of duplex ultrasound and gastric exercise tonometry (GET), followed by conventional digital subtraction angiography (DSA) of the gastrointestinal arteries is the current established approach for patients suspected of chronic gastrointestinal ischemia (CGI). GET is cumbersome and impossible to perform in a considerable proportion of patients. DSA is invasive and has a substantial complication rate. Alternative diagnostic methods have recently been developed, in particular 24-hour gastrointestinal tonometry (TM), and CT- or MR angiography (CTA or MRA). The latter alternatives seem to be promising, minimally invasive techniques to detect mucosal ischemia and define abdominal artery stenoses. We therefore challenged the use of TM in combination with CTA as an alternative approach to evaluate patients suspected of CGI.

Methods Patients referred for evaluation of possible CGI were prospectively evaluated using CTA or MRA, and TM. All patients were discussed in a multidisciplinary team and a consensus diagnosis was made. Patients diagnosed with CGI were offered therapy by means of revascularization or vasodilating drug therapy. The definitive diagnosis CGI, used as 'the gold standard' was made after persistent symptom relief on follow-up.

Results In 31 months, 186 patients were included; M 69, mean age 63 (range 17-87) yrs. A consensus diagnosis of CGI was made in 128 (69%) patients: 94 (73%) with occlusive and 34 (27%) patients with non-occlusive CGI. Of the 128 CGI patients, 66 (52%) received endovascular treatment, 25 (20%) surgical revascularization, and 25 (20%) vasodilating pharmacotherapy. After a follow-up of ≥ 12 months , 91% of the CGI patients were free of symptoms. None of the patients with a non-CGI consensus diagnosis developed ischemia.

Conclusion In patients clinically suspected of CGI, the combination of radiological imaging of the gastrointestinal arteries by CTA and TM provides a minimally invasive, reliable diagnostic approach. This approach seems very useful in clinical practice and seems to have similar outcome as the established diagnostic work-up.

INTRODUCTION

The diagnosis of chronic gastrointestinal ischemia (CGI) remains a clinical challenge. Three aortic branches, the celiac artery (CA), the superior (SMA) and inferior mesenteric artery (IMA), provide the arterial blood supply to the gastrointestinal tract. The anatomy of these arteries varies largely and abdominal artery stenotic disease is not uncommon (1). Occlusive gastrointestinal arterial disease often remains asymptomatic, due to the presence of abundant collateral circulation. Only patients with significant arterial stenosis in combination with insufficient collateral circulation develop clinical ischemia. In these cases, the diagnosis is however often missed due to lack of sensitive diagnostic tests. The diagnostic approach in patients referred for evaluation of possible CGI focuses on identification of gastrointestinal arterial stenosis and demonstration of mucosal ischemia (2). Currently, the combination of duplex ultrasound and exercise tonometry (GET) as a functional test, followed by conventional digital subtraction angiography (DSA) of the abdominal arteries is the established approach for patients suspected of chronic gastrointestinal ischemia (CGI) (3-8). GET uses sub-maximal exercise as a provocation of gastrointestinal ischemia, in essence very similar to the concept of exercise testing commonly used for the evaluation of cardiac ischemia. However, GET is cumbersome and impossible to perform due to the inability of many patients in this category to perform sub-maximal exercise for sufficient period of time to assess CGI. Recently, prolonged 24-hour gastrointestinal tonometry (TM) was introduced as alternative method, using meals as provocation of gastrointestinal ischemia. TM seems to be as accurate as GET for detection of CGI, while being less cumbersome and performable in every patient suspected of CGI (9). DSA remains the 'gold standard' for evaluation of arterial stenotic disease, but is an invasive diagnostic procedure with potential serious side effects including nefropathy and allergic reactions. In recent years, minimally invasive radiological evaluation of gastrointestinal arterial anatomy by means of computed tomography angiography (CTA) and magnetic resonance angiography (MRA) were introduced as possible alternative diagnostic methods for assessment of arterial patency (10, 11).

This study therefore aimed to investigate the efficacy of prolonged gastrointestinal TM with CTA or MRA as a new, minimally invasive, alternative approach to evaluate patients clinically suspected of CGI.

METHODS

Consecutive patients referred for evaluation of possible CGI were prospectively included after informed consent. The study was approved by the Institutional Review Board of the Erasmus MC- University Medical Center.

Diagnostic workup

In all patients more common causes of chronic abdominal symptoms had been previously excluded by appropriate diagnostic evaluation. Suspicion for CGI was defined as fulfilling at least two of the following criteria: 1) presence of postprandial pain, 2) otherwise unexplained weight loss (> 5% of normal body weight), and / or 3) significant stenosis of at least one of the gastrointestinal arteries on previous radiological evaluation. TM in combination with CTA or MRA to visualize the gastrointestinal arteries (CA, SMA and IMA) was performed as standard diagnostic workup. CTA was considered the first choice imaging technique, however MRA was used when earlier performed or in the presence of contra-indications for CTA such as contrast allergy or renal function failure. A significant stenosis of the gastrointestinal arteries was defined as a luminal reduction of >70 %.

Prolonged gastric and jejunal tonometry

A gastric and a jejunal tonometer were inserted nasogastrically (8 French, Datex Ohmeda, Helsinki, Finland) using endoscopy and fluoroscopy guidance (2). Intravenous infusion of omeprazole was started with a bolus of 80 mg in 30 minutes, followed by 8 mg/hour, using an infusion pump. The catheters were both connected to a Tonocap (Datex Ohmeda, Helsinki, Finland). The tonocaps were connected to a computer on which a data-collection program automatically registered the gastric and jejunal PCO_2 level every 10 minutes. All patients had meals at standard times: bread meal (01.00 PM), liquid compound meal (04.00 PM), bread meal (7.00 PM), breakfast (8.00 AM), liquid compound meal (10.00 AM) and dinner (12.00 PM) (12). The liquid compound meal consisted of two 200 ml packages (Nutridrink, Nutricia, the Netherlands). The patients were instructed to eat their meals within 15 minutes. The consumption of small amounts of liquids (noncarbonated) was allowed and noted; consumption of alcohol-, acid- and CO_2-containing beverages was strictly prohibited. With the catheters in situ, the subjects were capable of minor exercise. The cut-off values for elevated mucosal CO_2 levels, as evidence of mucosal ischemia, were a gastric or jejunal PCO_2 > 12.0 kPa after breakfast or a bread meal, > 13.6 kPA after dinner, or > 10.6 kPA after ingestion of a compound solution. The criteria for a positive test (abnormal result) on TM were: pathologic responses after three or more meals, or a combination of one or two pathologic responses after meals combined with a median PCO_2 > 8.0 kPa measured in between meals (12).

Consensus and definitive diagnosis and treatment

Medical history, physical signs and symptoms, and the results of all diagnostic procedures were discussed in a multidisciplinary team consisting of a vascular surgeon, intervention radiologist and gastroenterologist, all specialized in CGI, leading to a final expert-based *consensus diagnosis* using the following categorization: (1) absence of gastrointestinal arterial stenosis, absence of ischemia, (2) presence of gastrointestinal arterial stenosis, no signs of ischemia, (3) absence of gastrointestinal arterial stenosis, yet presence of ischemia, i.e. non-

occlusive mesenteric ischemia (NOMI), or (4) presence of gastrointestinal arterial stenosis and presence of ischemia, i.e. occlusive mesenteric ischemia. The diagnosis NOMI and occlusive gastrointestinal ischemia, codes (3) and (4), were together defined as CGI. NOMI was defined as all forms of non-occlusive mesenteric ischemia, based on clinical symptoms and positive TM despite normal gastrointestinal arterial anatomy on CTA or MRA. Patients with occlusive CGI were offered revascularization by either open surgery or by endovascular percutaneous transluminal angioplasty (PTA) with stent placement. Brachial artery cannulation was considered first choice route for therapeutic angiography. In patients with the diagnosis celiac artery compression syndrome, surgical release of the CA was treatment of choice (2, 13). Endovascular therapy was considered the first choice treatment in elderly patients, patients with comorbidity, severe cachexia, as well as in those with previous extensive abdominal surgery (14). Patients with the diagnosis of NOMI were offered a sequence of vasodilating drug therapy starting with isosorbidemononitrate (20 mg odd for one week, then 40 mg odd) or ketanserin (20 mg odd for one week, then 40 mg odd) when the complaints persisted, or returned, or when severe side-effects occurred. All patients with the diagnosis NOMI were also referred for cardiological evaluation (2).
Clinical response after treatment was scored as free of symptoms or persistent / worsening of symptoms. The 'gold standard' used for the *definitive diagnosis* of CGI was persistent relief of complaints after adequate therapy on long-term follow-up.

Follow-up

All patients diagnosed with ischemia, i.e. categories 3 and 4 with respectively non-occlusive and occlusive mesenteric ischemia, visited the out-patient clinic at six weeks, three months, six months and one year after treatment for repeat assessment of clinical status. A duplex ultrasound of the gastrointestinal arteries was performed at six months and one year after treatment. If complaints persisted after adequate treatment, the *consensus diagnosis* was revised, i.e. the diagnosis ischemia was changed into non-CGI. Patients diagnosed as non-CGI, i.e. diagnostic categories 1 and 2, were for further follow-up returned to the referring physician. Their follow-up data were obtained after 12 months from the treating physician by means of a survey focusing on current health status, presence of any persisting symptoms, further diagnostic procedures, and events such as hospital admission and death.

Statistical analysis

Data were expressed as number of patients (percentage) or mean (range) when appropriate. The data of the ischemic and non-ischemic patients were compared using Student's t-test or χ^2 testing. Statistical analysis was performed using the SPSS 16.0 program (SPSS Inc. Chicago, IL). A p-value <0.05 was considered statistically significant (all two-tailed).

RESULTS

During a period of two years and seven months, July 2006 - February 2009, 200 patients were referred for evaluation of possible CGI. Informed consent for participation in the study was obtained from 186 patients. Patient characteristics and presenting symptoms are presented in Table 1.

Table 1. Patient characteristics and presenting symptoms, data given are number of patients (percentages) or mean (range).

	All patients n=186	CGI patients n=128	Non-ischemia patients n=58
Age (years)	63 (17-87)	61 (20-86)	56 (17-87)
Gender M/F	69/117	44/75	25/42
Abdominal complaints	141 (76%)	97 (82%)	44 (66%)
Postprandial pain	132 (71%)	93 (78%)	39 (58%)
Exercise related pain	70 (38%)	46 (39%)	24 (36%)
Diarrhea	49 (26%)	25 (21%)	24 (36%)
Duration of complaints (months)	25 (1-312)	21 (1-144)	33 (1-312)
Weight loss	134 (72%)	89 (75%)	45 (67%)
Weight loss (kg)	10 (0.7-35.0)	10.6 (1.0-35.0)	11.5 (0.7-32.0)
BMI (kg/m^2)	21.9 (13.2-37.3)	22.4 (13.3-37.3)	22.6 (13.2-35.0)
Abdominal bruit	41 (22%)	34 (29%)	7 (10%)
Risk factors for CVD:			
· smoking*	132 (71%)	84 (71%)	48 (72%)
· other risk factors**	126 (68%)	84 (71%)	42 (63%)

CGI = chronic gastrointestinal ischemia; M = male; F= female; CVD= cardiovascular disease; * former or current smokers; ** including diabetes mellitus, obesity, hypertension, hyperlipidemia, hyperhomocysteinemia and familial history for cardiovascular disease.

Diagnostic work-up

TM was performed in 169 (91%) patients, TM was defined pathological in 117 (69%), normal in 48 (29%), and inconclusive in 4 (2%) patients. In seventeen patients, TM was not performed due to agitation (n=1) or because clinical signs were compatible with (semi-)acute CGI requiring immediate intervention (n=16). A CTA was performed in 168 (90%) patients and a MRA in 16 (9%) patients. In two (1%) patients a DSA had already been performed at the referring hospital. Radiological imaging showed single vessel stenosis in 75 (40%) patients (CA in 67, SMA in 8), 2-vessel stenosis in 22 (12%), and 3-vessel stenosis in 11 (6%) patients. The expert-based *consensus diagnosis* CGI was made in 128 (69%) patients: 94 (73%) with occlusive CGI and 34 (27%) patients with NOMI. The patient characteristics were comparable between patients defined having ischemia, i.e. CGI, and the non-CGI patients.

Treatment

Treatment was performed in 128 patients. PTA and stent placement was performed in 65 patients. In 33 (51%) patients a stent was placed in the CA, in 14 (21%) patients in the SMA, and in 18 (28%) patients both in the CA and the SMA. In one patient with fibromuscular dysplasia only PTA was performed. Of these patients, four patients had stent placement followed by

surgical revascularization. The reasons for combined treatment were stent placement serving as "bridge to surgery" (n = 3) and stent dysfunction (n = 1). Surgical revascularization was performed in 25 patients. In nine patients a bypass procedure was performed and in 16 patients the CA was released by cleavage of the arcuate ligament. In three patients no stenosis was seen during angiography and these patients were treated as non-occlusive ischemia.
Twenty-five (74%) patients diagnosed with NOMI were treated with vasodilating drug therapy. Four (12%) NOMI patients were diagnosed with cardiac dysfunction. Two patients had cardiac angina due to coronary arteriosclerosis, successfully treated with percutaneous transluminal coronary angioplasty in one and medical therapy in the other patient. One patient had constrictive pericarditis and was successfully treated with pericardiectomy. Finally, one patient had heart failure with ventricular tachycardia and was successfully treated by cardioverter defibrillator implantation. Two patients diagnosed with NOMI had severe chronic obstructive pulmonary disease and after optimisation of their pulmonary medical treatment, the gastrointestinal complaints improved. Three patients diagnosed with NOMI were found to have false-positive findings: two patients with celiac disease (Marsh IIIB), both successfully treated with a gluten-free diet, and one patient with spontaneous improvement of complaints, possibly related to a transient gastrointestinal infection.

Complications

No complications related to the TM or diagnostic radiological imaging were encountered. In total, in 23 (21%) patients complications related to therapy were noted. In 21 (32%) of 66 patients complications occurred during or after endovascular treatment. Two patients experienced a cerebral vascular stroke during and directly after PTA with stent placement, both patients had persistent neurological symptoms at one year follow-up. Two patients had extensive hematoma after brachial artery cannulation resulting fasciotomy in one, and need for transfusion in the other patient. In another two patients, brachial artery cannulation resulted in dissection which needed surgical repair and pseudo-aneurysm which was treated with local injection therapy. Two patients presented with deep venous thrombosis between 0 – 3 days after one diagnostic and after one therapeutic angiography. In 13 patients a hematoma occurred due to brachial artery cannulation during or after endovascular therapy. In these patients the hematoma resolved after conservative treatment. After surgical treatment two (8%) of 25 patients had complications. In both cases one day after celiac artery release a relaparotomy was needed, in both cases showing no abnormalities and uneventful recovery at follow-up.

Follow-up

After a median follow-up of 21 (range 12-44) months, 116 patients initially diagnosed with CGI and having received treatment, were free of symptoms. Therefore the *definitive diagnosis* CGI was confirmed in these patients: 62% of total, 91% of *consensus diagnosis* CGI group. In 12 (9%) patients the *consensus diagnosis* of CGI was not confirmed because of persistent

symptoms despite adequate treatment leading to arterial patency. During follow-up, none of the patients with a non-CGI consensus diagnosis developed ischemia or died of ischemic complications, nor did any of these patients develop progressive symptoms compatible with CGI. During follow-up four patients diagnosed with ischemia died. Three deaths in the CGI patients were unrelated to the ischemia. In one patient with CGI caused by 3-vessel disease, with a body mass index of 13 kg/m^2, a stent placement as 'bridge to surgery' was performed but proved clinically unsuccessful. Unfortunately, the patient presented with 'acute-on-chronic' ischemic complaints before elective surgical therapy. She died due to multiple organ failure after acute surgery, which revealed partial necrosis of the small bowel. The sensitivity of the consensus diagnosis was 91% with a specificity of 100%; see Figure 1.

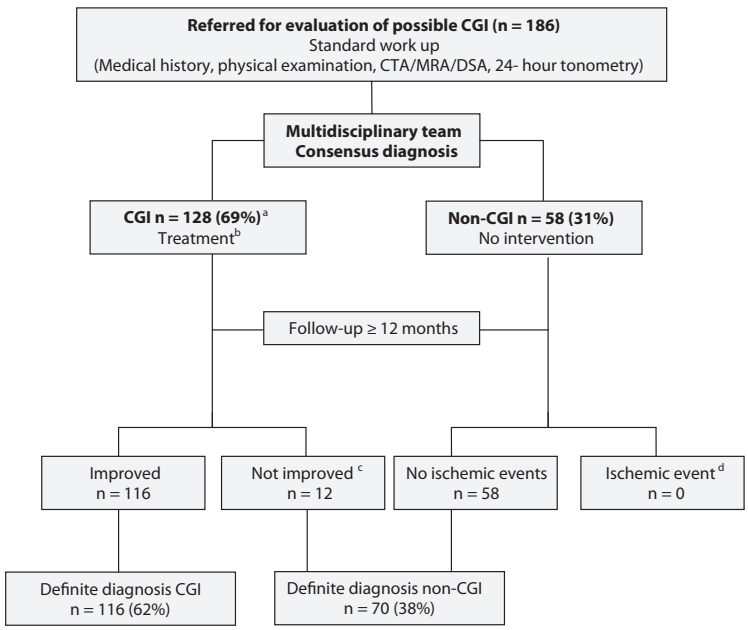

Figure 1: Flowchart of the study
CGI = chronic gastrointestinal ischemia;
CTA = computed tomography angiography;
MRA = magnetic resonance angiography;
DSA = digital subtraction angiography;
TM = 24-hour gastric and jejunal tonometry;
a 94 (73%) with occlusive CGI; 34 (27%) with non-occlusive CGI
b Occlusive CGI: PTA (n = 66), in 4 patients this was followed by surgery; no stenosis was seen during angiography (n=3) and these patients were treated as non-occlusive ischemia; surgery (n = 25) Non-occlusive CGI; vasodilating agents (n = 25)
c Symptoms unchanged despite adequate treatment
d Non ischemia related morbidity and mortality occurred during the follow-up
A definite diagnosis of CGI was made if a patient was free of symptoms after adequate therapy for at least 12 months of follow-up; A definite diagnosis of non-CGI was made if a patient was not diagnosed or hospitalized with ischemia related morbidity or mortality after follow-up

DISCUSSION

In patients clinically suspected of CGI, the combination of radiological imaging of the gastrointestinal arteries and TM provides a minimally invasive, reliable diagnostic approach. This approach seems very useful in clinical practice with a similar outcome as the established diagnostic work-up including GET in combination with duplex ultrasound followed by a diagnostic DSA (3). In particular the association between the diagnostic test results and the outcome of treatment are in line with earlier reports using this established diagnostic work-up.

Our minimal invasive approach prevents a diagnostic DSA by using CTA as primary imaging technique. In recent years CTA has evolved as very promising technique for evaluation of abdominal artery patency and thus for the evaluation of patients suspected of CGI. The main advantages of CTA are the non-invasive approach and the possibility to visualise the other abdominal organs during the same procedure. Only a few studies compared CTA with DSA as current gold standard in the evaluation of patients suspected for CGI. In these studies CTA was shown to be highly accurate with reproducible results (15). In an Australian study 52 patients underwent both CTA and DSA, the sensitivity of CTA for abdominal arterial stenosis proved 82%, with a specificity of 100% (16). Furthermore, CTA was shown to have better intra- and interobserver variability as compared to DSA (17). Interobserver variability also exists among Doppler measurements of gastrointestinal flow parameters (18, 19). In our study, only patients with doubt about significance of the stenosis or with suspicion of CACS underwent a diagnostic DSA to rule out atherosclerosis and to identify CACS. Therefore 21 patients underwent a diagnostic DSA, of whom 16 were diagnosed with CACS. In three patients no stenosis was seen during angiography and these patients were treated as non-occlusive ischemia. In two patients a DSA had already been performed at the referring hospital. All patients in our cohort with a pathological TM (34 patients) or pathological CTA/MRA (11 patients) or both (83 patients) would have had a diagnostic DSA following the established approach: a total of 128 patients. Seventeen patients in whom TM was not performed due to agitation or because clinical signs were compatible with (semi-)acute on chronic gastrointestinal ischemia were left out of consideration. Therefore in 107 (84%) patients a diagnostic and invasive DSA was prevented by using CTA or MRA as the preferred radiological imaging of the gastrointestinal arteries.

The established approach includes GET, which is impossible to perform in 10-15 % of patients due to patients' inability to perform exercise (4). In the current study, in 17 (9%) patients TM was not performed due to agitation (n = 1) or acute-on-chronic CGI (n = 16). Because of the nature of the test, measurements are performed in resting and postprandial conditions, TM is easier to perform than GET. Nevertheless, it remains a technique which requires 24 hours hospital admission. In two large patient cohorts evaluated for possible CGI including a total of 102 and 354 patients, GET proved to have a sensitivity and specificity of respectively 78–85%

and 82–92% for the detection of CGI (4, 6). TM has been described before in 33 patients suspected of CGI and was found to be as accurate as GET for detection of gastrointestinal ischemia with a sensitivity of 77% and a specificity of 94% (9). This is the first large cohort study describing the results of TM and the diagnostic combination using TM and CT- or MRA in patients suspected of CGI. Our study shows a sensitivity of 91% and a specificity of 100% and is therefore in line with earlier reports using the established approach.
This study has some limitations. Firstly, currently there is no definitive gold standard for the diagnosis CGI. The 'gold standard' used for the definitive diagnosis CGI was persistent relief of complaints after adequate therapy on long-term follow-up. Clinical response after treatment was scored as free of symptoms or persistent symptoms. A repeated TM after treatment was not incorporated in the current study protocol. However, we previously investigated the use of repeat TM in a selected group of patients and showed that TM improved or normalized after adequate treatment (8). Furthermore, DSA of the gastrointestinal arteries is still considered to be the 'gold standard' for diagnosing and staging of arterial abdominal stenosis. In this study, a diagnostic DSA was only performed in a selected group of patients as described above. Furthermore, the treatment options for NOMI patients are limited. NOMI patients are currently treated with a sequence of vasodilating drugs. Until now, treatment of NOMI patients has not been investigated prospectively.

In conclusion, in patients clinically suspected of CGI, the combination of radiological imaging of the gastrointestinal arteries by CTA or MRA in combination with 24-hour TM provides a minimally invasive, reliable diagnostic approach and thus an excellent alternative to the conventional diagnostic work-up using GET in combination with duplex ultrasound followed by a diagnostic DSA. The new approach is very useful in clinical practice and has similar outcome as the conventional diagnostic work-up.

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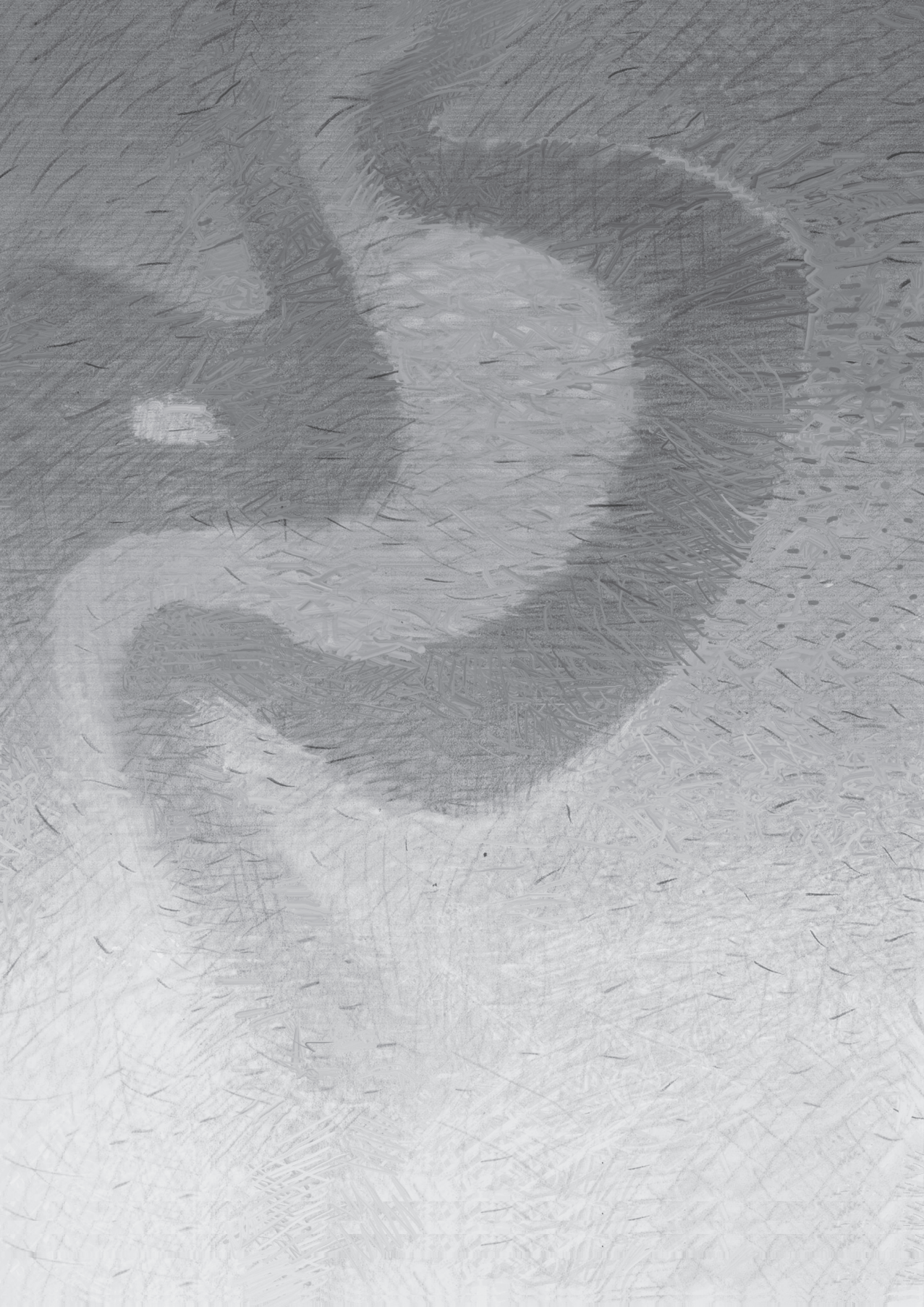

Chapter 4

Endoscopic visible light spectroscopy: a new, minimally invasive technique to diagnose chronic gastrointestinal ischemia

Désirée van Noord[1], Aria Sana[1], David A. Benaron[2], Peter M.T. Pattynama[3], Hence J.M. Verhagen[4], Bettina E. Hansen[1,5], Ernst J. Kuipers[1,6], Peter B.F. Mensink[1]

Departments of Gastroenterology and Hepatology[1], Intervention Radiology[3], Vascular Surgery[4], Biostatistics[5], Internal Medicine[6], Erasmus MC - University Medical Center, Rotterdam, The Netherlands
Stanford University School of Medicine, Palo Alto, CA, USA[2]
None of the authors have a conflict of interest regarding this article, except for D. Benaron, who is founder of Spectros with more than 5% equity stake.

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ABSTRACT

Background The diagnosis of chronic gastrointestinal ischemia (CGI) remains a clinical challenge. Currently, there is no single and simple test with a high sensitivity available. Visible light spectroscopy (VLS) is a new technique that non-invasively measures mucosal oxygen saturations during endoscopy.

Objective The diagnostic accuracy of VLS for detection of ischemia in a large cohort of patients.

Design Prospective study, adherence to the Standards for reporting of diagnostic accuracy.

Setting Tertiary referral center.

Patients Consecutive patients referred for evaluation of possible CGI.

Interventions Patients underwent VLS next to the standard work-up consisting of evaluation of symptoms, gastrointestinal tonometry and abdominal CT- or MR-angiography.

Main outcome measures VLS measurements and the diagnosis CGI as established with the standard work-up.

Results In 16 months, 121 patients were included: 80 in a trainee data set, followed by 41 patients in a validation data set. CGI was diagnosed in 89 (74%) patients. VLS cut-off values were determined based on the diagnosis CGI, and applied in the validation data set and the results compared to the gold standard, resulting in a sensitivity and specificity of VLS of 90% and 60%. Repeated VLS measurements showed improvement in 80% of CGI patients after successful treatment.

Limitations Single center study, only 43% of patients had repeated VLS measurements after treatment.

Conclusions VLS during upper endoscopy is a promising, easy to perform, minimally invasive technique to detect mucosal hypoxemia in patients clinically suspected for CGI, showing excellent correlation with the established ischemia work-up.

BACKGROUND AND AIMS

The diagnosis of chronic gastrointestinal ischemia (CGI) remains a challenge in clinical practice. For a long time, CGI was considered to be a very rare disease, only presenting in patients with multiple stenotic abdominal arterial disease. The introduction of gastrointestinal tonometry (TM) as the first functional test and one of the major keys in diagnosing CGI, has changed this view. Several studies with TM have shown that CGI is a clearly identifiable disease identity which can occur both in the presence of multi-vessel as well as single vessel abdominal arterial stenosis (1-3). Currently, a combination of clinical signs, radiological evaluation of abdominal arterial vascular anatomy and a functional test (TM) is the proposed diagnostic workup in this particular patient group (1, 3, 4). However, TM is only used in a limited number of dedicated centers with a CGI program, which means that the majority of potential CGI patients are still assessed without functional testing. Unfortunately, the wider use of gastrointestinal TM is hampered by its cumbersome and invasive nature.
Visible light spectroscopy (VLS) is a relatively new technique that enables non-invasive measurements of mucosal capillary hemoglobin oxygen saturations during endoscopy (5). The technique uses white light delivered by a fiberoptic probe via the endoscope to directly measure intra-mucosal hemoglobin saturation, relying on the marked difference in absorption spectra of oxygenated and deoxygenated hemoglobin. This saturation reflects the adequacy of mucosal perfusion and should therefore, in theory, be lowered in CGI. VLS could be of great value as a new and less invasive diagnostic tool in patients suspected of CGI, and a recent pilot study using VLS in a few CGI patients showed promising results (6). We therefore prospectively evaluated the diagnostic accuracy of VLS for detection of ischemia in a large cohort of patients clinically suspected for CGI, and evaluated by means of the 'gold standard' proposed diagnostic work up.

METHODS

Consecutive patients which were referred for evaluation of possible CGI to the department of Gastroenterology and Hepatology of a tertiary care center (Erasmus MC - University Medical Center) were asked to participate in the current study and prospectively included after informed consent. In all patients more common causes of upper gastrointestinal symptoms had been previously excluded by upper endoscopy, colonoscopy, abdominal ultrasound and / or CT- or MRA. Suspicion for CGI was defined as fulfilling at least two of the following criteria: 1) presence of postprandial pain, 2) otherwise unexplained weight loss (> 5%), and / or 3) significant stenosis of at least one of the gastrointestinal arteries on previous radiological evaluation. The potential value of VLS as a diagnostic test and the cut-off values were determined in a trainee data set and these established cut-off values were validated in

a validation data set. Mucosal saturation measurements during VLS were compared with the diagnosis of CGI. The study was approved by the Institutional Review Board of the Erasmus MC- University Medical Center. For this diagnostic study, we adhered to the Standards for reporting of diagnostic accuracy (STARD) Initiative (7).

Standard diagnostic workup

Prolonged (24 hour) gastric and jejunal TM in combination with CTA or MRA to visualize the gastrointestinal arteries (celiac artery (CA), superior mesenteric artery (SMA) and inferior mesenteric artery (IMA)) were performed as standard diagnostic workup. TM was performed using a standardized protocol, as described previously, enabling mucosal CO_2 measurements both in fasting and postprandial state with gastric and jejunal catheters (1). A significant stenosis of the abdominal arteries was defined as a luminal reduction of >70 %. Medical history, symptoms, physical exam, and the results of all diagnostic procedures except the VLS readings were discussed in a multidisciplinary team consisting of a vascular surgeon, intervention radiologist and gastroenterologist, all specialized in CGI, and a consensus diagnosis was made, classifying individual patients as either having (1) no arterial stenosis, no ischemia, (2) arterial stenosis, no ischemia, (3) non-occlusive mesenteric ischemia (NOMI) (4) occlusive ischemia. The diagnosis NOMI and occlusive gastrointestinal ischemia, codes (3) and (4), were together defined as CGI. The multidisciplinary team was blinded to the results of the VLS measurements, and thus based the consensus diagnosis on the combination medical history, physical examination, angiography, and TM. The team was aware of the fact that each of these parameters could be associated with both false-negative and false–positive findings of TM and for that reason based the consensus diagnosis on the total presentation. For the purpose of this study, we used both the baseline consensus working diagnosis, and also the follow-up history into account. Patients with occlusive CGI were offered revascularization of the vascular obstruction by either open surgery or by endovascular stent placement. Patients diagnosed with NOMI were offered medical treatment with vasodilation therapy, following a strict protocol using isosorbidedinitrate or ketanserin tartrate, in a maximum dose of 40 mg od. A definitive diagnosis of CGI was made after persistent relief of symptoms on follow-up after intervention or medical therapy.

Upper endoscopy and visible light spectroscopy measurements

VLS was performed during upper endoscopy, with continuous monitoring of peripheral oxygen saturation and heart rate. In standard fashion, midazolam intravenously (dose 2.5-5 mg), if necessary combined with fentanyl (0.05 mg), was used for conscious sedation. Furthermore, butylscopolamin (20 mg) was administered intravenously before start of VLS measurements to prevent luminal spasms. Peripheral saturation was kept above 94% and oxygen was administered intra-nasally if necessary to maintain this saturation level during the VLS measurements. Measurements were made using a fiberoptic catheter-based visible

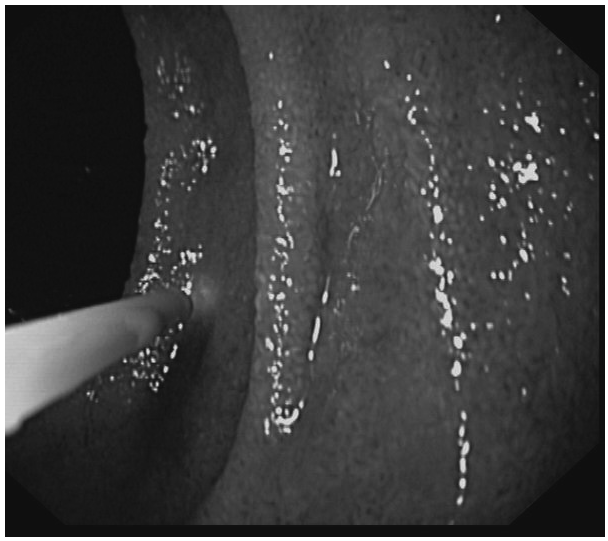


Figure 1. VLS measurements using a fiberoptic catheter-based visible light spectroscopy oximeter. The catheter is passed through the accessory channel of the endoscope and positioned approximately 1 to 5 mm above the mucosa.

light spectroscopy oximeter (T-Stat 303 Microvascular Oximeter, Spectros, Portola Valley, California, USA). This catheter was passed through the accessory channel of the endoscope after irrigation of the target area to remove any bile remnants. The probe was positioned approximately 1 to 5 mm above the mucosa (Figure 1). Similar to peripheral external saturation measurements, the reading showed small rapid variations consistent with true changes in saturation as well as reader variation due to small changes in the position of the probe. For VLS measurements, the probe was positioned close, perpendicular to the mucosa under direct saturation measurement. The actual measurement started once a stable reading was obtained with less than 5% variation in panel read-out. We then averaged three repeated readings per site as actual, most accurate reflection of mucosal saturation at that site. This was repeated at five different locations: descending duodenum, duodenal bulb, antrum, corpus and distal esophagus. The latter five locations were standardized in the way that in every patient the same anatomical locations were used. Subsequently, tonometer catheters were inserted in order to perform TM. The VLS technique measures the percent saturation of hemoglobin in the mucosa, relying on the marked difference in the absorption spectra of oxyhemoglobin and deoxyglobin (6, 8). With a lower total hemoglobin, the balance between oxyhemoglobin and deoxyglobin remains the same. All VLS measurements were performed by the same gastroenterologist (PM) who was kept blinded for the actual readings. The VLS measurements were noted and analysed by a research fellow (DvN). Both, the gastroenterologist and research fellow were unaware of and blinded to radiologic and TM results.

Follow-up and repeated VLS measurements

All patients diagnosed with ischemia visited the out-patient clinic at six weeks, three months, six months and one year after treatment for assessment of clinical status and repeated duplex ultrasound scanning of the gastrointestinal arteries. Patients diagnosed as not having ischemia, diagnosis code (1) and (2), had no intervention and were discharged from follow-up. Follow-up of the latter patients was however obtained by means of a survey which was conducted by contacting the primary care or referring physician 12 months after diagnostic evaluation.

All patients treated for CGI were asked to have repeated upper endoscopy with VLS measurements between 6 - 12 months after treatment. The repeated VLS measurements were performed following the same protocol as described earlier. The results of repeated VLS measurements were defined 'normalized' when mucosal saturation(s) were ≥ cut-off levels. The endoscopist (PM) and the research fellow (AS) noting and analyzing the repeated VLS results, were both blinded for the outcome after therapy.

Statistical analysis

In the 'trainee data set' the mean saturations between CGI patients and non-CGI patients and between single and multi-vessel CGI patients were compared with Student T-test. Test performances at different levels were investigated, and for each cut-off, the positive (PPV) and negative predicted value (NPV), as well as the sensitivity and the specificity for diagnosing CGI were calculated and in addition the odds ratio and the c-statistics were estimated. The c-statistics is a measure of discrimination, in this case the ability to distinguish patients with CGI from those without. The c-statistics is in our case equal to the area under the receiver-operating characteristic curve (AUC), a perfect discrimination is indicated by AUC=1 and a poor discrimination is indicated by an AUC equal to or smaller than 0.5. Logistic regression analysis was used to combine these into one useful guiding rule. Saturations were determined per location; patients with missing saturations were excluded from analysis with relation to that location as described in the tables. In case of missing saturation measurements, the impact of missing data was studied comparing the patient characteristics between patients with missing and without missing saturation measurements with either a chi-2 test or Student T-test. Statistical analysis was performed using the SPSS 16.0 program (SPSS Inc. Chicago, IL). A P-value <0.05 was considered statistically significant (all two-tailed). The diagnostic accuracy of the established cut-off values was validated in the 'validation data set' group. The same tests were used as described above.

RESULTS

During a period of 16 months (December 2007- March 2009), 131 patients were referred for evaluation of possible CGI. Ten patients refused informed consent and were therefore excluded from further evaluation. So, 121 patients were included in the present study. The first 80 patients were included in the trainee data set en the next 41 patients in the validation data set. CGI was diagnosed in 58 (73%) patients in the trainee data set and in 31 (76%) patients in the validation data set, see Table 1 for patient characteristics and presenting symptoms. The proportion of patients with ischemia was not significantly different before and after exclusion of patients with missing saturation measurements. No adverse events occurred during both the standard diagnostic work-up and the VLS measurements. In one patient within the trainee data set, VLS measurements were not possible because of agitation during endoscopy.

Table 1. Patient characteristics and presenting symptoms, data given as numbers of patients (percentages) or mean (range).

	Trainee data set n=80	Validation data set n=41
Age (years)	59 (17-86)	61 (21-86)
Gender M/F	30/50	19/22
Postprandial pain	57 (71%)	29 (71%)
Exercise related pain	32 (40%)	17 (42%)
Diarrhea	20 (25%)	8 (20%)
Weight loss	61 (76%)	25 (61%)
Weight loss (kg)	7.5 (1-32)	7.6 (3-30)
BMI (kg/m^2)	22.3 (14.7-35.5)	22.8 (15-37.3)
Abdominal complaints	74 (93%)	41 (100%)
Duration of complaints (months)	25 (1-312)	23 (2-144)
Risk factors for CVD:		
· smoking	30 (38%)	20 (49%)
· other risk factors*	58 (73%)	21 (51%)
Ischemia	58 (73%)	31 (76%)
· Single vessel stenosis:	25 (43%)	20 (65%)
CA/SMA	21/4	16/4
· Multi-vessel stenosis:	21 (36%)	3 (10%)
CA+SMA /CA+IMA /SMA+IMA	13/1/1	0/2/0
CA+SMA+IMA	6	1
· NOMI	12 (21%)	8 (26%)

M=male, F=female, BMI=body mass index, CVD=cardiovascular disease, * including diabetes mellitus, obesity, hypertension, hyperlipidemia, hyperhomocysteinemia and familial history for cardiovascular disease, CA=celiac artery, SMA=superior mesenteric artery, IMA=inferior mesenteric artery, NOMI=non-occlusive mesenteric ischemia

Endoscopy and VLS measurements

No patients had clear signs of endoscopic abnormalities compatible with acute gastrointestinal ischemia. During VLS measurements, mean peripheral oxygen saturation were comparable in both groups, in both groups 95.9% (ranges 95-100% in the trainee data set and 95-98% in the validation data set). In the total data set, the mean hemoglobin (8.3 mmol/l) in the

Table 2. VLS mucosal saturation in different locations during upper endoscopy in patients with and without ischemia (mean (SD), in percentages), trainee data set (n=80), validation data set (n=41) and total data set (n=121).

		Distal esophagus	Corpus	Antrum	Duodenal bulb	Descending duodenum	Overall
Trainee data set	Ischemia	60.2 (4.0) n=58	62.1 (5.6) n=55	62.9 (5.4)* n=51	58.9 (5.2)* n=52	54.4 (6.7)* n=58	59.8 (3.4)* n=49
	No ischemia	62.3 (5.3) n=19	64.9 (3.4) n=18	65.6 (3.8)* n=20	62.6 (4.4)* n=20	59.2 (4.1)* n=21	62.8 (2.3)* n=16
Validation data set	Ischemia	63.1 (3.8) n=29	62.6 (3.8) n=31	64.2 (3.7) n=31	60.1 (4.2) n=28	53.1 (5.1)* n=31	60.7 (2.4) n=26
	No ischemia	64.3 (5.4) n=10	65.0 (6.3) n=10	66.8 (5.5) n=10	61.1 (6.3) n=9	58.3 (7.1)* n=10	62.9 (5.5) n=9
Total data set	Ischemia	61.2 (4.2) n=87	62.3 (5.0)* n=86	63.4 (4.8)* n=85	59.3 (4.9)* n=80	53.9 (6.2)* n=89	60.1 (3.1)* n=75
	No ischemia	63.0 (5.3) n=29	64.9 (4.5)* n=28	66.0 (4.4)* n=30	62.1 (5.0)* n=29	58.9 (5.2)* n=31	62.8 (3.7)* n=25

SD = standard deviation

*P < 0.05

Table 3. Odds for ischemia and c-statistics for ischemia in different locations, trainee data set (n=80), validation data set (n=41) and total data set (n=121).

		Distal esophagus	Corpus	Antrum	Duodenal bulb	Descending duodenum
Trainee data set	Odds ratio (95%CI)	0.89 (0.79-1.02)	0.89 (0.80-1.00)	0.89 (0.79-1.00)	0.84 (0.73-0.96)	0.85 (0.75-0.95)
	c-statistics (95%CI)	0.61 (0.45-0.77)	0.64 (0.51- 0.77)	0.65 (0.51-0.78)	0.70 (0.57-0.84)	0.72 (0.60-0.84)
Validation data set	Odds ratio (95%CI)	1.00 (0.99-1.01)	0.88 (0.75-1.05)	0.84 (0.68-1.03)	0.95 (0.81-1.13)	0.84 (0.71-0.98)
	c-statistics (95%CI)	0.58 (0.34-0.82)	0.64 (0.41-0.86)	0.71 (0.48-0.94)	0.61 (0.36-0.86)	0.77 (0.55-0.99)
Total data set	Odds ratio (95%CI)	0.91 (0.83-1.01)	0.89 (0.81-0.98)	0.88 (0.79-0.97)	0.88 (0.79-0.97)	0.84 (0.77-0.93)
	c-statistics (95%CI)	0.59 (0.46-0.72)	0.65 (0.53-0.76)	0.67 (0.55-0.78)	0.67 (0.55-0.80)	0.75 (0.65-0.85)

non-ischemia group did not differ from the mean hemoglobin (7.9 mmol/l) in the ischemia group, p=0.31. The distribution of saturation levels did not diverge from a normal distribution (test for normality p=0.15). The mean saturation in the gastric corpus and antrum, as well as the duodenal bulb, and descending duodenum and the overall mean saturation from all five locations, were significantly decreased in CGI patients as compared to non-CGI patients in the overall patient group (n=121) (Table 2). Odds ratios (95% CI) and c-statistics (95% CI) are presented in Figure 2 and Table 3. Comparing VLS measurements in single and multi-vessel disease in the overall patient group (n=121), multi-vessel patients showed a significantly decreased saturation in the gastric corpus and antrum, as well as the duodenal bulb and the overall mean saturation (Table 4). The results of all patients (n=121) showed that patients

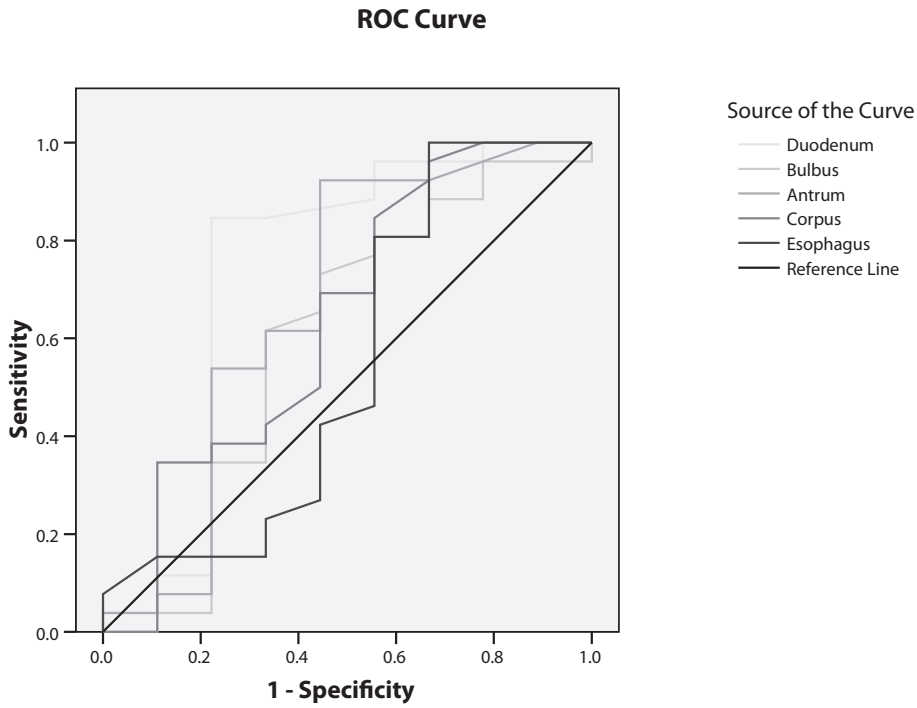


Figure 2. Receiver operating characteristic curve with VLS mucosal saturation in the different measurement locations.

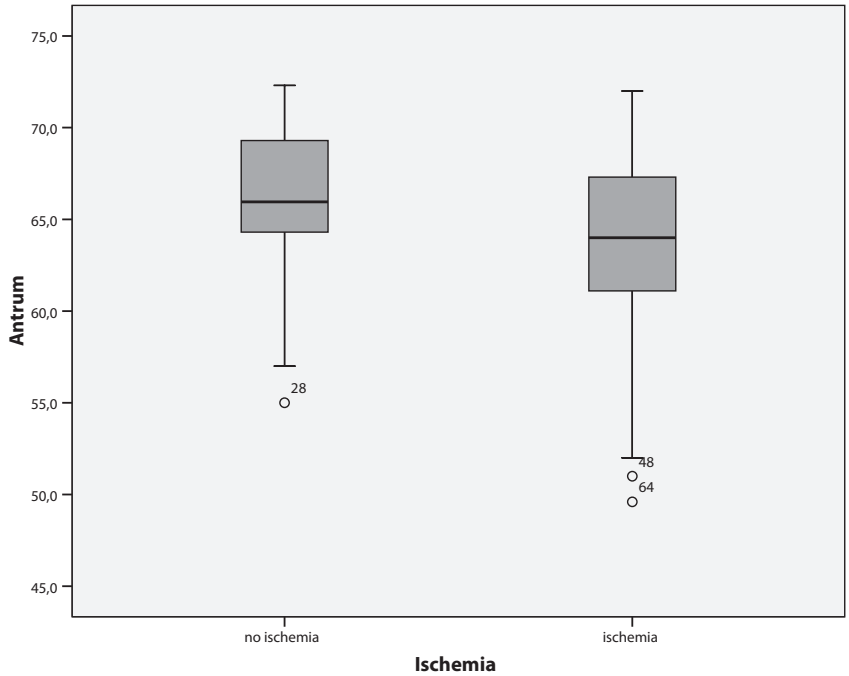
Table 4. VLS mucosal saturation in different locations during upper endoscopy in single- and multi-vessel stenosis patients (mean (SD), in percentages), trainee set (n=80), validation set (n=41) and total data set (n=121).

		Distal esophagus	Corpus	Antrum	Duodenal bulb	Descending duodenum	Overall
Trainee data set	Single vessel	59.2 (4.5) n=28	63.2 (5.2) n=26	65.1 (5.6)* n=25	59.7 (5.5) n=23	56.1 (5.6) n=29	60.6 (3.1) n=20
	Multi-vessel	60.4 (3.9) n=22	60.8 (5.8) n=20	61.4 (4.5)* n=21	57.7 (5.6) n=21	54.0 (7.4) n=22	59.0 (3.5) n=19
Validation data set	Single vessel	62.9 (4.3) n=23	62.7 (4.5) n=24	64.3 (3.6)* n=24	59.5 (4.3) n=24	53.0 (5.4) n=24	60.4 (3.2)* n=23
	Multi-vessel	63.5 (2.4) n=3	61.0 (4.7) n=3	58.9 (6.3)* n=3	58.9 (1.2) n=3	55.1 (5.2) n=3	59.6 (2.0)* n=3
Total data set	Single vessel	60.9 (4.7) n=51	62.9 (4.8)* n=50	64.7 (4.7)* n=49	59.6 (4.9)* n=46	54.7 (5.7) n=53	60.5 (3.1)* n=53
	Multi-vessel	60.8 (3.9) n=25	60.8 (5.6)* n=23	61.1 (4.6)* n=24	57.8 (5.4)* n=23	54.2 (7.1) n=25	58.9 (3.4)* n=25

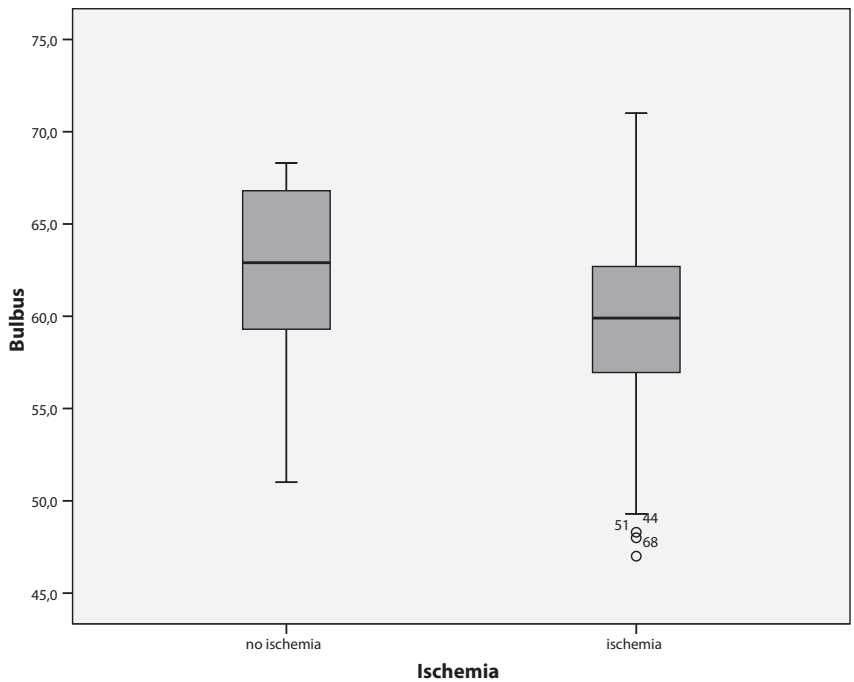
SD = standard deviation

*P < 0.05

A


75,0
70,0
65,0
60,0
55,0
50,0
45,0
Antrum
28
48
64
no ischemia
ischemia
Ischemia

B


75,0
70,0
65,0
60,0
55,0
50,0
45,0
Bulbus
51
44
68
no ischemia
ischemia
Ischemia

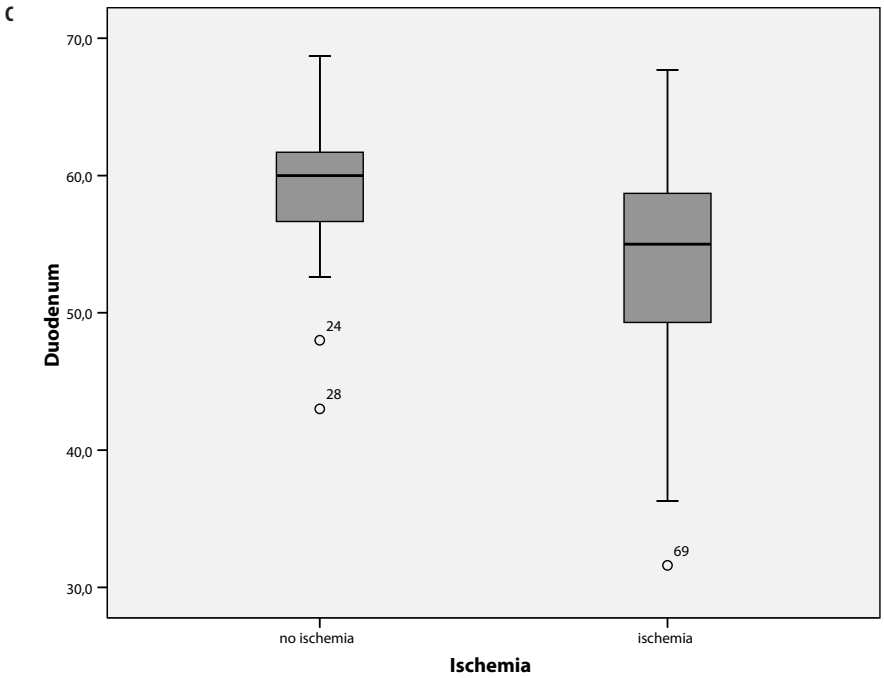


Figure 3. Stem-and-leaf plot for VLS measurements in ischemia and non-ischemia patients. Dots represent outliers.
A antrum (cut-off saturation level 63 %)
B duodenal bulb (cut-off saturation level 62 %)
C descending duodenum (cut-off saturation level 58 %)

without stenosis had significantly higher overall saturation levels (P=0.01), compared to patients with single vessel stenosis or multi-vessel stenosis, irrespective of the diagnosis gastrointestinal ischemia. In the ischemia patients, no significant differences were found comparing mucosal saturation levels in patients without stenosis, i.e. NOMI patients, with the stenotic single- or multi-vessel ischemia patients (P=0.40). A sensitivity analysis including all patients, including those with missing saturation measurements, did not change the estimates substantially.

Trainee data set and validation data set

Based on the significantly decreased saturation values in CGI patients in the trainee data set, cut-off saturation levels for ischemia were calculated for the antrum (63%), duodenal bulb (62%) and descending duodenum (58%) (Figures 3A-C). Measurements were considered positive for ischemia when the measured saturation in the antrum, duodenal bulb or descending duodenum was lower than the cut-off value used in each location. There were no significant differences regarding presenting symptoms of patients between the data sets. If any of the 3 locations yielded a positive test, indicating ischemia, VLS measurements were

classified pathological. Overall, pathological VLS measurements were found in 32 (78%) patients. Comparing VLS results with the diagnosis of ischemia based on previously established, above-specified criteria, the sensitivity and specificity of VLS measurement were 90% and 60%, with a PPV and NPV of 88% and 67%, respectively.

Follow-up and repeated VLS measurements

After a mean follow-up of 10 (range 1-32) months following intervention, 80 (90%) of the total 89 patients diagnosed with ischemia were free of symptoms. During follow-up, none of the patients with a non-CGI working diagnosis developed ischemia or died of ischemic complications, nor did any of these patients develop progressive symptoms compatible with CGI. Thirty-eight (43%) patients had repeated VLS measurements after treatment. The patient characteristics and clinical outcome after treatment were similar for the patients consenting and refusing repeated VLS measurements. Twenty-nine (76%) patients were free of symptoms, 7 (18%) had persistent symptoms, and 2 (6%) patients had recurrent symptoms after initial clinical success. Among the patients who had become symptom-free, repeated VLS measurements showed normalization in 19 (66%) patients, improvement in 4 (14%), and no change in 6 (20%) patients, compared to 0, 0 and 9 (100%) patients with persistent symptoms, respectively (P = 0.00).

DISCUSSION

Abdominal arterial stenosis is not uncommon and the widespread use of abdominal CT- and MR make clinicians with increasing frequency encounter these lesions. Nevertheless, the demonstration that an arterial stenosis is associated with CGI remains a clinical challenge (9). Single as well as multi-vessel disease often remains asymptomatic, due to the presence of abundant abdominal arterial collateral circulation. Only those patients with significant vascular stenosis in combination with insufficient collateral circulation will develop clinical ischemia (3, 10). Unfortunately, the diagnosis is in these cases often missed due to lack of sensitive diagnostic tests. The diagnosis of CGI and the subsequent decision for intervention can not be based on the results of an individual test. The diagnostic approach in patients referred for evaluation of possible CGI focuses on identification of abdominal arterial stenosis and demonstration of GI mucosal ischemia. At our institution, the current diagnostic strategy is a combination of radiological evaluation of vascular anatomy and functional testing by means of gastrointestinal TM to detect gastrointestinal mucosal ischemia. A diagnosis of presence or absence of CGI is then made in a dedicated multidisciplinary team, based on the combination of symptoms and medical history, and additional test results including gastrointestinal TM. However, despite its good sensitivity for diagnosing mucosal ischemia, TM is an invasive and

cumbersome technique which is not generally accepted as regular diagnostic method and also requires 24 hour hospital admission.

The results of the current study show that VLS during upper endoscopy, measuring mucosal oxygenation in a resting situation, can be used as an alternative diagnostic test in this particularly difficult patient group. Our data show a similar or even higher sensitivity, with a lower specificity, of VLS as compared to TM (1, 10). We have assessed the VLS performance in several ways: 1) compared to the current proposed standard approach 2) by assessing VLS performance in a confirmation cohort, and 3) by showing improved VLS measurements after successful intervention. Normalization of mucosal oxygenation was seen during the repeated VLS measurements in majority of patients after successful treatment. The latter finding underlines even more that lowered VLS measurements are associated with clinically evident mucosal ischemia, which can be reversed by adequate treatment. The fact that VLS is easy to perform could lead to a change in approach in patients clinically suspected for CGI, which is likely to allow more institutions and gastroenterologists to consider and test for this condition. The follow up of patients without established ischemia showed that no patients with CGI had been missed. This is of the utmost clinical importance, as earlier studies have shown that undiagnosed and therefore untreated ischemia correlates with evident morbidity and mortality (3, 4)

In a pilot study using VLS during endoscopy to evaluate the diagnostic value of VLS in CGI patients, Friedland et al. presented three CGI patients with 3-vessel stenosis and substantially decreased mucosal oxygenation from 19 to 50% in the duodenum. Endovascular treatment of the gastrointestinal arteries resulted in improvement of mean mucosal oxygen saturation in these CGI patients from 51 to 64% on repeated VLS measurements. In the same study, 'normal' mucosal hemoglobin oxygen saturation values were presented, obtained from 30 patients. These 'normal' mucosal saturation values as presented in the latter study are similar to our findings in patients with patent gastrointestinal arteries and no CGI, i.e. diagnosis code 1, showing mean mucosal saturation values of 68 (56 – 83) and 64 (56 – 73), respectively in both studies (6).

The present study included 121 patients, clinically suspected of CGI and is therefore the first large cohort study using VLS for the diagnosis of mucosal ischemia. In the current study a significant lower saturation was shown in ischemia patients as compared to non-ischemia patients in duodenum, antrum, corpus and overall mean saturation (in five locations). Only the distal esophagus did not show decreased saturation measurements in ischemia patients, which can be explained by the fact that the esophagus is not vascularized by one of the abdominal arterial arteries (TC, SMA or IMA). Overall mucosal saturation measurements were also decreased in patients with single vessel stenosis without ischemia, as compared to the 'normal values' presented by Friedland et al (6). We experienced a gradual lowered overall mucosal saturation level comparing the measurements in patients with no abdominal artery

stenosis, single vessel and multi-vessel stenotic abdominal arteries irrespective of the diagnosis ischemia. In patients with ischemia, there were no differences in patients with occlusive and non-occlusive (NOMI patients) CGI. Collateral circulation is often affected in this area of the gastrointestinal tract, giving rise to abnormal functional testing which can be used for diagnosis (3). These findings support the theory that VLS indeed measures lowered oxygen saturations, indicating a lowered capacity of collateral abdominal circulation.

A limitation of our study was the fact that the gold standard was based on a multidisciplinary decision on standard work-up consisting of evaluation of symptoms, gastrointestinal TM and abdominal CT- or MR-angiography. To partially overcome this, a definitive diagnosis of CGI was made after persistent relief of symptoms on follow-up after intervention or medical therapy. This was a less-than-ideal gold standard, but currently most reliable way to establish a diagnosis.
Another limitation of the present study is the possibility that mucosal ischemia is patchy and could be missed with repeated point measurements. Assessment of the gastroduodenal mucosa by means of a very large number of repeated point measurements might in theory increase the diagnostic yield of VLS, this remains to be established in future research. In the current setting, VLS performed similar to TM in defining patients with or without mucosal ischemia.
Furthermore, the possibility remains that ischemia only occurs in response to increased metabolic demand, such as after a meal. All patients were fasting because of the nature of the test as performed during endoscopy. In theory, in patients with less pronounced blood flow impairment, VLS measurements might show low-normal or even normal mucosal saturation measurements in the resting situation. However, we demonstrate with our findings that VLS can also detect the less pronounced musocal blood flow reduction in this range. Postprandial VLS measurements, for example in stomach with jejunal feeding, would be of great interest and is considered for further research. Unfortunately, only in 43% of patients endoscopy and VLS measurements were repeated after treatment. However, the patient characteristics and clinical outcome of treatment were comparable in the patients who had and who did not have repeated measurements, in this way minimizing bias.

In conclusion, VLS measurement of mucosal oxygenation during endoscopy is a promising technique for detection of actual mucosal hypoxemia reflecting ischemia in patients suspected for chronic gastrointestinal ischemia. The technique is easy to perform, can be operated in any endoscopy unit and shows excellent correlation with the established diagnostic methods.

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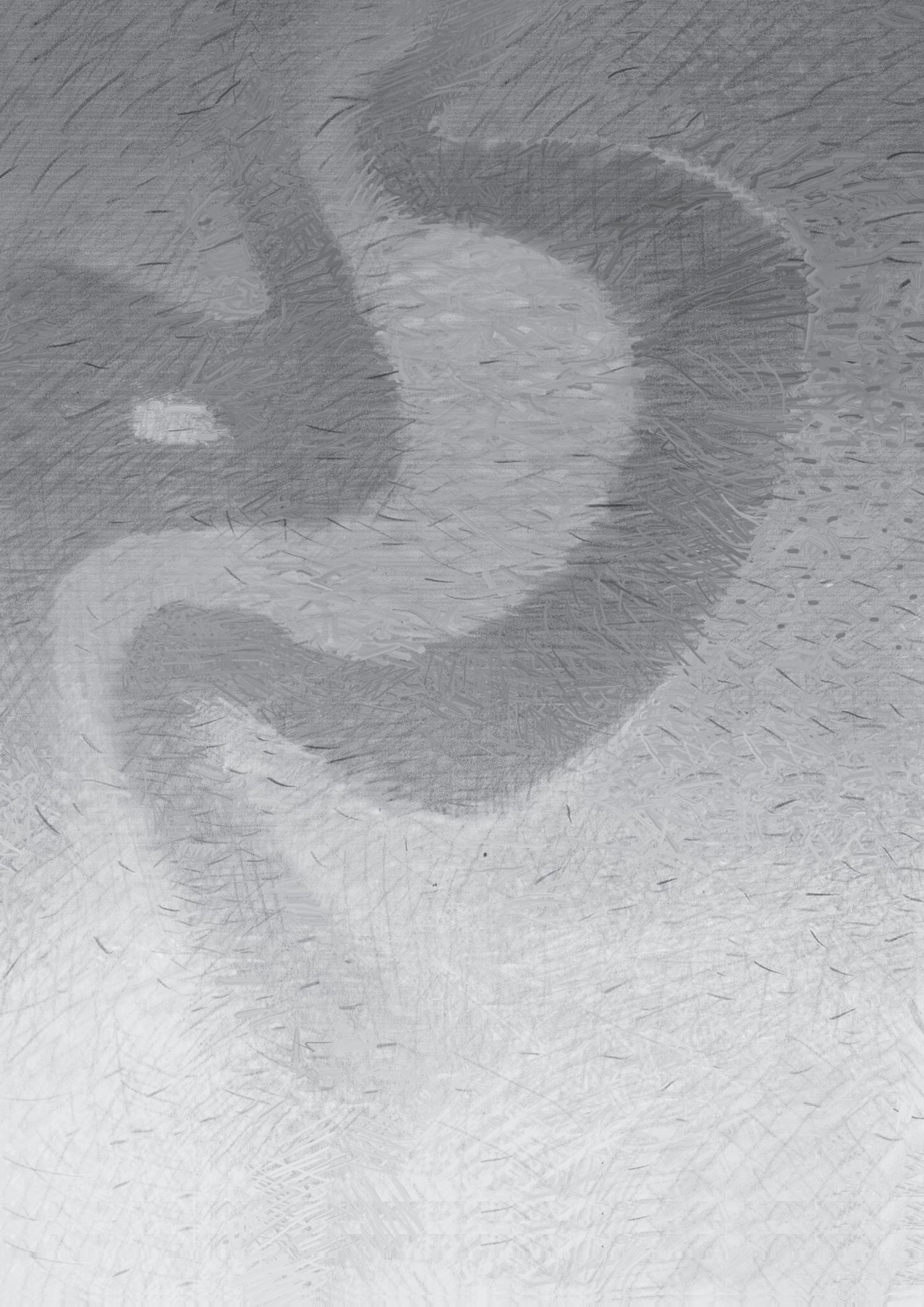

Chapter 5

Serum markers and intestinal mucosal injury in chronic gastrointestinal ischemia

Désirée van Noord[1], Peter B.F. Mensink[1], Robert J. de Knegt[1], Martine Ouwendijk[1], Jan Francke[1], Anneke J. van Vuuren[1], Bettina E. Hansen[1,2], Ernst J. Kuipers[1,3]

Departments of Gastroenterology and Hepatology[1],
Biostatistics[2] and Internal Medicine[3]
Erasmus MC - University Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Background Diagnosing chronic gastrointestinal ischemia (CGI) is a challenging problem in clinical practice. Serum markers for CGI would be of great diagnostic value as a non-invasive test method. This study investigated serum markers in patients with well-defined ischemia. Furthermore, intestinal mucosal injury was also evaluated in CGI patients.

Methods Consecutive patients suspected of CGI were prospectively enrolled and underwent a diagnostic work-up consisting of gastrointestinal tonometry and either CT- or MR angiography. Blood samples for analysis of intestinal fatty acid binding protein (I-FABP), D-dimer, lactate dehydrogenase (LDH), leucocyte counts, C-reactive protein (CRP), and L-lactate were drawn before and after a standard meal. Intestinal mucosal injury was assessed with glutamine, citrulline and arginine in blood samples and compared to a sugar absorption test (SAT). Test reproducibility was validated in healthy subjects.

Results Forty patients and nine healthy subjects were included. Ischemia was diagnosed in 32 patients (80%). I-FABP, leucocyte counts, LDH, CRP, glutamine, citrulline, arginine and SAT levels did not differ between patients with and without ischemia. L-lactate concentration showed a significant elevation in ischemia patients as compared to non-ischemia patients. In ischemia patients, D-dimer levels showed a significant elevation postprandially as compared to D-dimer levels at baseline. However, these ischemia patients did not show intestinal mucosal injury.

Conclusion I-FABP, leucocyte counts, LDH and CRP levels are not clinically useful for the diagnosis of CGI. However, postprandial rises in L-lactate and D-dimer serum levels can serve as non-invasive indicators of CGI.

INTRODUCTION

Chronic gastrointestinal ischemia (CGI) is a diagnostic challenge. There is no single, simple test with adequate predictive value to diagnose or exclude this condition. Presenting symptoms of CGI are postprandial and exercise-related pain, weight loss, and malabsorption (1). Patients referred for evaluation of possible CGI are usually evaluated with computed tomography angiography (CTA) or magnetic resonance angiography (MRA). In a few expert centres, these angiographic methods are combined with gastrointestinal tonometry (TM), a functional test for mucosal saturation (2). CTA and MRA are minimally invasive techniques to detect and define abdominal artery stenoses, while TM is a functional test that measures tissue ischemia. However, TM is an invasive and cumbersome procedure to perform, which explains the very limited use of this technique. Serum markers for CGI would be of great additional value as a non-invasive diagnostic test method.

In acute GI ischemia, several 'late' serum markers like lactate dehydrogenase (LDH), leucocyte counts, C-reactive protein (CRP) and L-lactate have been shown to have predictive value (3-5). In the same patient group, 'early' serum markers like intestinal fatty acid binding protein (I-FABP), D-dimer and citrulline, have already been shown to be of value in diagnosing acute GI ischemia at an early stage (3, 6-10). In contrast to acute GI ischemia, chronic GI ischemia is often reversible and usually limited to certain provocating factors, such as during exercise or after a meal. The value of 'early' serum markers to diagnose CGI patients is currently unknown. A recent study suggested a possible relationship between serum I-FABP and transient postprandial mucosal ischemia detected with TM in CGI patients (7). D-dimer is a fibrinolytic marker of acute vascular events. It has been described as an early marker for acute mesenteric ischemia (11-15). Small bowel function might be altered in CGI patients due to hypoperfusion of the small bowel region caused by compromised blood flow in the superior mesenteric artery. Therefore, malabsorption syndrome and unexplained diarrhea may be the initial or the dominant feature of the clinical presentation in these patients (16). Furthermore, since enterocytes are the predominant generators of serum citrulline, we hypothesized that citrulline could act as marker of intestinal mucosal injury in patients with CGI (17).

This study was performed to establish the potential diagnostic role of 'early' serum markers of GI ischemia and intestinal mucosal injury in patients suspected of CGI.

METHODS

Consecutive patients referred for evaluation of possible CGI were asked to participate and were prospectively included after informed consent was obtained. The study was approved by the Institutional Review Board of the Erasmus MC- University Medical Center.

Diagnostic work-up

In all patients, more common causes of chronic abdominal symptoms had been previously excluded by appropriate diagnostic evaluation. Medication use, including use of platelet aggregation inhibitors, was scored in all participants. All patients were evaluated with our multidisciplinary CGI algorithm using our previously published protocol, which consists of TM combined with either CTA or MRA to visualize the celiac artery (CA), superior mesenteric artery (SMA) and inferior mesenteric artery (IMA)). A significant stenosis of the abdominal arteries was defined as a luminal obstruction of > 70 %. The findings from the assessment including medical history, symptom description, and the results of all diagnostic procedures were discussed in a multidisciplinary team consisting of a vascular surgeon, intervention radiologist and gastroenterologist. A consensus diagnosis was made with one of the following conclusions: (1) no gastrointestinal stenosis, no ischemia, (2) gastrointestinal stenosis, no ischemia, (3) non-occlusive mesenteric ischemia (NOMI) (4) gastrointestinal stenosis and ischemia (i.e. CGI). Patients with CGI were offered revascularization of the vascular obstruction by either open surgery or by endovascular stent placement. A definitive diagnosis of CGI was confirmed after persistent relief of symptoms on post-treatment follow-up.

Twenty-four hour gastric and jejunal tonometry

TM was performed to obtain mucosal CO_2 measurements, both in fasting and postprandial states with gastric and jejunal catheters. All patients had meals at standard times during TM: liquid compound meal (12.00 PM), bread meal (6.00 PM), breakfast (8.00 AM), liquid compound meal (10.00 AM) and dinner (12.00 PM) (18). The liquid compound meal consisted of two Nutridrink (Nutricia, Zoetermeer, The Netherlands) 200 ml packages. The patients were instructed to eat their meals in 15 minutes. The cut-off values for elevated mucosal CO_2 levels, as evidence of mucosal ischemia, were a gastric or jejunal PCO_2 > 12.0 kPa after breakfast or a bread meal, > 13.6 kPA after dinner, or > 10.6 kPA after ingestion of a compound solution. The criteria for a positive test (abnormal result) on TM were: pathologic responses after three or more meals, or a combination of one or two pathologic responses after meals combined with a median PCO_2 > 8.0 kPa measured in between meals. This was all done according to previously published standards (2).

Healthy subjects

In all healthy subjects, abdominal artery stenosis was excluded by duplex ultrasound after fasting for 6 hours. Subsequently, blood samples were drawn at baseline and then at 30, 60, 120 and 240 minutes after a standard liquid compound meal. No TM was performed in the healthy subjects.

Blood samples serum markers

During TM, blood samples for analysis of I-FABP and D-dimer were drawn at a baseline fasting state and at 30, 60, 120 and 240 minutes after the first standard liquid compound meal (18). Blood samples for analysis of LDH, leucocyte counts, CRP and L-lactate were drawn at baseline and at 60 and 240 minutes after the first standard liquid compound meal.

For I-FABP analysis, blood samples were collected in SST tubes at room temperature. The serum was separated by centrifugation and stored at -70°C until the assay was performed. Serum I-FABP was measured in duplicate at room temperature using enzyme-linked immunosorbent assay (Human I-FABP ELISA test kit, Hycult biotechnology B.V., Uden, The Netherlands). This kit has a minimum detection level of 0.02 µg/l and the I-FABP level was defined as abnormal above 0.1 µg/l.

For D-dimer analysis, blood samples were collected in citrate tubes at room temperature. D-dimer concentration was determined using a quantitative immunofiltration assay method (D-Dimer VIDAS, BioMérieux, France). A D-dimer level above a cut-off of 0.50 mg/l was considered abnormal.

For LDH and CRP analysis, blood samples were collected in SST tubes at room temperature. LDH was determined using a quantitative in vitro test on Roche automated clinical chemistry analyzers (LDH, Modular P analyzer, Roche, Almere, The Netherlands). The LDH cut-off level was 449 U/l. CRP concentration was determined using a quantitative immunoturbidimetric assay on Roche automated clinical chemistry analyzer (CRPLX, Modular P analyzer, Roche, Almere, The Netherlands). The CRP cut-off level was 9 mg/l.

For leucocyte count analysis, blood samples were collected in EDTA tubes at room temperature. Leucocyte counts were determined using a flowcytometric assay on Sysmex XE-2100 (WBC, Sysmex Se-2100, Goffin Meyvis, Etten-Leur, The Netherlands). The reference range for leucocyte counts was 3.5-10.0 $*10^9$/l.

For L-lactate analysis, blood samples were collected in heparin tubes at room temperature. L-lactate was determined using an electrochemical assay on ABL 825 (L-lactate, ABL 825, Radiometer, Kopenhagen, Denmark). The reference range for L-lactate concentrations was 0.5-1.7 mmol/l. False L-lactate elevations due to peripheral vein sampling with venous stasis was avoided by using an intravenous catheter.

Small bowel function tests

After a fasting period of six hours, a sugar absorption test (SAT) was performed, consisting of an enzymatic measurement of mannitol/raffinose/sucrose/lactose in a five-hour urine sample. The reference range for the raffinose/mannitol ratio was 5-20. Also at baseline, blood samples for determination of citrulline and its precursor glutamine and its resultant arginine were collected in EDTA tubes at room temperature. Plasma was isolated by centrifugation at 2650 g_{max} for 10 minutes at 20 °C, and samples were stored at -80 °C until assay. Plasma was deproteinized with 5-sulphosalicylic acid (6%, w/v) containing norvaline and homoserine as internal standards. Amino acids were assayed by high-performance liquid chromatography (HPLC) using automated precolumn derivatization with o-phthaldialdehyde and fluorescence detection (19). The normal references for fasting plasma glutamine, citrulline and arginine concentrations were 432-726, 18-47 and 26-107 µmol/l, respectively.

Statistical analysis

Data were expressed as mean (range). The means were compared using the Mann-Whitney U test at all different times of measurement. The D-dimer levels measured at subsequent points in time were compared using the Wilcoxon signed ranks test. Statistical analysis was performed using the SPSS 16.0 program (SPSS Inc. Chicago, IL, USA). Because serum marker measurements in subsequent blood samples of the same subject were correlated, the association between the levels of serum markers and the diagnosis chronic gastrointestinal ischemia was examined by means of linear regression repeated measures analyses as implemented in PROC MIXED (Statistical Analysis System). A p-value <0.05 was considered statistically significant (all two-tailed). To correct for multiple testing, a Bonferroni correction was used (5 tests $p<0.010$, 3 tests $p<0.017$).

RESULTS

During a period of five months, October 2008-April 2009, 49 patients were referred for evaluation of possible CGI to our tertiary referral centre with a dedicated CGI program. Informed consent for participation in the study was obtained from 42 patients and 10 healthy participants. In two patients and one healthy participant, blood sample collections were incomplete due to venous catheter problems; they were consequently excluded from further evaluation. Ischemia was diagnosed in 32 patients (80%). Patient characteristics and presenting symptoms are presented in Table 1.

Healthy subjects

Duplex scanning of the abdominal arteries showed normal flow patterns in the CA and SMA in all healthy participants. The serum levels of I-FABP remained undetectable, the serum

levels of glutamine, citrulline, arginine, leucocyte counts and L-lactate remained within normal range and the serum levels of D-dimer, LDH and CRP remained low before and after the standard test meal in all healthy participants. No healthy participants reported use of platelet aggregation inhibitors.

Table 1. Patient characteristics and presenting symptoms, data given are number of patients (percentages) or mean (range).

	n=40
Age (years)	60 (20-86)
Gender M/F	24/16
Postprandial pain	29 (73%)
Exercise related pain	24 (60%)
Diarrhea	8 (20%)
Weight loss	25 (63%)
Weight loss (kg)	13 (4-22)
BMI (kg/m^2)	22.4 (15.0-37.3)
Abdominal symptoms*	37 (93%)
Duration of symptoms (months)	22 (2-180)
Risk factors for cardiovascular disease	
· Smoking	19 (48%)
· Other risk factors**	31 (78%)
Ischemia	32 (80%)
· Single vessel stenosis	18
· Multi-vessel stenosis	4
· Non-occlusive mesenteric ischemia	10
Platelet aggregation inhibitor use	
· Ischemia patients	12 (38%)
· Non-ischemia patients	4 (50%)

* including postprandial pain, exercise related pain and diarrhea

** including diabetes mellitus, obesity, hypertension, hyperlipedemia, hyperhomocysteinemia and familial history for cardiovascular disease.

Early serum markers: intestinal fatty acid binding protein and D-dimer

The serum levels of I-FABP remained undetectable in non-ischemia patients at all different times of measurement. The serum levels of I-FABP were elevated in four patients diagnosed with ischemia; in three patients at all different times of measurement and in one patient at baseline and 30 minutes after a meal. The levels did not differ between patients with and without ischemia at all different times of measurement (Table 2).

Table 2. Levels of early serum markers in ischemia (n=32) and non-ischemia (n=8) patients (mean). Blood samples of both I-FABP and D-dimer were drawn at baseline and 30, 60, 120 and 240 minutes after a standard meal.

		Baseline	30 min	60 min	120 min	240 min
I-FABP (µg/l)	Ischemia	0.06	0.05	0.05	0.05	0.03
	Non-ischemia	<0.02	<0.02	<0.02	<0.02	<0.02
D-dimer (mg/l)	Ischemia	0.72	0.87	0.73	0.80	0.80
	Non-ischemia	0.44	0.47	0.46	0.46	0.48

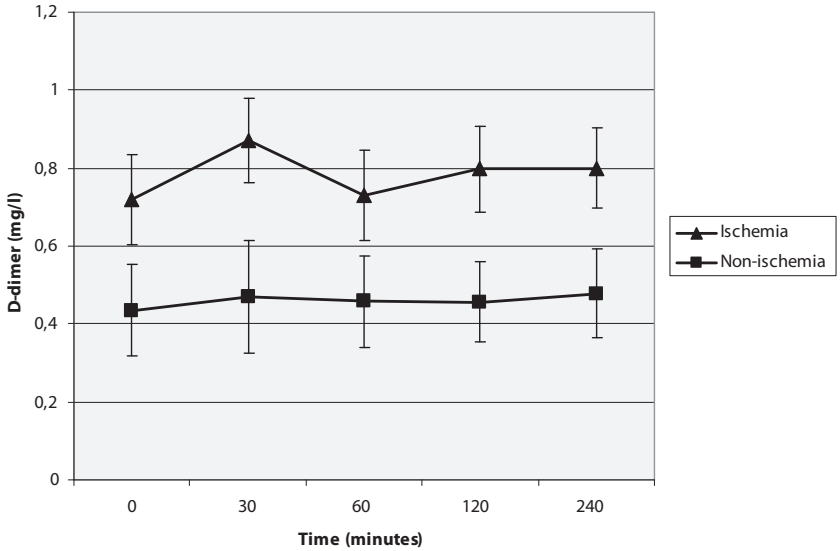

Figure 1. Mean levels of D-dimer with 95% confidence intervals in ischemia (n=32) and non-ischemia (n=8) patients at baseline and 30, 60, 120 and 240 minutes after a meal.
Ischemia patients: significant elevation at baseline-30 minutes interval (p= 0.00), significant decrease at 30-60 minutes interval (p=0.00).

The mean D-dimer levels were elevated in ischemia patients and remained low in patients without ischemia. A non-significant D-dimer elevation of 0.33 (95% CI 0.15-0.80) mg/l was seen in ischemia patients as compared to non-ischemia patients (p= 0.17). These levels did not differ between patients with and without ischemia at all different times of measurement (Table 2). Nevertheless, comparing D-dimer levels in patients diagnosed with ischemia at baseline and 30 minutes after the standard meal, a significant ($p < 0.01$) elevation in D-dimer levels was shown. Comparison of 30 minute and 60 minute measurements demonstrated a significant decrease in D-dimer levels in these patients ($p < 0.01$) (Figure 1). The sensitivity and specificity of the postprandial elevation of D-dimer were both 63%.

Table 3. Levels of late serum markers in ischemia (n=32) and non-ischemia (n=8) patients (mean with range). Blood samples of LDH, leucocyte counts, CRP and L-lactate were drawn at baseline, 60 and 240 minutes after a standard meal.

		Baseline	60 min	240 min
LDH (U/l)	Ischemia	333 (204-633)	363 (203-721)	319 (204-546)
	Non-ischemia	332 (272-424)	310 (202-369)	320 (216-446)
Leucocyte counts (*109/l)	Ischemia	6.7 (2.7-12.5)	7.3 (2.5-12.5)	7.7 (2.6-13.9)
	Non-ischemia	5.6 (3.9-8.8)	5.8 (3.7-9.0)	6.3 (4.5-9.2)
CRP (mg/l)	Ischemia	7 (1-113)	7 (1-108)	6 (1-98)
	Non-ischemia	17 (1-67)	18 (1-68)	17 (1-67)
L-lactate (mmol/l)	Ischemia	1.4 (0.8-2.4)	1.7 (1.0-2.9)	1.3 (0.6-2.3)
	Non-ischemia	1.1 (0.7-1.3)	1.4 (1.0-2.0)	1.0 (0.6-1.3)

Late serum markers: LDH, leucocyte counts, CRP, L-lactate

The LDH and CRP levels remained low and did not differ between patients with and without ischemia at all different times of measurement. The leucocyte counts remained within normal range and did not differ between patients with and without ischemia at all different times of measurement (Table 3). A significant L-lactate elevation of 0.29 (95% CI 0.10-0.49) mmol/l was seen in ischemia patients as compared to non-ischemia patients ($p < 0.01$) (Figure 2). The sensitivity and specificity of postprandial elevation of L-lactate were 34% and 88% respectively.

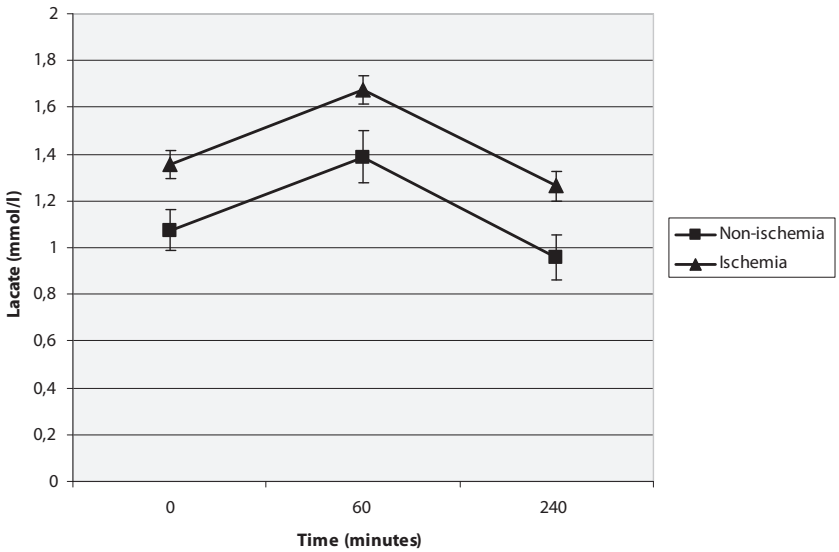

Figure 2. Mean levels of L-lactate with 95% confidence intervals in ischemia (n=32) and non-ischemia (n=8) patients at baseline and 60 and 240 minutes after a meal.
Ischemia patients compared to non-ischemia patients: significant L-lactate elevation (p=0.00).

Intestinal mucosal injury

The SAT, glutamine, citrulline and arginine levels remained within normal range and did not differ between patients with and without ischemia (Table 4).

Table 4. Levels of serum markers in ischemia (n=32) and non-ischemia (n=8) patients (mean with range). Blood samples of glutamine, citrulline and arginine were drawn at baseline. SAT was performed in a urine sample at baseline.

Glutamine (µmol/l)	Ischemia	598 (461-821)
	Non-ischemia	582 (407-678)
Citrulline (µmol/l)	Ischemia	31 (20-48)
	Non-ischemia	30 (25-38)
Arginine (µmol/l)	Ischemia	65 (32-122)
	Non-ischemia	61 (40-100)
SAT (Raffinose/Mannitol ratio)	Ischemia	9 (3-20)
	Non-ischemia	10 (4-20)

DISCUSSION

In patients clinically suspected of CGI, the early serum markers I-FABP and D-dimer and the late serum markers LDH, leucocyte counts, and CRP were not different between patients with and without ischemia. Only L-lactate showed a significant elevation in ischemia patients compared to non-ischemia patients. Furthermore, in ischemia patients postprandial D-dimer levels were significantly higher compared to the fasting state. Small bowel function in ischemia patients, as assessed with citrulline and compared to SAT, was within normal range and therefore intestinal function seems unaffected in these patients.

Until now, only one study has prospectively described increased I-FABP levels, indicating epithelial damage in patients with transient and reversible gastrointestinal mucosal ischemia, as detected with gastrointestinal TM (7). In that study, blood samples were drawn at baseline and at 60, 120 and 240 minutes after a test meal. However, the half-life of I-FABP in humans is 22 minutes and therefore the maximal peak I-FABP levels may have been missed. Our study adjusted the timeline of blood sampling by adding a 30 minute blood sample to the protocol in order to optimize the timing of measurements. Nevertheless, the results of the previous study were not reproducible. The serum levels of I-FABP in the current study remained undetectable in non-ischemia patients and were only elevated in four patients diagnosed with ischemia, and these levels did not differ between patients with and without ischemia. However, the fact that a rise in I-FABP levels was only found in CGI patients is striking, suggesting I-FABP might be of interest as a possible diagnostic tool to confirm the diagnosis of CGI. On the contrary, the expected prevalence of CGI in the patient group examined would be high (at least >40%) so this test, with a high specificity but poor sensitivity, may be less useful. Furthermore, a sample size of greater than 800 patients suspected of CGI would be needed to demonstrate a statistically significant difference using our I-FABP findings, which is unlikely to happen considering the low incidence of this disease entity. Therefore, it would be difficult to ever demonstrate a statistically significant difference using this test.
It is thought that in CGI patients, transient mucosal ischemia only occurs in response to increased metabolic demand, such as after a meal or exercise. In the current study, patients diagnosed with ischemia showed a significant postprandial rise in D-dimer levels as compared to the fasting state (Figure 1). However, our observation of (non-significant) increased baseline levels of D-dimer in patients diagnosed with ischemia might suggest impaired mucosal perfusion during resting conditions as well. The lack of a statistically significant difference in the elevation of D-dimer levels in ischemia patients as compared to the normal D-dimer levels in patients without ischemia could possibly be due to insufficient sample size to achieve sufficient power to demonstrate this effect (Figure 1). Several earlier studies that investigated the use of D-dimer in acute gastrointestinal ischemia showed that an elevated D-dimer level had a high sensitivity, but lacked specificity (3, 15). D-dimer measurements can

be routinely determined in every hospital laboratory and therefore could be a useful tool contributing to the diagnosis CGI.

Plasma L-lactate has been advocated as a promising marker of acute gastrointestinal ischemia in human studies (20, 21). However, experimental studies in pigs suggest that peripheral plasma L-lactate is not a useful early marker (5, 22). In our study, the time course of L-lactate concentration showed a significant elevation in chronic ischemia patients compared to non-ischemia patients. This is in contrast to the theory that the capacity of the liver to clear large quantities of L-lactate from the porto-mesenteric circulation may prevent systemic L-lactate elevations (23). Since L-lactate is considered to be a marker for the more advanced phase of acute abdominal disorders, it was thought to not be a relevant marker in the early transient stages of gastrointestinal ischemia. However, in the current study chronic ischemia patients showed elevated L-lactate levels after meal-provocation, which were also significantly increased in ischemia patients as compared to non-ischemia patients, suggesting that L-lactate levels could indeed be used as a possible early marker. However, L-lactate is often found in non-gastrointestinal disorders, such as shock, septicemia, hepatic and renal failure and diabetic ketoacidosis and therefore, is not specific to CGI. Despite this limitation, the change in pre- and post-prandial L-lactate measurements could be a useful supplementary diagnostic test contributing to the diagnosis CGI. The major advantage of L-lactate measurements is that it can be measured easily in any hospital laboratory and provides a rapid result.
Citrulline is thought to detect decreased intestinal absorption, which is regarded as a marker of intestinal failure. The role of citrulline as a biomarker has been previously investigated in patients with short bowel syndrome, celiac disease, intestinal graft versus host disease and radiation-induced small bowel injury, showing promising results (17, 24-27). Since bowel function is thought to be altered in CGI, citrulline was measured to assess intestinal mucosal injury in patients diagnosed with ischemia and compared with SAT, which is the gold standard for bowel function. The time required to achieve abnormal citrulline levels after a reversible ischemic event is a matter of days. Therefore citrulline and its precursor glutamine and its resultant arginine were only tested at baseline to evaluate the bowel function in CGI patients. Both the levels of the index test and the reference standard remained within the normal range and did not differ between ischemia and non-ischemia patients. As a result, intestinal function seems to be preserved in patients diagnosed with ischemia.

A possible limitation of the study is the relatively small number of patients without ischemia compared to the large number of patients diagnosed with ischemia. However, serum levels of all early and late markers showed normal values in the non-ischemia patients. Therefore, this population seems to be similar to the "normal population." A second limitation is the use of platelet aggregation inhibitors, which could lead to possible bias. One study reported elevated I-FABP levels in a healthy participant after the use of NSAIDs (7). Platelet aggregation

inhibitor use, including "over the counter" use of NSAIDs, was reported by 12 (38%) ischemia patients and four (50%) non-ischemia-patients, and in 50% of the ischemia patients with elevated I-FABP levels in this study. However, higher I-FABP levels in patients using platelet aggregation inhibitors were not seen as compared to non-users, after statistical correction for the use of these drugs.

In conclusion, I-FABP, leucocyte counts, LDH and CRP levels did not differ in patients with and without CGI, both before and after a test meal, and therefore do not seem to be clinically useful for the diagnosis CGI. Small bowel function appears not to be affected in patients diagnosed with ischemia. L-lactate and D-dimer serum levels, both before and after provocation, seem to be promising early indicators of mucosal ischemia. Future studies are necessary to investigate the use of L-lactate and D-dimer levels in the diagnosis of CGI.

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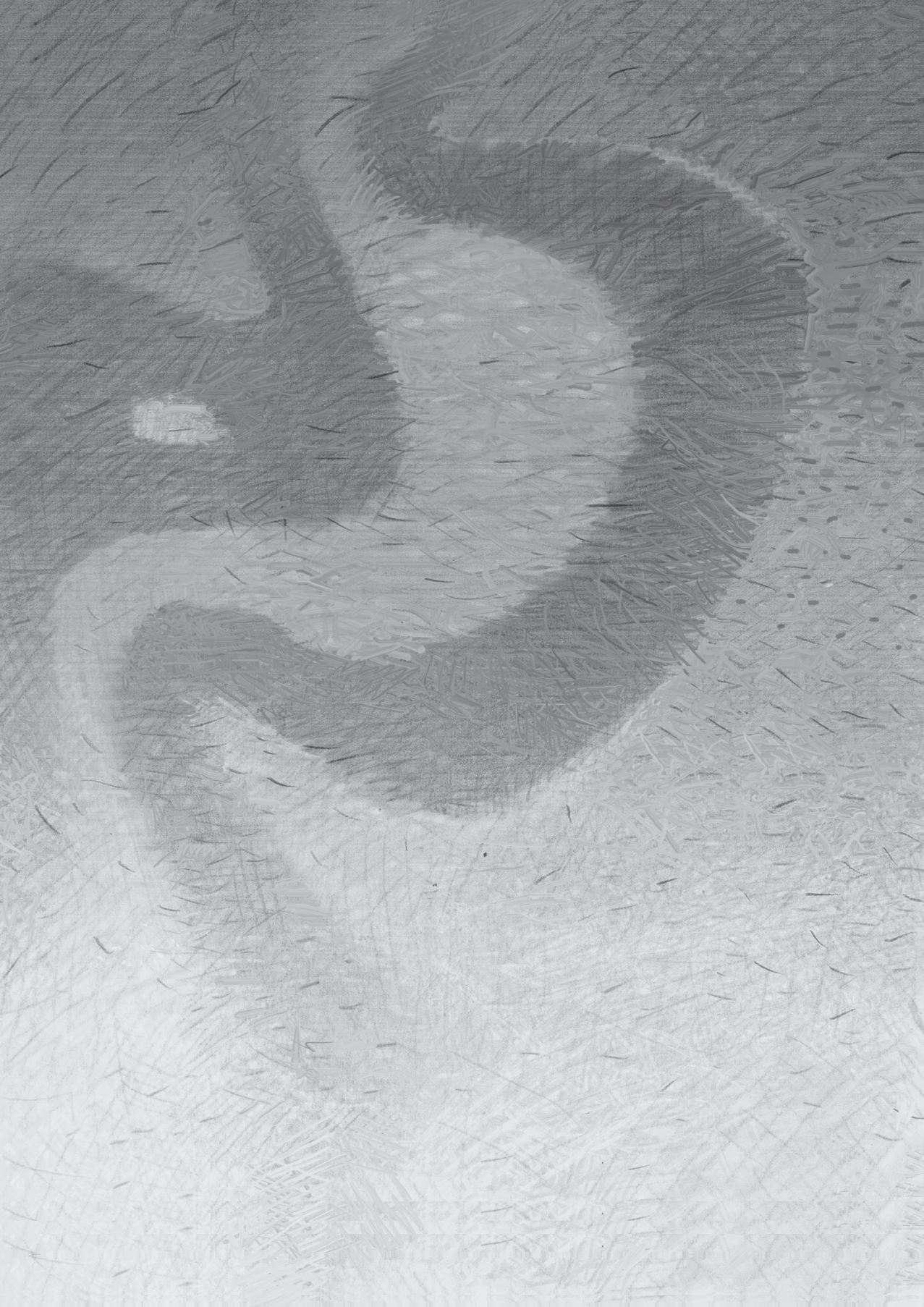

Chapter 6

Upper endoscopic findings in patients with chronic gastrointestinal ischemia

Désirée van Noord[1], Leon M.G. Moons[1], Peter M.T. Pattynama[2], Hence J.M. Verhagen[3], Ernst J. Kuipers[1,4], Peter B.F. Mensink[1]

Departments of Gastroenterology and Hepatology[1], Intervention Radiology[2], Vascular Surgery[3], Internal Medicine[4], Erasmus MC - University Medical Center, Rotterdam, The Netherlands

Submitted

ABSTRACT

Background and study aims Diagnosing chronic gastrointestinal ischemia (CGI) remains a challenge in clinical practice. Based on the assumption that patients with symptomatic CGI have typical gastroduodenal abnormalities, upper endoscopy is often used for the assessment of patients with suspected CGI. However, the character and prevalence of endoscopic pathological findings in CGI have only been described sporadically. The aim of this study was to investigate and describe the upper endoscopic findings in patients with well-defined CGI.

Patients and methods A prospective cohort study was performed in a tertiary care center with a dedicated CGI referral program. Diagnostic work-up existed of gastrointestinal tonometry, and CT- or MR angiography to define gastrointestinal arterial stenosis, including upper endoscopy. Upper endoscopic findings were scored using the Paris classification and the Sydney System.

Results In 32 months, 148 patients were included: 58 males, mean age 59 (17-86) years. CGI was diagnosed in 103 (70%) patients, of which 57 (55%) had pathological endoscopic findings, compared to 20 (44%) of the patients without ischemia (p=0.28). No significant differences in prevalence and character of upper endoscopic findings were found comparing patients with single- versus multiple-vessel CGI. Repeated upper endoscopy after initiation of treatment showed improvement of pathological findings in majority of patients.

Conclusions Normal endoscopic findings on upper endoscopy have a limited negative predictive value for the presence of CGI. The presence of otherwise unexplained gastric or duodenal ulcerative lesions, reduced vascularity, and / or mucosal paleness during upper endoscopy, should trigger the thought of CGI.

BACKGROUND

A diagnosis of chronic gastrointestinal ischemia (CGI) remains a challenge in clinical practice. For a long time, CGI was considered to be a very rare disease, only presenting in patients with multiple gastrointestinal arterial stenosis. However, the introduction of newer diagnostic techniques such as gastrointestinal tonometry (TM) have clarified that CGI is much more common than previously thought, and that CGI patients may present with a wide range of symptoms such as postprandial and / or exercise related pain, weight loss, and malabsorption (1-3). At the moment, the diagnostic workup for this particular patient group includes a medical history, radiological evaluation of abdominal arterial vascular anatomy, and TM as a functional test (1, 4, 5). However, TM is only used in a limited number of dedicated centers with a CGI program, which means that the majority of possible CGI patients are still assessed without TM. Therefore, upper gastrointestinal endoscopic examination is often used to diagnose or exclude CGI. The latter strategy is based on the assumption that patients with symptomatic CGI may have typical gastroduodenal abnormalities like mucosal breaks, reduced vascularity, paleness and otherwise unexplained ulcerative lesions. However, many CGI patients demonstrate transient reversible mucosal ischemia only after provocation by meal or exercise, and the question remains of this reversible, short-lived, ischemia leads to endoscopically visible mucosal changes (1, 4). In colonic ischemia, endoscopy is the mainstay of diagnosis. The typical picture consists of a spectrum of injuries including reversible colonopathy, transient colitis, chronic ulcerating colitis, stricture, gangrene and fulminant universal colitis (6, 7). Until now, little is known about the true prevalence and characteristics of gastroduodenal lesions in patients with CGI. The endoscopic findings in CGI have only been described sporadically. The aim of this study was to investigate and describe upper endoscopic findings in patients with well-defined CGI.

METHODS

The department of Gastroenterology and Hepatology of the Erasmus MC - University Medical Center has a tertiary CGI referral program. Consecutive patients who were referred to our department for evaluation of possible CGI were asked to participate in the current study and were prospectively included. In all patients more common causes of upper GI complaints had been previously excluded by upper endoscopy, (complete) colonoscopy, abdominal ultrasound and / or abdominal computed tomography. Suspicion of CGI was defined as fulfilling at least two out of three following criteria: 1) postprandial pain, 2) other wise unexplained weight loss (> 5%), and / or 3) significant stenosis of one, or more, of the gastrointestinal arteries on previous radiological evaluation. The study was approved by our Institutional Review Board.

Upper endoscopy

After an overnight fast, all patients underwent a standard diagnostic work-up including oesophago-gastroduodenoscopy (GIF Q40 endoscope, Olympus, Japan) under conscious sedation with midazolam intravenously (dose 2.5-5 mg), if necessary combined with fentanyl (0.05 mg). Butylscopolamin (20 mg) was administered intravenously to prevent luminal spasms. Continuous monitoring of peripheral oxygen saturation and heart rate was performed during the endoscopy. Biopsy samples were taken for histological examination to rule out other diseases, such as *Helicobacter pylori* (*H. pylori)* gastritis and celiac disease.
Prior to biopsy sampling, endoscopic findings were scored in the gastric cardia, corpus and antrum, duodenal bulb, and descending duodenum. The following findings were scored as potential 'ischemia-associated' abnormalities: 1) *H.pylori* negative and otherwise unexplained gastric ulcerations, 2) *H. pylori* negative duodenal mucosal breaks, 3) gastric reduced vascularity, and 4) mucosal paleness. Furthermore, all gastric abnormal findings were scored using the simplified and updated Paris classification for the endoscopic appearance of superficial neoplastic lesions on the mucosal surface of the digestive tract (8, 9) and the Sydney System for the classification of endoscopic gastritis (the Endoscopic Division) (10). All endoscopies were performed and scored by the same gastroenterologist (PM) and results were analysed by a research fellow (DvN). Both the gastroenterologist and research fellow were unaware of, and blinded to, radiologic findings, TM results and the definitive diagnosis. In patients with gastric and / or duodenal erosive lesions, in which the diagnosis CGI was made and treatment was initiated, a repeated upper endoscopy was performed three to six months after treatment.

Diagnostic workup

In all patients, more common causes of chronic abdominal symptoms had previously been excluded by appropriate diagnostic evaluation. Gastrointestinal TM in combination with CTA or MRA to visualize the gastrointestinal arteries (celiac artery (CA), superior mesenteric artery (SMA) and inferior mesenteric artery (IMA)), were performed as standard diagnostic workup. TM was performed using a standardized protocol, as described previously, enabling mucosal CO_2 measurements both in fasting and postprandial state with gastric and jejunal catheters(1). The criteria for a positive test (abnormal result) on TM were a gastric or jejunal PCO_2 > 12.0, 13.6 and 10.6 kPa after breakfast (or bread meal), dinner or compound solution respectively, after three or more meals, or a combination of one or two pathologic responses after meals combined with a median PCO_2 > 8.0 kPa in between meals. A significant stenosis of the abdominal arteries was defined as a luminal reduction of >70 %. Medical history, complaints and the results of all diagnostic procedures were discussed in a multidisciplinary team consisting of a vascular surgeon, intervention radiologist and gastroenterologist, all specialized in CGI, and a consensus diagnosis was made, classifying individual patients as either having (1) no arterial stenosis, no ischemia, (2) arterial stenosis, no ischemia, (3) non-occlusive mesenteric ischemia (NOMI) (4) arterial stenosis and ischemia. The diagnosis NOMI

and occlusive gastrointestinal ischemia, codes (3) and (4), were both defined as CGI. Patients with CGI were offered revascularization of the vascular obstruction by either open surgery or by endovascular stent placement. Patients diagnosed with NOMI were offered medical treatment with vasodilation therapy, consisting of cedocard 20 or 40 mg od. In case of side effects or no clinical improvement after 4 weeks use of cedocard 40 mg od, the cedocard was replaced by ketanserin 20 mg or 40 mg od for the same period of time. A definitive diagnosis of CGI was made after persistent relief of symptoms on follow-up after adequate revascularization or medical therapy.

Statistical analysis

Data were expressed as mean (range) or median (interquartile range) when appropriate. The data of the ischemic and non-ischemic patients were compared using χ^2 testing or Fisher's Exact Test when appropriate. Statistical analysis was performed using the SPSS 16.0 program (SPSS Inc. Chicago, IL, USA). A p-value <0.05 was considered statistically significant (all two-tailed).

RESULTS

Between July 2006 and February 2009, 186 patients were referred for evaluation of possible CGI. Informed consent for participation in the study was obtained from 148 patients. CGI was diagnosed in 103 (70 %) patients: 76 (74 %) had occlusive ischemia, 47 single vessel and 29 multi-vessel stenosis, and 27 (26 %) patients were diagnosed as having non-occlusive mesenteric ischemia (NOMI). Patient characteristics and presenting symptoms are presented in Table 1.

Table 1. Patient characteristics and presenting symptoms, data given are number of patients (percentages) or median (interquartile range).

	n = 148
Age (years)	63 (49-71)
Gender M/F	58/90
Abdominal complaints	112 (76%)
Postprandial pain	103 (70%)
Exercise related pain	56 (38%)
Diarrhea	39 (26%)
Weight loss	107 (72%)
Weight loss (kg)	10.0 (6.0-14.0)
BMI (kg/m^2)	22.0 (19.1-25.7)
Duration of complaints (months)	12 (6-24)
Risk factors for cardiovascular disease:	
- smoking	110 (74%)
- other risk factors*	103 (70%)

M=male, F=female; BMI=body mass index

* including cardiovascular disease, diabetes mellitus, obesity, hypertension, hyperlipedemia, hyperhomocysteinemia and positive familial history for cardiovascular disease.

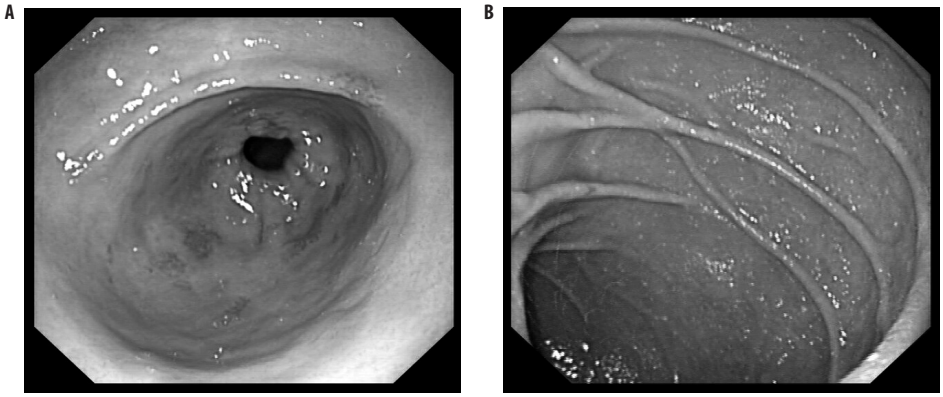

Figure 1: Endoscopic examples of patients with definitive diagnosis of chronic gastrointestinal ischemia due to multi-vessel disease.
A Pale gastric antrum with superficial erosions in a 61 year old male patient.
B Superficial duodenal erosions in a 62 year old female patient.

Endoscopic pathological findings

Overall, endoscopic pathological findings were found in 77 (52 %) patients (Figure 1A and B). Comparing the frequency of pathological findings in patients with and without ischemia, 57 (55 %) and 20 (44 %) respectively, no significant differences were found (p = 0.28). Comparing the frequency of potential 'ischemia associated' pathological findings, defined as at least one pathological finding per patient, the ischemia patients showed significantly (p = 0.00) more abnormal findings than the patients without ischemia, 39 (38 %) and 4 (9 %) respectively

Table 2. Pathological endoscopic findings in ischemia and non-ischemia patients.

	Non-ischemia patients n=45	Ischemia patients n=103	P-value
Overall endoscopic abnormalities	20 (44 %)	57 (55 %)	0.28
'Ischemia associated' endoscopic abnormalities:			
- 'unexplained' gastric ulcerations*	0	6 (6 %)	
- duodenal mucosal breaks*	2 (4 %)	26 (25 %)	
- reduced vascularity	2 (4 %)	10 (10 %)	
- mucosal paleness	0	13 (13 %)	
Total (patients with ≥1 abnormal finding)	4 (9 %)	39 (38 %)	0.00
Paris classification			
- ulcerative lesions	0	6 (6 %)	
- other	0	5 (5 %)	
Total (patients with ≥1 abnormal finding)	0	11 (11 %)	0.02
Sydney classification			
- gastritis	19 (42 %)	45 (44 %)	
- oedema	15 (33 %)	36 (35 %)	
- erythema	17 (38 %)	42 (41 %)	
- erosions	2 (4 %)	14 (14 %)	
- other	8 (18 %)	25 (24 %)	
Total (patients with ≥1 abnormal finding)	20 (44 %)	49 (48 %)	0.86

* *H. pylori* and NSAID negative

(Table 2). All patients with gastric ulcerative lesions and / or duodenal mucosal breaks were found to be *H. pylori* negative and reported no use of NSAID's. Comparing single- and multi-vessel CGI patients, no significant differences were found.

The Paris classification

Lesions according to the Paris classification were found significantly ($p = 0.02$) more in the patients with ischemia as compared to the patients without ischemia, 11 (11 %) and 0 respectively. Six (6 %) ischemia patients had unexplained *H. pylori* negative ulcers, which were located in the greater curvature of the corpus in four patients, in the lesser curvature of the corpus and the greater curvature of the antrum. Histological examination showed neutrophilic infiltration, mucosal oedema and epithelial regeneration fitting ischemia in two patients, intestinal metaplasia in one patient and no histopathologic abnormalities in three patients. In three patients sessile protruding superficial lesions were found. Two of these lesions were identified as fundic gland polyps and one lesion showed no pathology on histological examination. One patient had a superficial elevated lesion in the greater curvature of the corpus, which was identified as a fundic gland polyp. One patient had a prepyloric flat lesion, which showed no pathology on histological examination. Prevalence and character of the lesions did not differ between single and multi-vessel ischemia patients.

The Sydney scoring system

Overall, endoscopic pathological findings using the Sydney scoring system were found in 69 (47 %) patients: in 49 (48 %) patients diagnosed with ischemia and in 20 (44 %) patients without ischemia, not statistically different ($p = 0.86$). Erosive *H. pylori* negative lesions, flat ($n=13$) or raised ($n=3$), were found in 14 patients: 12 ischemia and 2 non-ischemia patients ($p = 0.23$) (Table 3). Histological examination showed neutrophilic infiltration, mucosal oedema and epithelial regeneration, fitting ischemia in three patients and no pathologic findings in 11 patients. Also comparing other abnormal findings, no significant differences were found between patients diagnosed with and without ischemia. Furthermore, prevalence and character of gastritis did not differ between NOMI, single and multi-vessel ischemia patients.

Repeated upper endoscopy after treatment

In 14 (54 %) out of 26 patients diagnosed with ischemia and who had gastric and / or duodenal erosive lesions on first upper endoscopy, a repeated upper endoscopy was performed: ten patients refused repeated upper endoscopy and two patients died before repeated upper endoscopy could be performed. One patient died due to complications of bronchial carcinoma and one patient died because of complicated, end-stage, ischemic disease. During repeated upper endoscopy, 12 (86%) patients showed improvement, normalization in seven, improvement in five patients, and two (14 %) patients showed no change in shape and appearance of pathological findings after initiation of therapy.

Table 3. The Sydney system, endoscopic division, data given are number of lesions in ischemia (NOMI, single and multi-vessel stenosis disease respectively) and non-ischemia patients.

		Non-ischemia patients n=45	Ischemia patients n=103			
			Total n=103	NOMI n= 27	SVD N=47	MVD n=29
Topography	Gastritis of antrum	14	28	7	13	8
	Gastritis of corpus	3	8	2	4	2
	Pangastritis	2	9	4	3	2
Descriptive terms	Oedema	15	36	11	14	11
	Erythema	17	42	13	17	12
	Friability	0	0	0	0	0
	Exudate	0	0	0	0	0
	Flat erosion	2	11	3	3	5
	Raised erosion	0	3	1	2	0
	Nodularity	0	0	0	0	0
	Rugal hyperplasia	0	2	0	1	1
	Rugal atrophy	0	6	1	3	2
	Visibility of vascular pattern	4	6	2	3	1
	Intramural bleeding spots	0	0	0	0	0
Categories of endoscopic gastritis	Erythemous/exudative	16	38	12	15	11
	Flat erosive	2	11	4	3	4
	Raised erosive	0	3	1	2	0
	Atrophic	4	7	2	3	2
	Haemorrhagic	0	0	0	0	0
	Reflux	0	0	0	0	0
	Rugal hyperplastic	0	4	0	3	1

NOMI = non-occlusive mesenteric ischemia; SVD = single vessel disease; MVD = multi vessel disease.

DISCUSSION

In this study we investigated upper endoscopy findings in patients with well-defined CGI. Overall, no significant differences in prevalence of upper endoscopic findings were found comparing patients with and without ischemia. However, the character of upper endoscopic lesions was different, and we did find significantly more 'ischemia-associated' abnormal findings in CGI patients. However, almost two-third of CGI patients did not show these particular endoscopic findings and therefore CGI is often missed using upper endoscopy as sole diagnostic method for this disease entity.

Little is known about the prevalence and character of specific gastroduodenal lesions in patients with CGI. Ulcers in CGI patients were described in literature as atypical lesions with regard to the location, number and appearance; they tend to be multiple and irregular in shape (11). These ulcers can heal progressively after revascularization therapy of the gastrointestinal arterial arteries (12-16). In the current study, six patients diagnosed with ischemia presented with unexplained *H. pylori* negative ulcers fitting CGI, occurring in the greater and lesser curvature of the corpus and the greater curvature of the antrum. Histological

examination of biopsy sampling showed ischemic changes in two patients. At the moment, a histological classification for chronic gastrointestinal ischemia is lacking. In addition, the improvement of pathological lesions in majority of patients (86 %) on repeated upper endoscopy in CGI patients after treatment, indicates a relation between the presence of these lesions and mucosal ischemia.

Currently, no endoscopic classification for CGI is available. The Sydney System for endoscopic gastritis and the updated Paris classification for superficial neoplastic lesions in the stomach, were the best alternatives to score the endoscopic findings in a standard manner. Nevertheless, the Paris classification only comprises the esophagus, stomach and colon, excluding the duodenum and small bowel. Using the Paris classification, in the ischemia patients significantly more lesions were found compared to the non-ischemia patients. Majority of these positive Paris classification lesions consisted of protruded ulcerative lesions. Using the established Sydney classification no differences were found comparing the ischemia and the non-ischemia patients. Potential 'ischemia associated' lesions were significantly more common in the ischemia patients as compared to the non-ischemia patients. The outcome of this study indicates that these type of lesions are indeed related to CGI.

Overall, in only 55% of patients diagnosed with CGI endoscopic mucosal abnormalities were seen. The negative predictive value of a normal upper endoscopy for the presence of CGI seems limited. Therefore, endoscopists should be aware of the fact that a negative upper endoscopy does not exclude the diagnosis CGI (Figure 2A and B). In patients clinically suspected for CGI, additional diagnostic evaluation should be performed before the diagnosis is rejected.

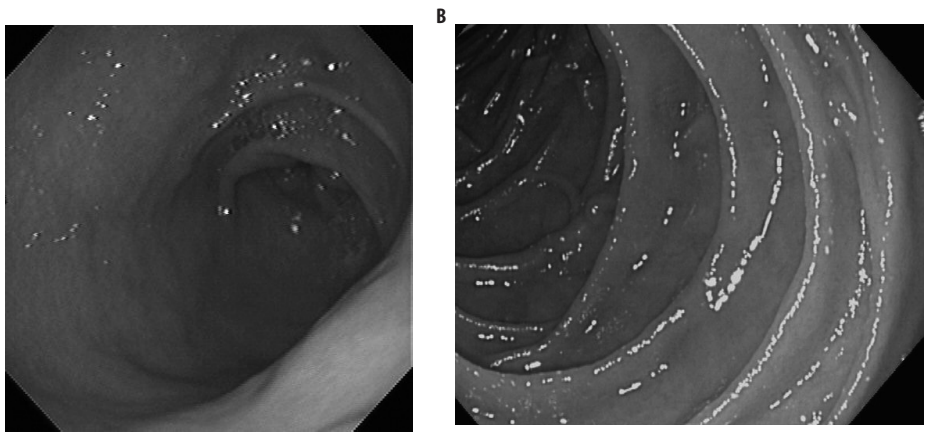

Figure 2

A Endoscopic picture of normal gastric antrum in a 59 year old female patient with definitive diagnosis of chronic gastrointestinal ischemia due to multi-vessel disease.

B Endoscopic picture of normal duodenum descendens in a 69 year old female patient with definitive diagnosis of chronic gastrointestinal ischemia due to a stenosis in the superior mesenteric artery.

Even, if patients present with multiple gastroduodenal lesions caused by CGI, they often remain unrecognized (17). Despite the often typical symptomatic presentation of patients with CGI, the possibility is frequently overlooked and the diagnosis subsequently delayed (18). Since the differential diagnosis of multiple gastroduodenal lesions is limited, CGI should be considered earlier. Correctly diagnosed and adequately treated CGI patients can improve rapidly after restoring of gastrointestinal arterial blood supply (11, 17, 19-21). In theory, pathological endoscopic changes are expected to appear more frequently in patients with multi-vessel stenosis than in patients with single vessel stenosis, because of the more pronounced reduction of gastrointestinal arterial blood flow in patients with multi-vessel stenosis. However, prevalence and character of the lesions did not differ between single and multi-vessel ischemia patients.

The present study has some limitations. Firstly, a possible drawback of the present study is the single center setting. The Erasmus MC is a large tertiary care center and one of the two referral centers in the Netherlands with a dedicated CGI working group for patients suspected of CGI. Secondly, repeated upper endoscopy can be useful to evaluate improvement of endoscopic pathological findings after treatment. Unfortunately, a repeated upper endoscopy after endovascular or surgical revascularization was only performed in just over 50% of the patients diagnosed with ischemia and endoscopic pathological changes. At last, the use of proton pump and platelet aggregation inhibitors may be a major confounding factor, as at time of the upper endoscopy most patients were using these types of medication. However, the use of these medications was comparable in both the ischemia- and the non-ischemia patient groups.

In conclusion, the results of this study show that normal endoscopic findings on upper endoscopy have a limited negative predictive value for the presence of CGI. Non-specific abnormal findings were seen in just over half of the patients diagnosed with CGI. Findings as *H. pylori* negative and otherwise unexplained gastric ulcerations and / or duodenal mucosal breaks, gastric reduced vascularity, and mucosal paleness during upper endoscopy might be related to ischemia, and therefore CGI should be considered in patients presenting with these endoscopic features.

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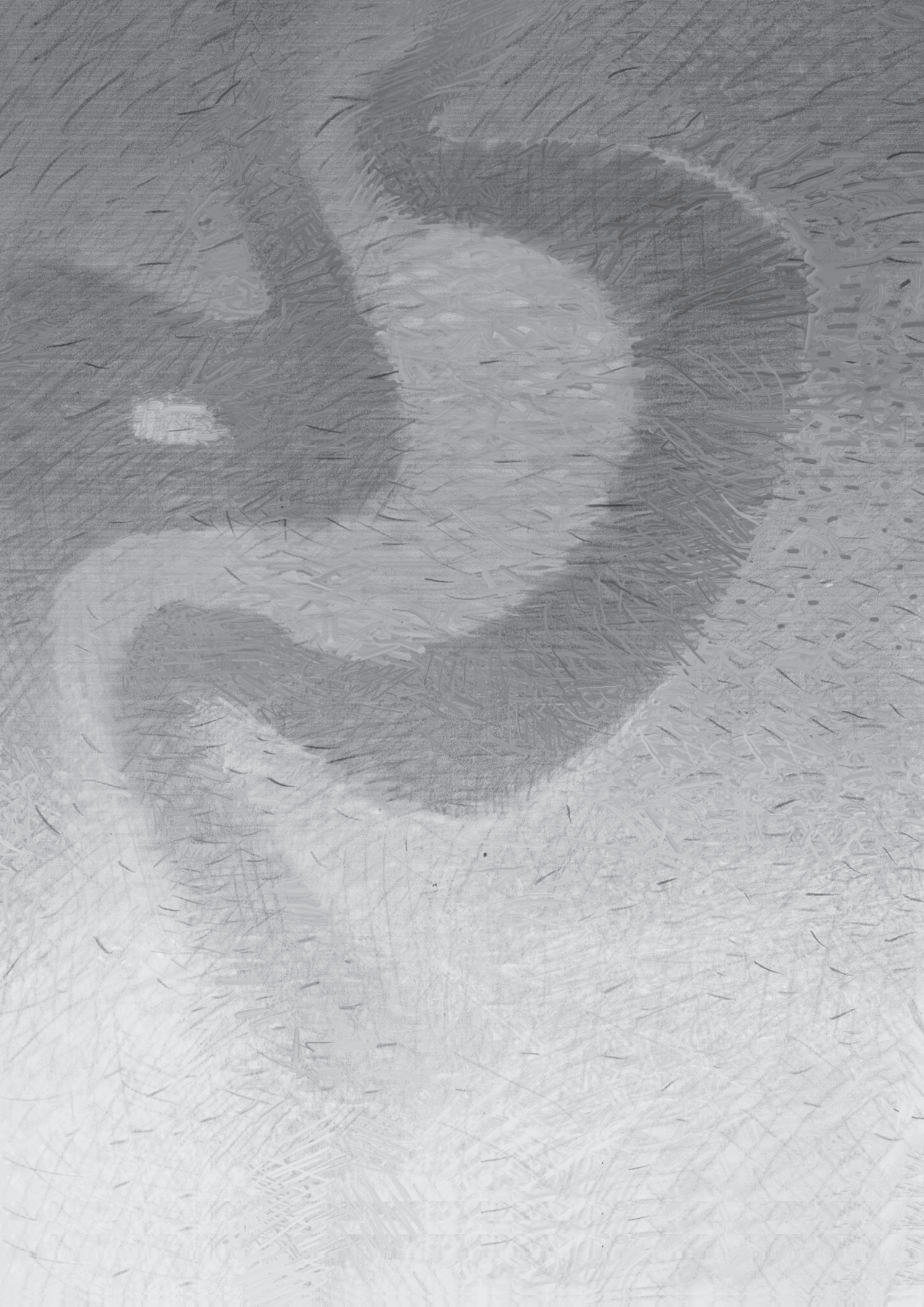

Chapter 7

Histological changes in patients with chronic gastrointestinal ischemia

Désirée van Noord[1], Katharina Biermann[2], Leon M.G. Moons[1], Peter M.T. Pattynama[3], Hence J.M. Verhagen[4], Ernst J. Kuipers[1,5], Peter B.F. Mensink[1]

Departments of Gastroenterology and Hepatology[1], Pathology[2], Intervention Radiology[3], Vascular Surgery[4], Internal Medicine[5], Erasmus MC - University Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Aims Diagnosing chronic gastrointestinal ischemia (CGI) remains a challenge in clinical practice. Histological examination of biopsy material currently plays no role in the diagnosis of transient CGI as little is known about gastrointestinal histology in these patients. This study therefore aimed to investigate upper gastrointestinal histology in patients with well-defined CGI.

Methods and results Consecutive patients suspected of CGI were prospectively included and underwent a diagnostic work-up existing of upper endoscopy, gastrointestinal tonometry and CT or MR angiography. Results were discussed in a multidisciplinary team and a consensus diagnosis was made. Endoscopical biopsy samples were taken from the descending duodenum, gastric antrum and corpus, and scored using the Sydney, Vienna, Chiu, Marsh and OLGA classifications. Gastropathy was scored present or absent. In eight months time, 79 patients were analyzed: 36 males, mean age 60 (17-86) years. CGI was diagnosed in 41 patients (52%). Prevalence of gastropathy was significantly higher in patients with ischemia ($p=0.025$). No other differences were found between patients with and without ischemia.

Conclusion Histological examination of biopsy samples plays no definitive role in diagnosing CGI, but the presence of histological signs of reactive gastropathy can be used to support the clinical diagnosis of ischemia.

INTRODUCTION

The diagnosis of chronic gastrointestinal ischemia (CGI) remains a challenge in clinical practice. For a long time, CGI was considered to be a very rare disease, only presenting in patients with multiple stenotic abdominal arterial disease. However, newer diagnostic techniques such as gastrointestinal tonometry (TM) have made clear that CGI is more common than previously thought, and that CGI patients may present with a range of symptoms such as postprandial pain, exercise related pain, weight loss and diarrhea (1, 2). At the moment, the proposed diagnostic workup in this particular patient group includes a combination of assessment of clinical symptoms and physical examination, radiological evaluation of the abdominal arterial vascular anatomy, and a functional test for the diagnosis of mucosal ischemia (1, 3, 4). The majority of CGI patients only demonstrate transient reversible mucosal ischemia during provocation, in particular postprandial or exercise related. In theory, this short-lived, 30 to 90 minutes maximum, reversible mucosal ischemia could lead to minor mucosal damage. More severe cases can present with malabsorption, which may be related to small bowel villous atrophy. Histological examination of biopsy material currently plays no major role in the diagnosis of transient chronic gastrointestinal ischemia. Pathologists are frequently asked to interpret more pronounced ischemic changes, for example in suspected acute gastrointestinal ischemia or ischemic colitis (5, 6). Pathologists rarely encounter gastric or small intestinal biopsies for interpretation of chronic ischemic changes.

Histological findings related to acute gastrointestinal ischemia have been described in the past, mainly as a result of animal studies. This resulted in several histological ischemia classifications, firstly from dog studies (1970), followed by a more sophisticated system from studies in rats (1980, 1992). The grading system of Chiu has also been adapted for man by Haglund (1975) (7-10).

Currently, no PubMed (National Library of Medicine) sited articles are available concerning CGI. Only in Gastrointestinal Diseases, Atlas of Nontumor Pathology (Armed Forces Institute of Pathology) Noffsinger et all have described histological changes in CGI (11). These may include architectural distortion in the epithelium, marked regenerative activity, Paneth cell metaplasia and endocrine cell hyperplasia. In some cases, a prominent submucosal collection of mononuclear cells is present; this may present as lymphoplasmacytosis in the deep lamina propria, simulating chronic inflammatory bowel disease. Early damage may also include epithelial detachment and intercellular edema. Depending on the duration and severity of the injury, mucosal and submucosal necrosis may be present, and in severe cases, transmural necrosis occurs. Reperfusion can then lead to marked congestion, hemorrhage, and emigration of neutrophils in the lamina propia. Intraepithelial neutrophils also may become prominent and

pseudomembranes develop. Fibrosis, hemosiderin-laden macrophages, and serosal adhesions may also be present. The remaining epithelium may show marked regenerative changes. In conclusion, little is known about the prevalence and histological features of stomach and small bowel in patients with chronic gastrointestinal ischemia. This study therefore aimed to investigate histology findings in patients with well-defined chronic gastrointestinal ischemia.

MATERIALS AND METHODS

Consecutive patients who were referred for evaluation of possible CGI to the department of Gastroenterology and Hepatology of the Erasmus MC - University Medical Center were asked to participate in the current study and were prospectively included. The department has a tertiary CGI referral program. The study was approved by the Institutional Review Board.

Biopsy sampling and tissue preparation

After an overnight fast, all patients underwent upper gastrointestinal endoscopy under conscious sedation with midazolam intravenously (dose 2.5-5 mg), if necessary combined with fentanyl (0.05 mg). Continuous monitoring of peripheral oxygen saturation and heart rate was performed during the endoscopy. Biopsy sampling was performed during endoscopy: two biopsies in the descending duodenum, one in the lesser and one in the greater curvature of the antrum within two to three cm from the pylorus and two samples from the greater curvature of the corpus, approximately eight cm from the cardia. Tissues were fixed by immersion in phosphate-buffered formalin (pH 7.0) and embedded in paraffin using standard techniques.

Biopsies from antrum and corpus were scored using the updated Sydney System for the classification of gastritis, the Vienna classification for gastrointestinal epithelial neoplasia and the Operative Link for Gastritis Assessment (OLGA classification), a staging system using the updated Sydney System for assessment of the distribution and severity of atrophic gastritis

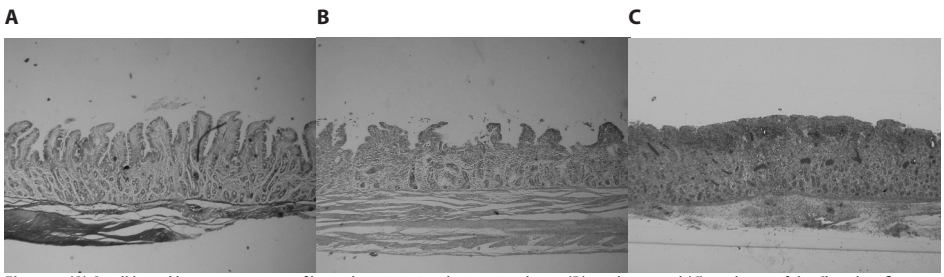

Figure 1 (**A**) Small bowel biopsy specimens of large domestic pigs showing grade 0-1 (**B**) grade 2-3 and (**C**) grade 4-5 of the Chiu classification for ischemia.

Table 1. Chiu classification for gastrointestinal mucosal ischemia.

Grades	
0	Normal mucosal villi
1	Development of subepithelial Gruenhagen's space at the apex of the villi, often with capillary congestion.
2	Extension of the subepithelial space with moderate lifting of epithelial layer from the lamina propia
3	Massive epithelial lifting down the sides of the villus. A few tips may be denuded.
4	Denuded villi with lamina propia and dilated capillaries exposed. Increased cellularity of lamina propria may be noted.
5	Digestion and disintegration of lamina propia, hemorrhage and ulceration

(12-16). In addition to gastritis assessment, endothelial or epithelial cell damage and regeneration without associated inflammation were independently assessed as gastropathy (17). In the absence of a classification, gastropathy was scored present or absent.

Biopsies from duodenum were scored using a modification of the original Marsh classification and the ischemia classification of Chiu (Table 1, Figure 1) (7, 18, 19).

All endoscopies were performed by the same gastroenterologist (PM). All biopsies were scored after sampling by a random pathologist followed by an expert pathologist (KB). The latter was unaware of the results of the clinical work-up.

Standard diagnostic workup

In all patients, more common causes of chronic abdominal symptoms had been previously excluded by appropriate diagnostic evaluation. At our institution, the current diagnostic strategy for evaluation of possible CGI involves a combination of radiological evaluation of vascular anatomy with CT- or MR-angiography to visualize the gastrointestinal arteries (celiac artery (CA), superior mesenteric artery (SMA) and inferior mesenteric artery (IMA)) and upper gastrointestinal tonometry to detect gastrointestinal mucosal ischemia. Angiography reveals vascular abnormalities. Tonometry in contrast is a functional test assessing mucosal blood flow. This can be done over 24 hours both during fasting and with food intake as provocation for ischemia. The technique is based on continuous measurement of intra-luminal CO_2, which reflects the adequacy of mucosal perfusion. A combined naso-gastric and naso-jejunal tube allows measurement of intraluminal CO_2 levels in the stomach and small bowel. These levels can be correlated with symptoms. In patients with insufficient postprandial mucosal blood flow, mucosal CO_2 will rise in particular after provocation by a meal. Cut-off values for normal CO_2 have been established earlier in healthy volunteers and patient studies (20). Tonometry was performed using a standardized protocol enabling mucosal CO_2 measurements both in fasting and postprandial state (1). A significant stenosis of the abdominal arteries was defined as a luminal reduction of >70 %. Non-occlusive mesenteric ischemia (NOMI) was defined as all forms of non-occlusive mesenteric ischemia, based on clinical symptoms and positive TM despite normal gastrointestinal arterial anatomy on CTA or MRA. Medical history, complaints and the results of all diagnostic procedures were discussed in a dedicated multidisciplinary team

consisting of a vascular surgeon, intervention radiologist and gastroenterologist, all specialized in CGI, and a consensus diagnosis was made: (1) no abdominal arterial stenosis, no ischemia, (2) abdominal arterial stenosis, no ischemia, (3) NOMI (4) abdominal arterial stenosis and ischemia (i.e. CGI). Patients with GI ischemia were offered therapy, by either revascularization of the vascular obstruction by open surgery or by endovascular stent placement, or medical treatment (NOMI patients). The definitive diagnosis of CGI was made after persistent relief of symptoms on follow-up after intervention. The latter definition was also used as the "gold standard" for CGI.

Statistical analysis

Data were expressed as mean (range). The data of the ischemic and non-ischemic patients were compared using Student's t-test, χ^2 testing or Fisher's Exact Test when appropriate or by binary logistic regression analysis. Statistical analysis was performed using the SPSS 16.0 program (SPSS Inc. Chicago, IL, USA). A p-value <0.05 was considered statistically significant (all two-tailed).

RESULTS

During a period of 8 months (July 2008- March 2009), 80 patients were referred for evaluation of possible CGI. Informed consent for participation in the study was obtained from 79 patients. CGI was diagnosed in 41 patients (52%) and 12 patients (15%) were diagnosed with NOMI. Patient characteristics and presenting symptoms are presented in Table 2.

Table 2. Patient characteristics and presenting symptoms, data given are number of patients (percentages) or mean (range).

	n=79
Age (years)	60 (17-86)
Gender M/F	36/43
Postprandial pain	52 (66%)
Exercise related pain	31 (39%)
Diarrhea	16 (20%)
Weight loss	53 (67%)
Weight loss (kg)	7.8 (0.7-30.0)
BMI (kg/m^2)	22.8 (15.0-37.7)
Abdominal complaints	72 (91%)
Duration of complaints (months)	23.6 (2-180)
Risk factors for cardiovascular disease:	
· Smoking	30 (38%)
· Other risk factors*	49 (62%)
Ischemia**:**	53 (67%)
· Chronic gastrointestinal ischemia	41
- single vessel stenosis	27
- multi-vessel stenosis	14
· Non-occlusive mesenteric ischemia	12

* including diabetes mellitus, obesity, hypertension, hyperlipidemia, hyperhomocysteinemia and familial history for cardiovascular disease.

Gastric biopsies

Patients with and without ischemia did not differ with respect to Sydney gastritis scores (Table 3). Although ischemia patients more often had signs of active gastritis, i.e. neutrophilic infiltration, and signs of chronic gastritis, i.e. gastric atrophy and increase of mononuclear cells, than non-ischemia patients, these differences were not significant. In only three patients diagnosed with ischemia both neutrophils and gastric atrophy were observed together (p= 0.55).

Table 3. Updated Sydney classification, data given are number of patients (percentages) and p-value.

	Ischemia patients antrum (n=51) corpus (n=52)	**Non-ischemia patients** antrum (n=26) corpus (n=26)	p-value
Helicobacter pylori Antrum	2	2	0.64
Helicobacter pylori Corpus	2	2	0.73
Total	2	3	0.33
Neutrophils Antrum	6	0	0.15
Neutrophils Corpus	1	0	1.00
Total	7	0	0.09
Mononuclear cells Antrum	32	17	0.91
Mononuclear cells Corpus	14	9	0.73
Total	32	17	1.00
Atrophy Antrum	18	6	0.38
Atrophy Corpus	5	1	0.77
Total	21	6	0.21
Intestinal metaplasia Antrum	5	2	0.86
Intestinal metaplasia Corpus	2	1	1.00
Total	6	3	1.00

Ischemia patients: 1 biopsy missing corpus, 2 biopsies missing antrum

The degree of gastric atrophy according to the OLGA classification is presented in table 4. No patients had signs of gastrointestinal epithelial neoplasia according to the Vienna classification. The prevalence of gastropathy was significantly higher in ischemia patients (p-value 0.025). Gastropathy was scored in 18 (33%) of 55 ischemia patients (33%) and two (8%) of 24 non-ischemia patients.

Table 4. Operative Link for Gastritis Assessment (Olga classification).

	Ischemia patients (n=50)	**Non-ischemia patients (n=26)**	**P-value**
Stage 0	31	20	
Stage I	11	3	0.23
Stage II	7	2	0.34
Stage III	0	1	1.00
Stage IV	1	0	1.00

Duodenal biopsies

One patient without ischemia had subepithelial space at the tips of the villi, grade I according to the classification of Chiu (p=0.34).Three patients with ischemia had increased numbers of intraepithelial lymphocytes and villous atrophy in the small intestinal biopsies, consisting with Marsh I in one patient and Marsh IIIC in two patients. Celiac disease was ruled out by determination of serum endomysial and anti-gliadin antibodies.

DISCUSSION

In this study we investigated histology findings in patients with well-defined chronic gastrointestinal ischemia. The major histological finding in ischemia patients was the significantly higher prevalence of reactive gastropathy compared to non-ischemia patients. However, using established histological classifications, i.e. the updated Sydney System, the Vienna and OLGA classification for antrum and corpus and the Marsh and Chiu classification for duodenum, no significant differences in prevalence and character of histological findings existed between patients with and without ischemia. This implies that histology of stomach and duodenum is of little aid in the diagnosis of chronic gastrointestinal ischemia. This is in contrast to well established criteria of lower intestinal ischemia in colonic biopsies, where histological changes vary with the duration and severity of the injury.

Gastropathy indicates endothelial or epithelial cell damage and regeneration (foveolar hyperplasia) without associated inflammation, which is usually caused by irritants such as drugs, bile reflux, but can also result from hypovolemia, chronic congestion and very rarely ischemia (17). Therefore, the term "gastropathy" is not describing a specific histological finding in ischemia patients, but, to our experience, can be used to support the clinical diagnosis of ischemia. Our study demonstrated a high prevalence of reactive changes in patients with CGI. Therefore, histopathologists should be aware of a differential diagnosis including CGI in a proper clinical setting. Overall, more specific lesions for ischemia as defined by Chiu et al. (7) could not be identified, however patients diagnosed with ischemia did often present with non-specific histological changes such as atrophy, fibrosis and infiltration of neutrophils and mononuclear cells.

Most importantly, there may be a significant discrepancy between the macroscopic and microscopic images of the stomach and duodenum. Endoscopic ischemic appearances frequently do not predict histological alterations. Some patients diagnosed with ischemia and normal endoscopic features were identified with relevant histological changes (Figure 2). Several studies described experimental models designed to stimulate hypoperfusion of the intestine which occurs in shock, in occlusive or non-occlusive intestinal ischemia, similar to acute or irreversible ischemia (7, 8). In these conditions, the earliest lesion seen in the intes-

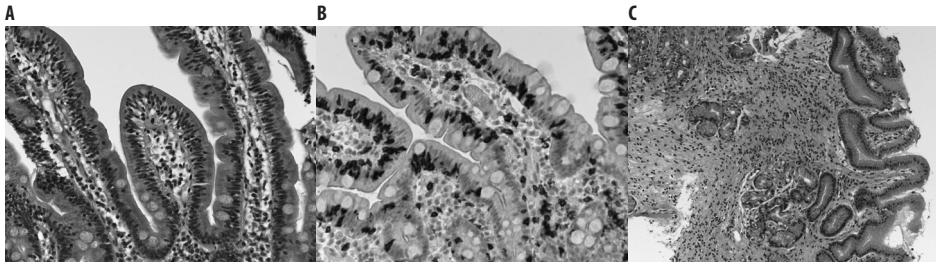

Figure 2 (**A**) Biopsy specimen of the descending duodenum showing Marsh I with (**B**) immunohistochemistry CD3 staining showing infiltration of intra-epithelial T-lymphocytes and (**C**) gastric antrum biopsy specimen showing atrophy, fibrosis and infiltration of mononuclear cells in 54 year old male patient diagnosed with chronic gastrointestinal ischemia with normal upper endoscopic findings.

tinal mucosa with light microscopy is the development of sub-epithelial space near the tips of the villi, i.e. Chiu grade I. We investigated patients with chronic or reversible, occlusive or non-occlusive ischemia, who did not show these changes in the intestinal mucosa. Ischemic preconditioning might be a possible explanation for the lack of changes according to the Chiu classification in chronic ischemia (21). Preconditioning is thought to protect the intestines against mucosal ischemic injury in patients with CGI. In these patients, the tolerance to subsequent sustained ischemia is enhanced by occurrence of brief periods of ischemia in the past. A polygenetic adaptive response defends against injury to the ischemic tissue after the return of adequate circulation. Therefore, continuous arterial hypotension in the intestine seems of pathogenetic importance for the development of the mucosal lesions.

A limitation of the current study is the possibility that the mucosal ischemia is thought to be patchy and that histological findings could be missed due to sampling error. Assessment of the entire endoscopic field by taking multiple biopsy specimens throughout the gastric and duodenal mucosa simultaneously for focal areas of ischemia would be preferred, but the limited findings in our study suggest that more extensive biopsy sampling would not strongly increase the yield of specific histological findings in this patient category. The use of non-steroidal anti-inflammatory drugs, acetylsalicylic acid or biphosphonates may be a confounding factor. At referral, medication use was scored in all patients, however we did not explicitly ask for over the counter use of non-steroidal anti-inflammatory drugs.

In conclusion, the prevalence of gastropathy was significantly higher in patients with ischemia. No other differences were found between patients with and without ischemia.
Histological examination of biopsy samples seems to play no definitive role in diagnosing CGI, but the presence of histological signs of gastropathy can be used to support the clinical diagnosis of upper gastrointestinal ischemia in a proper clinical setting.

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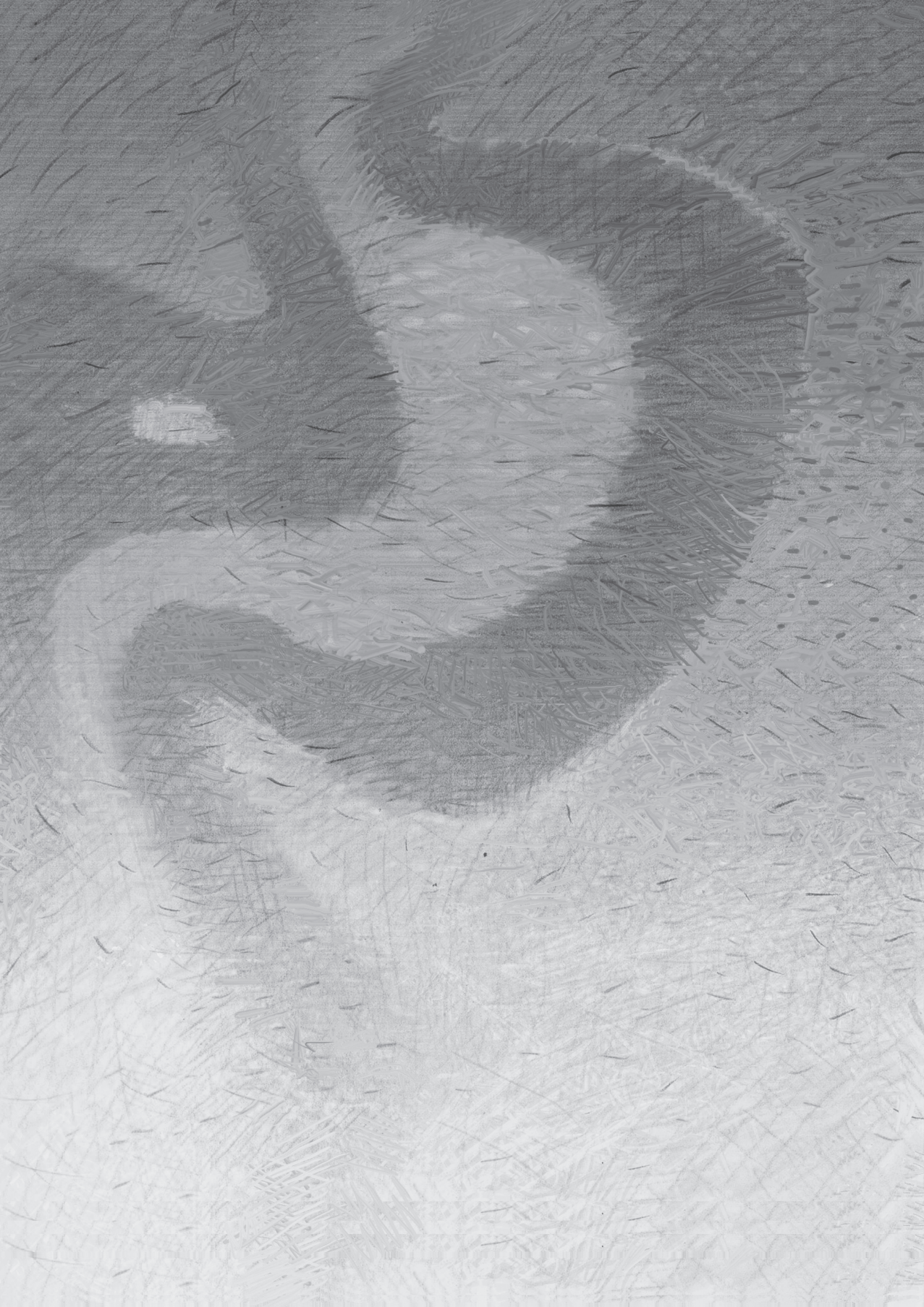

Chapter 8

Chronic gastrointestinal ischemia due to atherosclerotic narrowing is related to classical risk factors for cardiovascular disease

Aria Sana[1], Désirée van Noord[1], Stephanie Kooij[2], Kim van Dijk[2], Bert Bravenboer[3], Louis G. Lieverse[4], Eric J.G. Sijbrands[2], Janneke G. Langendonk[2], Peter B.F. Mensink[1]

Departments of Gastroenterology and Hepatology[1], Internal Medicine[2], Erasmus MC - University Medical Center, Rotterdam, The Netherlands
Department of Internal Medicine, Catharina Ziekenhuis, Eindhoven, The Netherlands[3]
Department of Internal Medicine, Maxima Medisch Centrum, Eindhoven, The Netherlands[4]

Submitted

ABSTRACT

Introduction Chronic gastrointestinal ischemia (CGI) is most commonly caused by atherosclerotic stenosis of the gastrointestinal arteries. Although CGI is an extracardial manifestation of atherosclerosis, its relationship with classical risk factors of cardiovascular disease (CVD) is unclear. The primary objective of this study was to determine whether classical risk factors of cardiovascular disease associate with atherosclerotic CGI (ath-CGI). In addition, we compared the patients with those in whom CGI was not confirmed (non-CGI).

Methods A prospective cohort study was performed in patients with unexplained chronic abdominal symptoms referred for evaluation of suspected CGI. A standard work-up was conducted including CTA or MRA for imaging the abdominal vessels and gastrointestinal tonometry. Additionally, an extensive evaluation for atherosclerotic risk factors was performed. Control subjects from the DiaGene Study population served as controls. The controls were previously not diagnosed with CGI or diabetes.

Results Between 2006 and 2009 195 patients were evaluated. Ath-CGI was diagnosed in 69 patients: 21 males, median age (IQR) 66 (57-75) years. The controls consisted of 69 males, median age (IQR) 66 (63-72). The prevalence of hypercholesterolemia, the personal and family history of CVD, smoking, use of statins and anti-hypertensive agents were significantly higher in ath-CGI patients compared with controls. Weight loss was reported in 74% of ath-CGI patients. Total LDL-cholesterol was lower in ath-CGI vs. controls (median (IQR): 2.2 (1.8-2.9) vs. 3.5 (3.0-3.4), P = 0.001), this can be explained by higher statin use and substantial weight loss. We did not find relevant differences between CGI and non-CGI patients.

Conclusion CGI due to atherosclerotic stenosis is associated to classical CVD risk factors. This advocates secondary prevention therapy for patients with CGI. This atherosclerotic disease has a remarkable female preponderance.

INTRODUCTION

Gastrointestinal ischemia is a potential life-threatening disease and the burden in the average patient is large. Chronic gastrointestinal ischemia (CGI) is in the majority of patients caused by atherosclerotic stenosis of the gastrointestinal arteries. In younger patients, stenoses can also be the result of external compression of the celiac artery, the so-called celiac artery compression syndrome (CACS). Gastrointestinal arterial stenoses rarely lead to symptoms due to the presence of abundant collateral circulation. The current diagnostic approach for suspected CGI includes radiological imaging of the gastrointestinal arteries, combined with a functional test for mucosal perfusion (1).

Atherosclerotic disease of the coronary and cerebral circulation is the leading cause of death in the western world. The conventional risk factors for cardiovascular disease (CVD) are: male gender, age, diabetes mellitus, smoking, hypertension, hypercholesterolemia, positive family history of cardiovascular disease, obesity, and physical inactivity (2, 3). Co-existence of CVD in different vascular beds, i.e. polyvascular disease, is common due to the systemic nature of atherosclerosis. After any ischemic event, the absolute risk for a recurrent ischemic event in the same or in any other vascular bed is very high (4-7). Likewise, patients with polyvascular disease have a doubled risk of cardiovascular related mortality compared to patients with monovascular disease (8).

Although CGI is an extracardial manifestation of atherosclerosis, its relationship with classical risk factors of CVD is unclear. Previous studies in which endovascular and surgical treatment for CGI were compared, reported a large range of prevalences of classical CVD risk factors. The disagreement between these studies could be explained by differences in age distributions and small sample sizes (9-16). The primary objective of the current study was to determine whether classical risk factors of cardiovascular disease associate with atherosclerotic CGI (ath-CGI). The secondary objective was to compare risk factors for CVD between patients with atherosclerotic CGI and non-CGI.

METHODS

Study population

A case-control study was conducted. All consecutive patients clinically suspected of CGI were evaluated in the department of Gastroenterology and Hepatology of a tertiary care center (Erasmus Medical Center). Other causes of upper GI complaints were excluded by upper endoscopy, (complete) colonoscopy, abdominal ultrasound and / or abdominal computed

tomography. Patients were suspected for CGI when having postprandial pain, and/or unexplained weight loss, and / or a significant stenosis of at least one gastrointestinal artery.

Control subjects from the DiaGene Study population served as controls. DiaGene is a case-control study, including patients with diabetes (cases) and subjects without a previous history of diabetes (controls). The DiaGene is conducted in three hospitals in Eindhoven, The Netherlands. The controls were previously not diagnosed with CGI or diabetes. They were unrelated relatives of the cases or recruited through advertisement in newspaper (17). The Institutional Review Boards of the Erasmus Medical Center and the Eindhoven hospitals approved the study. Only patients with written informed consent entered the present study.

Standard diagnostic work up

All patients underwent through a standard work up, consisting of accurate assessment of medical and family history, physical examination including measurement of height, weight and blood pressure, and imaging of gastrointestinal arteries (celiac artery, superior mesenteric artery and inferior mesenteric artery) by computed tomography angiography (CTA), magnetic resonance angiography (MRA) or conventional digital subtraction angiography (DSA). A significant stenosis of an artery was defined as a luminal reduction of >70 %.
Additionally, 24-hour gastrointestinal tonometry was performed in order to detect mucosal ischemia. Gastrointestinal tonometry was performed to assess mucosal PCO_2 measurements, both during fasting and postprandial state with gastric and jejunal catheters. All patients had meals at standard times during gastrointestinal tonometry: liquid compound meal (400 ml) (12.00 p.m.), bread meal (6.00 p.m.), breakfast (8.00 a.m.), liquid compound meal (10.00 a.m.) and dinner (12.00 p.m.)(18). The patients were instructed to eat their meals within 15 minutes. The criteria for a pathologic response was a gastric or jejunal PCO_2 > 12.0, 13.6 and 10.6 kPa after breakfast (or bread meal), dinner or compound solution, respectively as described previously (19). A positive (suggestive of ischemia) tonometry test was defined as: 1) a pathologic response after 3 or more meals, or 2) a combination of one or two pathologic responses after meals combined with a median PCO_2 > 8.0 kPa in between meals.

Consensus and definitive diagnosis of CGI

Current physical complaints, medical history and the results of all diagnostic procedures were discussed in a dedicated multidisciplinary team consisting of a vascular surgeon, intervention radiologist and gastroenterologist. The discussion resulted in a final expert-based consensus diagnosis of: 1) no stenosis, no ischemia, 2) stenosis, no ischemia, 3) no stenosis, presence of ischemia, and 4) presence of stenosis and ischemia (see figure 1) (13). Patients in the first two consensus diagnoses were not confirmed with CGI (non-CGI). On the contrary, the latter 2 consensus diagnoses were defined as CGI. The consensus diagnosis of mesenteric ischemia in the absence of luminal stenosis (3) is defined as non-occlusive mesenterial ischemia (NOMI).

Patients with arterial stenosis and presence of mesenterial ischemia (4) had atherosclerotic CGI (ath-CGI) or CACS. All patients diagnosed with CACS and NOMI were excluded from the present analyses. All remaining patients with CGI were considered ath-CGI and underwent endovascular or surgical revascularization.

Due to the absence of a "gold-standard" diagnostic tool, the definitive CGI diagnosis was made after persistent relief of symptoms on long-term follow-up of at least 12 months after initiation of therapy. Patients treated for ath-CGI were redefined as non-CGI when symptoms persisted despite revascularisation, symptoms were assessed at a follow-up visits 3, 6 and 12 months after intervention.

Baseline measurements

Venous blood sampling (after 9-hours fasting) was obtained for measurement of serum cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, and blood glucose. The renal function was calculated using the MDRD formula (20). Impaired renal function was defined as MDRD < 60 and severe renal disease was defined as MDRD < 30.

Cardiovascular disease and classical risk factors

Documented coronary artery disease included at least one of the following criteria: history of (un)stable angina pectoris, myocardial infarction (MI), percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). Documented CVA included diagnosis of transient ischemic attack (TIA) or ischemic stroke. Documented peripheral vascular disease (PVD) consisted of claudicatio intermittens or previous treatment such as angioplasty, endovascular stent placement, peripheral arterial bypass graft or atherectomy. Hypercholesterolemia was considered present when subjects reported hypercholesterolemia, statins use in the absence of cardiovascular disease, or when LDL-cholesterol or total cholesterol were above the 95th percentile for age and gender. Hypertension was defined as known with hypertension or using anti-hypertensive medication or a systolic blood pressure above 140 mmHg or a diastolic blood pressure above 90 mmHg. Diabetes mellitus was defined according to WHO criteria or use of blood glucose lowering agents.

Statistical analysis

Continuous data were described as mean (range) and median (interquartile range 25-75, IQR) in case of skewed data for continuous data and percentages were given for categorical data. Mean values between patients with ath-CGI and controls and ath-CGI and non-CGI were compared with student's T-test and categorical data were compared with Chi-square test. A p-value of 0.05 was considered as statistical significant.

RESULTS

Between January 2006 and September 2009, a total of 195 patients were referred for evaluation of possible CGI; see figure 1. CGI was defined in 131 cases (67% of all referred); the data from the patients with NOMI (n = 30) and CACS (n = 23) were not used in the analysis. Definitive diagnosis of ath-CGI was defined in 69 patients; 36 (52%) patients had single vessel stenosis and 33 (48%) patients had multi-vessel stenosis. Non-CGI was observed in 66 patients. Patient characteristics are presented in table 1.

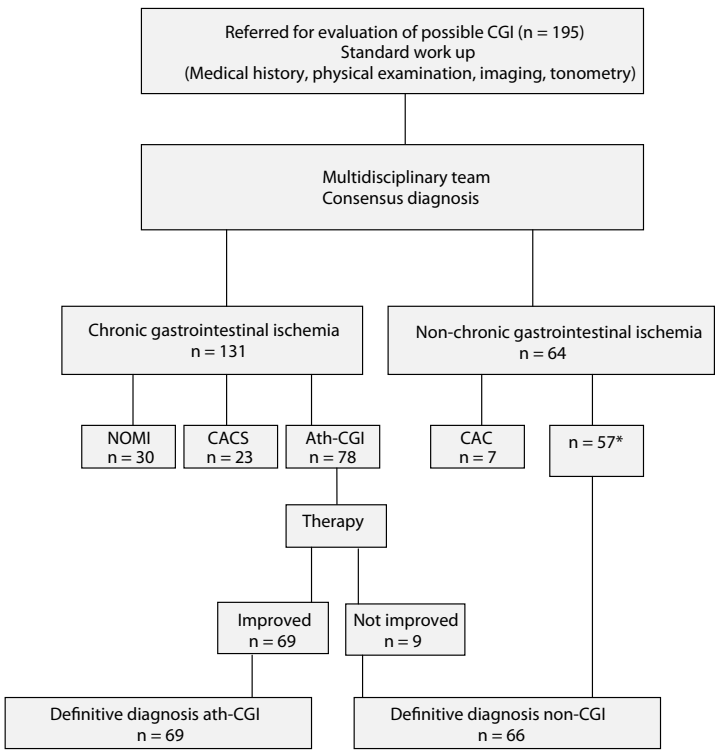

Figure 1. Flowchart of the study
NOMI = non-occlusive mesenterial ischemia
CACS= celiac artery compression syndrome
Ath-CGI = atherosclerotic CGI; treated with endovascular stent placement or surgery
CAC = celiac artery compression without ischemia
Symptoms improvement
Symptoms unchanged despite adequate treatment
A definite diagnosis of CGI was made if a patient was free of symptoms after adequate therapy for at least 12 months of follow-up;
A definite diagnosis of non-CGI was made if a patient was not diagnosed or hospitalized with ischemia related morbidity or mortality after follow-up
* n=7 with stenoses

Table 1 Patient characteristics and risk factors for cardiovascular disease

Patient characteristics	Non-CGI		Ath-CGI		Controls	
	n = 66		n = 69		n = 132	
Age, years	62	(49-70)†	66	(57-75)	66	(63-72)
Male gender	25	(38%)	21	(30%)	69	(52%)†
Diabetes	6	(9%)	14	(20%)	7	(5%)†
Hypercholesterolemia	13	(20%)*	26	(38%)	32	(24%)*
Hypertension	31	(47%)*	46	(67%)	81	(61%)
Current smoker	28	(42%)	27	(39%)	17	(13%)†
Cardiovascular disease	30	(46%)	35	(51%)	10	(8%)†
Family history of premature CVD	26	(39%)	35	(51%)	43	(33%)†
Cholesterol lowering agent	13	(20%)†	32	(46%)	23	(17%)†
Anti-hypertension agents	32	(48%)	36	(52%)	39	(30%)†
Previous BMI (kg/m2)	25	(23.0-28.6)	24.9	(22.2-28.2)	-	-
Current BMI (kg/m2)	21.8	(19.5-25.9)	22.0	(19.4-24.3)	25.8	(24.1-28.0)†

Ath-CGI = atherosclerotic chronic gastrointestinal ischemia; CVD = cardiovascular disease;
BMI= body mass index
Data are presented as median (IQ 25-75), unless otherwise specified;
P-values are for non-CGI vs. ath-CGI and controls vs. ath-CGI . * $p < 0.05$ † $p < 0.01$

The prevalence of CVD was higher among ath-CGI patients than among controls (see Table 1). Patients with ath-CGI were often smokers, and they had more frequently a family history of premature CVD than the controls. The prevalence of hypercholesterolemia was also higher among patients with ath-CGI as well as the use of statins was reported more often in ath-CGI patients than in controls. Consequently, total cholesterol and LDL cholesterol were lower in patients with ath-CGI than in controls; 4.3 (3.6-5.0) mmol/l vs. 5.2 (4.4-5.9) mmol/l, $P < 0.001$; and 2.2 (1.8-2.9) vs. 3.5 (3.0-3.4), $P = 0.001$, respectively. There was no difference concerning HDL-cholesterol, triglycerides and glucose in both groups (data not shown). Weight loss occurred in 74% of patients with ath-CGI; their median weight loss was 9 kg (IQR 6-12 kg). Patients with ath-CGI used much more anti-hypertensive drugs resulting in higher blood pressure levels in the controls but still in the normal range (data not shown). Impaired renal function was twice as frequent in ath-CGI patients compared to controls, 15 (22%) and 13 (10%), $P = 0.02$, respectively. Four out of 13 ath-CGI patients had severe renal disease.

Patients with ath-CGI were on average four years older than patients with non-CGI and had more often hypercholesterolemia and hypertension compared to non-CGI patients. Weight loss was reported in 71% of patients with non-CGI; median 10 kg (6-15). There was no difference in prevalence of diabetes, smoking, cardiovascular disease, family history of premature CVD and renal disease between patients with ath-CGI and non-CGI. Median HDL-cholesterol, triglyceride and glucose were comparable between the two groups.
There was no difference in the prevalence of CVD risk factors between ath-CGI patients due to single vessel and multi-vessel stenosis (data not shown).

After one year, 13 % of ath-CGI patients had died (9/71). Three deaths occurred within 60 days; two due to acute-on-chronic GI ischemia and one due to septic endocarditis. Six patients died within one year after treatment: two patients died due to acute MI and four patients died of a malignancy. The mortality rate in the non-CGI patients was 5%. None of these patients died because of a ischemia related cause.

DISCUSSION

The results of the presented study show that CGI due to atherosclerotic stenosis is associated to classical CVD risk factors. This advocates secondary prevention therapy for patients with CGI. DM, current smoking, previous CVD and a family history of premature cardiovascular disease were significantly more prevalent in patients with ath-CGI compared to healthy controls.

Previous studies comparing endovascular or surgical treatment for CGI, have reported variable prevalence of classical CVD risk factors. This could partly be explained by different age ranges and the size of the separate cohorts (9-16). Moreover, except for one study (14), patients with CACS were included in the analysis in all these study cohorts. Despite variable prevalences in separate publications, their combined averages are comparable to our results. In total 765 patients are described in 8 studies, mean age (range) was 65 (55-70) years. The combined mean prevalence of DM, hypercholesterolemia, hypertension, history of CVD and smoking were 12%, 40%, 66%, 60% and 62%, respectively. However, the current study was prospectively designed to compare the prevalence of the classical CVD risk factors in patients with CGI and healthy controls. All patients underwent a standard work up including assessment of medical and family history. This study reflects more accurate prevalence of CVD risk factors in patients with ath-CGI.

Patients suspected with CGI were referred to our tertiary center and all these patients underwent a standard work up. Current physical complaints, medical history and the results of imaging of gastrointestinal arteries and tonometry were discussed in a dedicated multidisciplinary team. The discussion resulted in a final expert-based consensus diagnosis of CGI or non-CGI. Patients with consensus diagnosis of ath-CGI were offered treatment by means of stent placement and surgical revascularization. The definitive CGI diagnosis was made after persistent relief of symptoms on long-term follow-up of at least 12 months after initiation of therapy. Comparison of CVD risk factors between patients with ath-CGI and non-CGI demonstrated that ath-CGI patients were older and had more hypercholesterolemia. However, no clinically relevant differences in CVD risk factors were observed. Patients evaluated for CGI generally represent a selected population, clinicians are more likely to consider CGI in the presence of CVD risk factors. This could be an explanation in comparable prevalence of CVD

risk factors in ath-CGI and non-CGI patients. Resultantly, based on CVD risk factor we can not distinguish between patients with ath-CGI and non-CGI.

A remarkable predominance of female gender in patients with ath-CGI was observed. Sixty six percent of patients with ath-CGI were female; this is in line with earlier reports of larger cohorts of CGI patients (9, 11, 13, 16). In a population-based study in independent elderly Americans, the Cardiovascular Health Study (CHS), the prevalence of gastrointestinal arterial stenosis was 18% using duplex sonography (21). No difference was found in gender distribution. This could imply that women more often develop symptoms, due to other mechanisms than atherosclerosis. CACS causes symptoms of CGI by external compression of the celiac artery by the median arcuate ligament. Earlier case series reveal high prevalence of this syndrome in women (22-24), however we excluded patients with CACS in our study. Mean age of female with ath-CGI was 63 years comparing to 68 years of male with ath-CGI. However, there were no clinically relevant differences in age and other CVD risk factors in female and male. Possible explanations for the female preponderance in CGI patients could be that women with chronic abdominal pain are more often referred to medical specialists, or have less potential for collateral circulation and therefore are more prone to develop CGI.

In the reported cohort, the measured levels of cholesterol, glucose and blood pressure were nearly normal. Pre-existent prevalence of hypercholesterolemia and hypertension were high, deduced from the pre-existent substantial use of lipid lowering agents and antihypertensive drugs. This difference can be explained by a severe weight loss in patients with CGI (13, 25), weight loss occurred in 73% of patients (9, 10, 15). Weight loss is the first line treatment option for hypercholesterolemia, hypertension and hyperglycaemia.

The healthy control subjects of the DiaGene Study served as a control population in the current study. Most of the controls were unrelated family members of patients with diabetes mellitus. This DiaGene cohort is comparable in age, BMI, and hypertension to two population based studies in the Netherlands: the ERGO study (26) which consists residents of a suburb in Rotterdam, and The Hoorn Study (27) which is another cohort of older Dutch subjects. There were more smokers in ERGO and in the Hoorn study. In addition, the DiaGene controls were selected on absence of previous diabetes, yet 5% was diagnosed with diabetes de novo. According to this, the DiaGene cohort seems a reasonable representation of the general Dutch population.

In conclusion, the results our study indicates that CGI due to atherosclerotic stenosis is associated with the classical CVD risk factors. A history of CVD, current smoking and a family history of premature CVD were significantly more prevalent in patients with ath-CGI compared to healthy controls. These features advocate secondary prevention therapy in patients with ath-CGI such as statin use. Future research is needed to observe a positive effect of the secondary prevention therapy in these patients.

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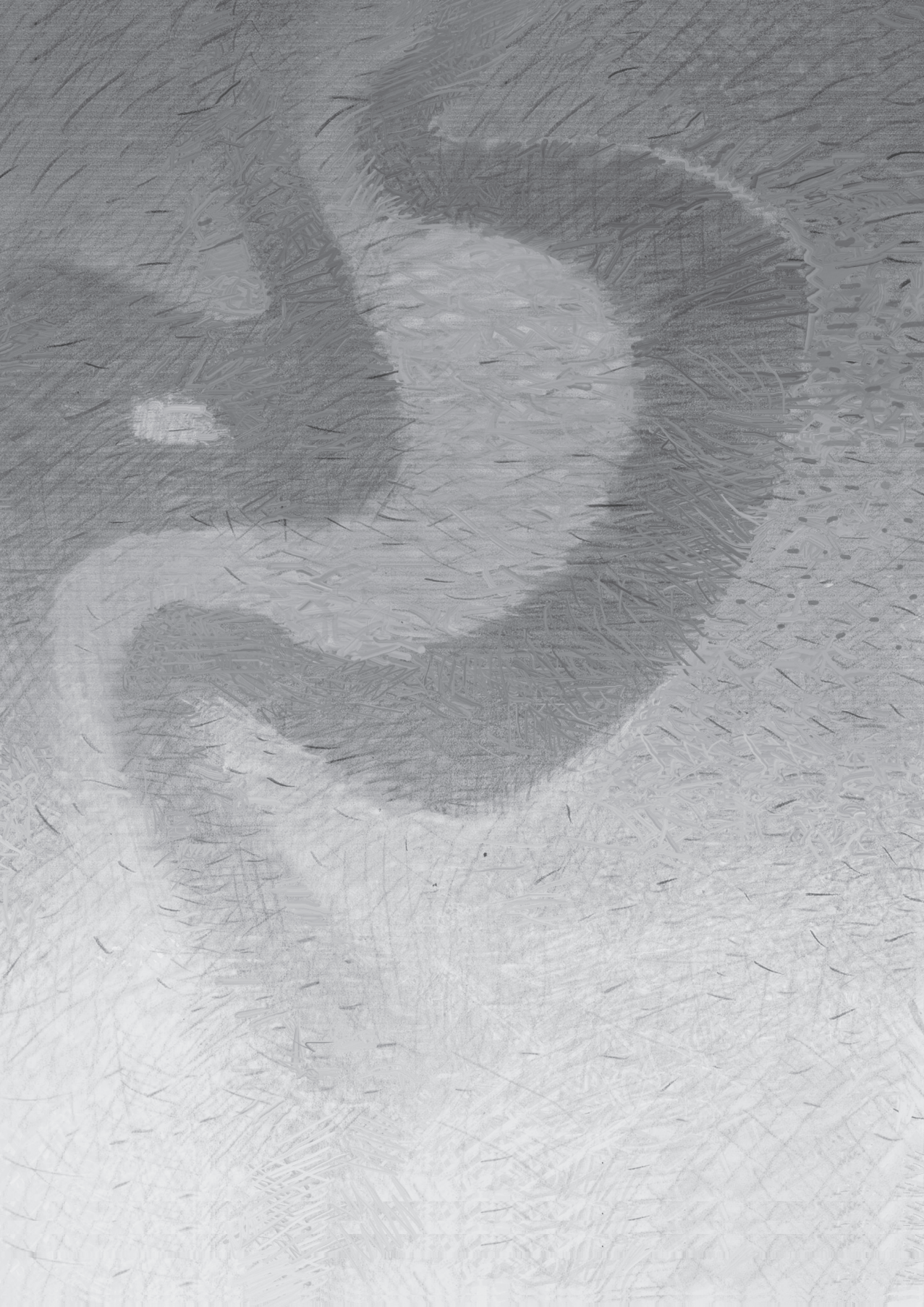

Chapter 9

Diarrhea caused by a stenosis of the celiac artery: suggestive for mesenteric steal

Désirée van Noord[1], Peter B.F. Mensink[1], Pieter C. ter Borg[1], Peter M.T. Pattynama[2], Hence J.M. Verhagen[3] and Ernst J. Kuipers[1,4]

Departments of Gastroenterology and Hepatology[1], Intervention Radiology[2], Vascular Surgery[3], Internal Medicine[4], Erasmus MC - University Medical Center, Rotterdam, The Netherlands

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SUMMARY

The classical triad of postprandial pain, weight loss and an abdominal bruit is thought to be the most common presentation of chronic gastrointestinal ischemia. We describe a patient with severe diarrhea as an uncommon presenting symptom of small bowel ischemia, suggesting a mesenteric steal phenomenon due to a significant atherosclerotic celiac artery stenosis. The stenosis and concomitant steal effect was successfully treated by stent placement. The latter is supported by the patient's uneventful course after stent placement. This case illustrates that chronic gastrointestinal ischemia has to be considered in patients with otherwise unexplained diarrhea.

BACKGROUND

Abdominal artery occlusive disease is not uncommon. It mostly consists of single vessel disease and often remains asymptomatic, due to the presence of abundant abdominal arterial collateral circulation (1). Only in those patients with vascular stenosis and insufficient collateral circulation will clinical ischemia be present. Postprandial pain and weight loss are considered the typical presenting symptoms of patients with chronic gastrointestinal ischemia (CGI). Other less frequent presenting symptoms include exercise related pain (frequency 60%) and diarrhea (frequency 24%) (2). The classical triad of intestinal angina—postprandial pain, weight loss and an upper abdominal bruit—is only seen in a minority of patients (2,3). The diagnostic approach in patients suspected of CGI focuses on identification of an abdominal arterial stenosis and demonstration of gastrointestinal (GI) mucosal ischemia. At our department, the combination of computed tomography angiography (CTA) and 24 hour tonometry (TM) (4) is the established diagnostic approach in patients suspected of CGI.

Steal syndrome is defined as reversed arterial blood flow due to stenotic lesions causing symptoms of ischemia. "Steal syndromes" have been described in several vascular systems. It was first described in 1961 as the "subclavian steal syndrome" by Fisher (5). This vascular disorder causes reversal of the normal direction of blood flow in the vertebral artery due to stenosis or occlusion of the subclavian artery proximal to the vertebral artery origin. The reversed vertebral arterial flow causes cerebral ischemia with associated symptoms. The steal phenomenon is also well known to occur in coronary arteries, leading to myocardial ischemia (6). Aorto-iliac steal syndrome is rare and occurs when a diversion of blood flow from visceral arteries to the lower limbs is caused by occlusive disease (7). Splanchnic–renal steal is manifested by renovascular hypertension (8,9). Additionally, steal phenomenon is a common iatrogenic disorder following liver transplantation (10) or placement of a haemodialysis shunt (11).

Intra-arterial steal has also been described for the abdominal arteries (12-14). In a few cases celiac artery (CA) stenosis resulted in a retrograde filling of the CA from the superior mesenteric artery (SMA) branch collateral vessels. Another example of mesenteric steal phenomenon is diverted blood flow from the inferior mesenteric artery (IMA) to supply the SMA (15). In the present case report we describe a patient with severe diarrhea as an uncommon presenting symptom of CGI suggesting a mesenteric steal phenomenon due to a significant CA stenosis.

CASE PRESENTATION

In 2007, a 79-year-old man was referred to our hospital for evaluation of possible CGI. His extensive medical history revealed hypertension, non-insulin dependent diabetes mellitus, familiar hypercholesterolaemia, a cerebrovascular accident (1992), a right hemicolectomy (1995) because of persistent bleeding from diverticular disease, and a coronary artery bypass graft (1997). He complained of abdominal pain for the last 5 years. During the past 12 months, the abdominal pain had decreased in intensity, but progressive symptoms of diarrhea (up to eight episodes of watery stools a day) led to clinical dehydration and electrolyte disturbances. He reported no postprandial or exercise related pain. His body weight had decreased 5 kg in 3 months (body mass index 24 kg/m^2). Physical examination revealed an upper abdominal bruit and severe peripheral oedema. A colonoscopy, with biopsy sampling, had been performed previously to rule out microscopic colitis.

INVESTIGATIONS

Computed tomographic angiography (CTA) showed a significant (>70%) concentric stenosis of the CA (figure 1A) and a possible non-significant stenosis of the SMA. TM showed severe postprandial jejunal ischemia with postprandial mucosal CO_2 pressure values rising to 15.9 kPa (maximal normal values 10.6–13.6 kPa, varying after different meals) without evident gastric ischemia (figure 2) (4,16).

TREATMENT

These results were discussed in our multidisciplinary CGI team, consisting of a vascular surgeon, an intervention radiologist and a gastroenterologist. The diagnosis of CGI was made and an abdominal angiography with stent placement (Genesis stent 6.0 mmx15 mm, Cordis) in the CA origin was performed (figure 1B). The angiography showed a normal SMA.

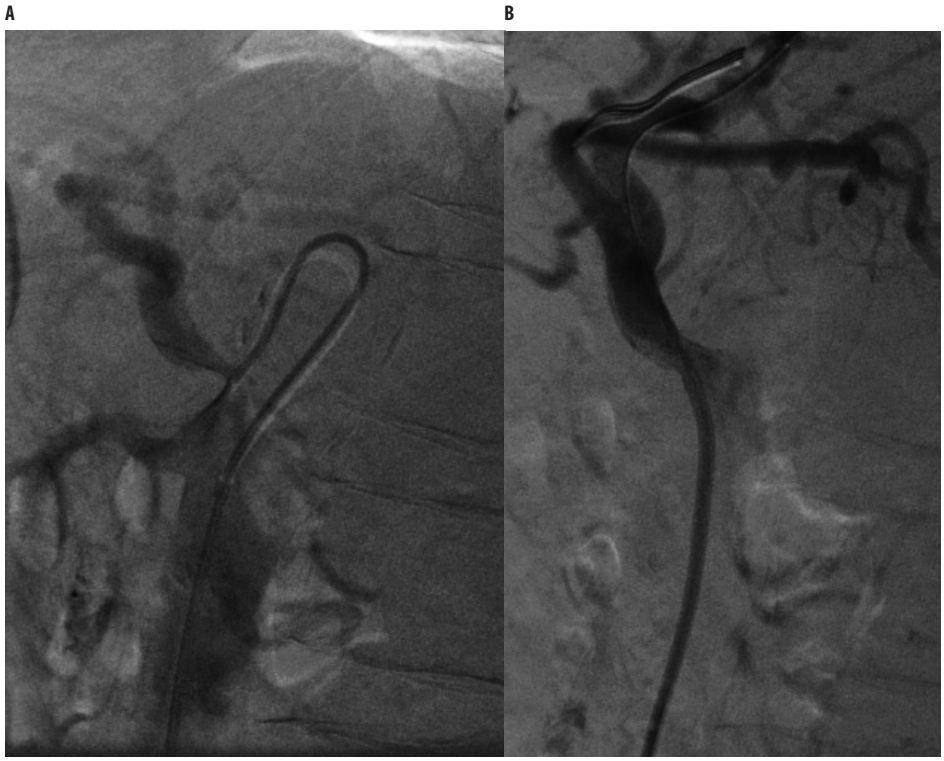

Figure 1. (**A**) Abdominal angiography: selective injection of contrast in the celiac artery, showing a significant atherosclerotic stenosis. (**B**) Abdominal angiography: stent placement in the origin in the celiac artery.

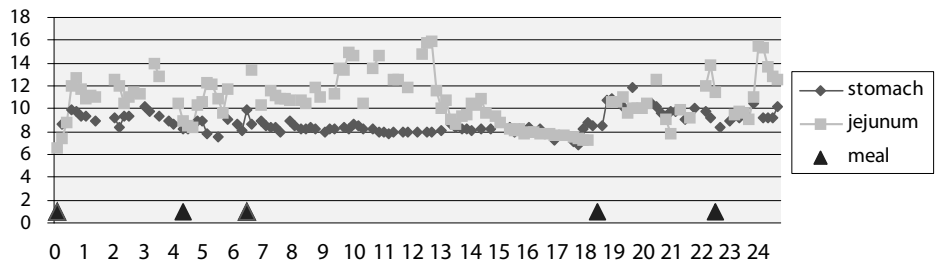

Figure 2. 24 hour tonometry: postprandial jejunal ischemia with repeated pathological postprandial CO_2 peaks rising to 15.9 kPa; normal gastric measurements (no ischemia). Normal values CO_2 maximal 10.6–13.6 kPa varying after different meals. Y axis: CO_2 in kPa. X axis: Time in hours.

OUTCOME AND FOLLOW-UP

The course was uneventful and the patient's complaints had completely resolved within 2 days after the treatment. He remained without complaints until now (15 months follow-up) and regained 3 kg weight.

DISCUSSION

The anatomy of the abdominal arteries varies largely. The common variant is that the CA supplies the stomach, liver and spleen and the SMA supplies the small bowel and proximal part of the colon. The normal anatomy of the gastrointestinal blood supply defines that significant stenoses in the CA and SMA lead to hypoperfusion of, respectively, the stomach–duodenum and the small bowel–proximal colon region. In general, the normally abundant collateral circulation protects against clinical relevant ischemia, but can also give rise to significant arterial shunts, leading to hypoperfusion of anatomically uninvolved areas. Vascular steal syndromes are caused by anatomic configurations in which a stenotic segment proximal to a major arterial bifurcation impedes inflow, leading to reversal of flow in one of the distal branches. This reversed flow pattern can give rise to ischaemic conditions in otherwise anatomically normally vascularised organs. Therefore, selective shunting of blood from a high pressure system to a low pressure system results in clinical ischemia in the area of the organ that donates the blood. That this phenomenon can also occur in the mesenteric system was previously illustrated by a case report of a patient with a splenic artery aneurysm, complicated by arteriovenous fistula formation in which high flow through the central splenic shunt led to small bowel ischemia due to a mesenteric steal syndrome (17). In general, intestinal perfusion is regulated by the local GI arterial–venous pressure gradient. Therefore, homeostatic activity of the GI vascular system will maintain portal pressure and/or hepatic blood flow in case of decreased portal flow (18). In one case perfusion of the colonic mucosa was comprised by portal hypertension. Portal decompression (TIPS shunt) enhanced the blood pressure gradient across the bowel and improved mucosal perfusion (19).

Our patient presented with predominant symptoms of diarrhea and weight loss. CTA showed a significant atherosclerotic stenosis of the CA, which was confirmed on conventional angiography. Tonometry showed normal gastric measurements but evident jejunal ischemia. The presence of jejunal ischemia in our patient with a CA stenosis but normal SMA could be explained by the occurrence of a mesenteric steal phenomenon in which the jejunal blood flow is compromised in favour of collateral gastric and/or hepatic perfusion: blood from the SMA is shunted to the low pressure celiac distribution through the collateral circulation. The stenosis and concomitant steal effect was successfully treated by stent placement, reversing the flow and ending the steal phenomenon. This is supported by the patient's uneventful course after stent placement.

Chronic gastrointestinal ischemia has to be considered in patients with otherwise unexplained diarrhea and a medical history of vascular diseases. This case suggests that, due to a collateral mesenteric steal phenomenon, a stenosis in the celiac artery can lead to small bowel ischemia.

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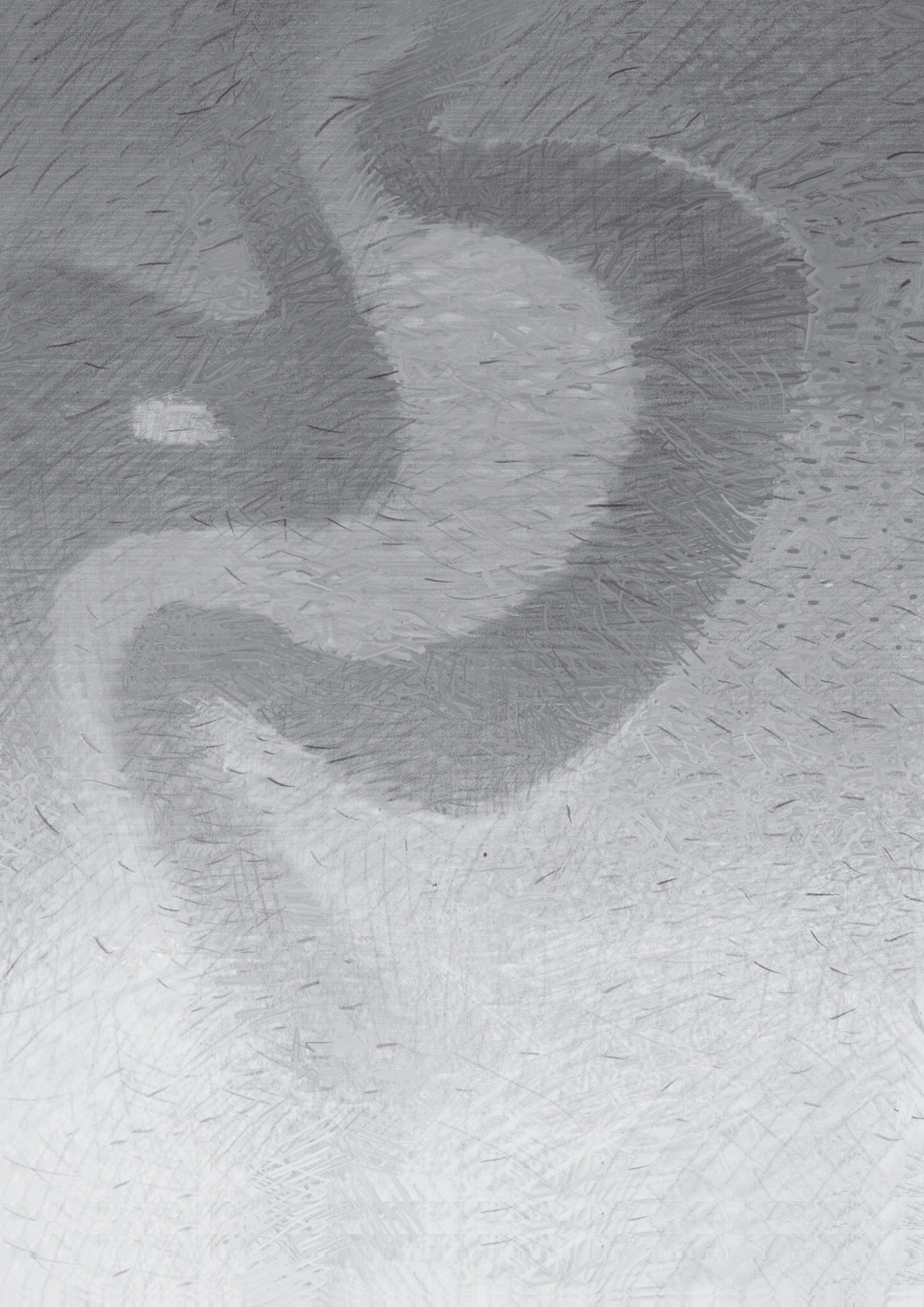

Chapter 9

A giant antral ulceration evoked by a rare cause of single vessel chronic gastrointestinal ischemia

Jan M. Vrolijk[1], Désirée van Noord[1], Hence J.M. Verhagen[2],
Peter M.T. Pattynama[3], Peter B.F. Mensink[1]

Departments of Gastroenterology and Hepatology[1], Vascular Surgery[2], Intervention Radiology[3], Erasmus MC - University Medical Center, Rotterdam, The Netherlands

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INTRODUCTION

The stomach is mainly vascularized by the arteria gastrica sinistra, which branches off the celiac artery (CA). Chronic GI ischemia caused by isolated stenosis of the CA is rare (1). Ulceration of the stomach caused by solitary CA stenosis has been described in only a few case reports (2,3).

Fibromuscular dysplasia has been described as a rare cause of abdominal arterial stenosis (4). Fibromuscular dysplasia of the CA causing gastric ulceration has been presented in only one previous article written in French (5).

CASE REPORT

A 56-year-old man who underwent bilateral lung transplantation 2 years earlier because of familial idiopathic pulmonary fibrosis had slowly progressive postprandial vomiting and upper abdominal pain over the previous 6 months, with significant weight loss. An upper GI endoscopy was performed, showing stasis of gastric contents and a large, circumferential prepyloric ulcer (Fig. 1). Histopathological evaluation of biopsy specimens revealed diffuse active ulceration negative for *Helicobacter pylori* and other infectious causes or systemic inflammatory diseases. Gastric outlet syndrome caused by perioperative damage of the vagal nerve, combined with medication-induced ulceration was suspected. Therefore, all potential ulcerative medications were stopped, and doses of immunosuppressants (steroids, mycophenolate) were tapered. A proton pump inhibitor (omeprazole 40 mg twice daily) was added. Serum gastrin levels were determined shortly after the addition of the proton pump inhibitor and were only slightly elevated at 198 ng/L (normal value _115 ng/L). On follow-up, the patient reported progressive symptoms.

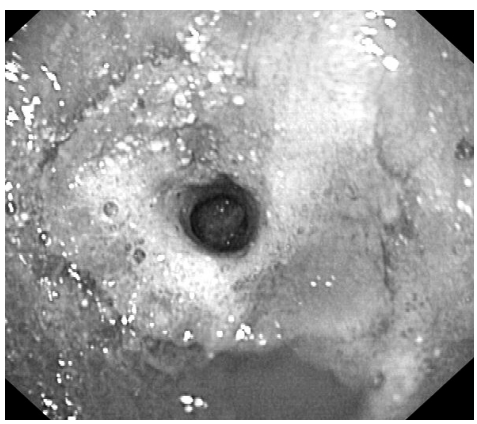

Figure 1. Upper GI endoscopic picture showing circumferential prepyloric ulceration up to the distal corpus.

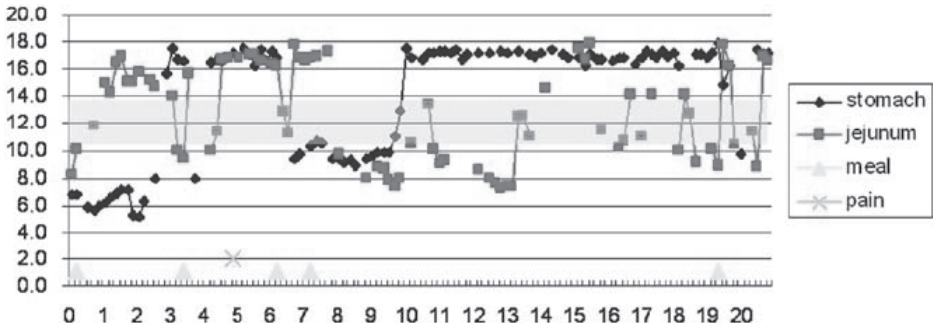

Figure 2. 24 hour tonometry showing gastric and jejunal ischemia with repeated pathological CO_2 peaks rising to 18 kPa (Shaded areas presenting normal values CO_2 maximal 10.6-13.6 kPa varying after different meals). X-axis: Time in hours. Y-axis: CO_2 in kPa.

A repeated upper GI endoscopy showed unchanged findings. To evaluate possible chronic GI ischemia, a multislice CT angiogram was made, which showed a short, 80% diameter stenosis of the proximal CA in the absence of atherosclerosis of the aorta and its side branches. After this finding was made, GI tonometry with measurements of intraluminal partial pressure of carbon dioxide (PCO_2) was performed to determine adequacy of mucosal blood flow (6). Tonometry showed evident pathological peaks of intraluminal CO_2 (Fig. 2). A consensus

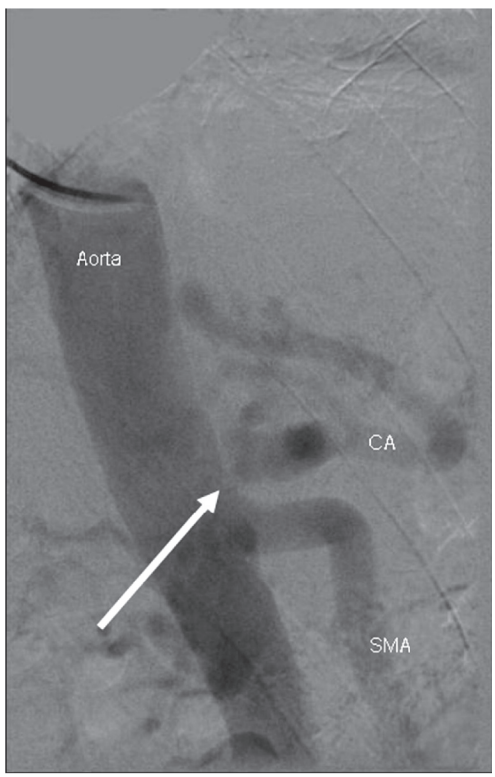

Figure 3. Digital subtraction angiography showing significant celiac artery stenosis (arrow) with web-like appearance suggestive of intimal fibromuscular dysplasia. *CA,* celiac artery; *SMA,* superior mesenteric artery.

diagnosis of chronic GI ischemia caused by CA stenosis was made by our multidisciplinary team, consisting of an intervention radiologist, a vascular surgeon, and a gastroenterologist. Digital subtraction angiography confirmed the stenosis of the origin of the CA, which had the radiological appearance of a web, suggestive for fibromuscular dysplasia (Fig. 3). The stenosis was treated with percutaneous transluminal angioplasty, showing normalization of the CA origin. Our patient reported immediate relief of symptoms afterward, and repeated upper GI endoscopies revealed progressive healing of the lesion (Fig. 4A and B).

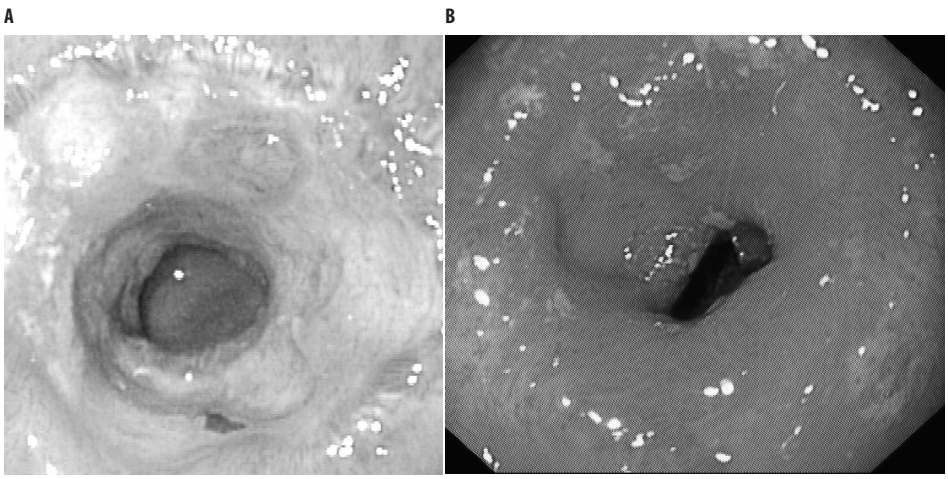

Figure 4. A-B. Upper GI endoscopic pictures showing regression of the antral ulceration within 10 months.

DISCUSSION

We present a unique case of gastric ulceration caused by stenosis of the CA, thought to be caused by web-like structuring of the origin of the CA. Other possible causes of CA stenosis are atherosclerotic disease, vasculitis, and thrombosis, which were all considered less likely because of the presentation, laboratory test findings, and radiological aspect of the CA stenosis in thispatient. Fibromuscular dysplasia is a noninflammatory, nonatherosclerotic angiopathy with unknown etiology leading to narrowing and finally stenosis of mostly single, medium-sized arteries (4). It is a rare disease with an incidence of 1% and a predominance in female patients.

Most commonly involved vessels include the renal (65% of cases), cerebral, subclavian, iliac, and, rarely, the mesenteric arteries. The typical finding of fibromuscular dysplasia is the string-of-beads appearance of the strictures, but single, significant, concentric stenosis can be seen, especially in intimal fibroplasia (4). Clinical manifestations vary from asymptomatic conditions to severe ischemic complications. Digital subtraction angiography is the criterion

standard for evaluating fibromuscular dysplasia, and treatment includes revascularization by either percutaneous transluminal angioplasty or surgical bypass. In our patient, we suspected a cause related to his medical history of lung transplantation or familial idiopathic pulmonary fibrosis. However, a relationship between fibromuscular dysplasia and the transplantation and/or familial idiopathic pulmonary fibrosis could not be found. The typical presenting symptoms, combined with the otherwise unexplained *H Pylori*–negative antral ulceration, led us to perform the proper diagnostics, leading to the presented diagnosis and treatment.

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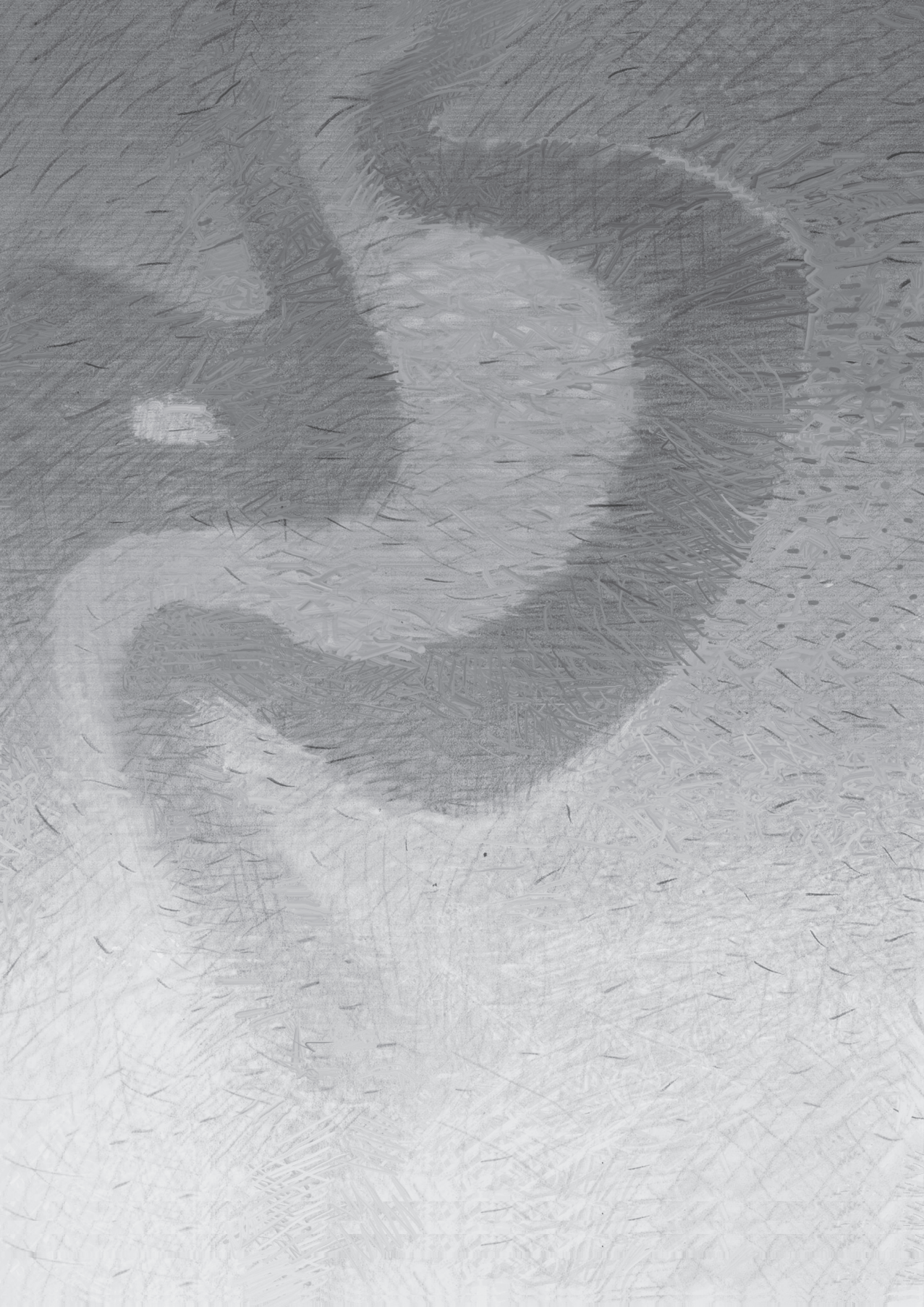

Chapter 10

Summary and General Discussion

The diagnostic approach in patients referred for evaluation of possible chronic gastrointestinal ischemia (CGI) focuses on identification of gastrointestinal arterial stenosis and demonstration of mucosal ischemia. This thesis deals with the diagnosis of CGI which remains a clinical challenge in the daily practice of gastroenterologists, general physicians, and surgeons. Currently, there is no single and simple test with a high sensitivity available.

In **chapter 1** the aims and outline of this thesis are described.

SINGLE VESSEL ABDOMINAL ARTERIAL DISEASE

Chapter 2 addresses the long-standing discussion of the mere existence of single vessel abdominal arterial disease. In the past years, different larger cohort studies have shown that this disease entity exists, can be diagnosed correctly and treated successfully and in a safe manner. The most important celiac artery (CA) stenosis aetiology is extrinsic compression due to the median arcuate ligament (i.e. CACS). Atherosclerosis is the second most common cause of single vessel mesenteric disease. In both asymptomatic and symptomatic patients isolated atherosclerotic stenosis is more common in the CA than in the superior mesenteric artery (SMA). Arterial atherosclerotic disease is the major cause of abdominal arterial stenosis in the elderly patient, while in the younger patient CACS is the most common cause. The clinical symptoms of CGI caused by single vessel abdominal arterial disease are postprandial pain, weight loss, exercise-related pain and are comparable with the complaints of multivessel abdominal arterial disease patients.
Abdominal duplex ultrasound, computed tomography angiography (CTA) and magnetic resonance angiography (MRA) can be used as a screening method to diagnose abdominal arterial stenosis. The classical angiography is still considered the 'gold standard' but especially CTA and MRA are evolving rapidly and improving non-invasive techniques. The established diagnostic approach to detect mucosal ischemia in patients suspected of CGI is gastrointestinal tonometry. The use of gastrointestinal tonometry has improved the detection of actual mucosal ischemia, and is especially of importance in patients with single vessel abdominal arterial stenosis. CA release during open surgical treatment is the established approach for CACS. Recently laparoscopic release of the CA has been introduced, with promising results. First-choice treatment of isolated atherosclerotic abdominal arterial stenosis in a relatively young patient without co-morbidity is surgical revascularisation, especially with the known long-term patency of surgical as compared to endovascular therapy. Endovascular stent placement therapy is advised in elderly patients, in patients with co-morbidity and as 'bridge-to-surgery' in patients with severe weight loss.

DIAGNOSTIC TECHNIQUES

A new, minimally invasive diagnostic approach for patients suspected of CGI is discussed in **chapter 3**. The current established approach includes a combination of duplex ultrasound of the gastrointestinal arteries and gastric exercise tonometry (GET) as a functional test, followed by conventional digital subtraction angiography (DSA) of the gastrointestinal arteries. We challenged the use of 24-hour tonometry (TM) in combination with CTA as an alternative approach to evaluate patients suspected of CGI. Patients referred for evaluation of possible CGI were prospectively evaluated using CTA and TM. All patients were discussed in a multidisciplinary team and a consensus diagnosis was made. Patients diagnosed with CGI were offered therapy by means of revascularization or vasodilating drug therapy. The definitive diagnosis CGI, used as 'the gold standard' was made after persistent symptom relief on follow-up. In 31 months, 186 patients were included. A consensus diagnosis of CGI was made in 128 (69%) patients: 94 (73%) with occlusive and 34 (27%) patients with non-occlusive CGI. Of the 128 CGI patients, 66 (52%) received endovascular treatment, 25 (20%) surgical revascularization, and 25 (20%) vasodilating pharmacotherapy. After a follow-up of ≥ 12 months, 91% of the CGI patients were free of symptoms. None of the patients with a non-CGI consensus diagnosis developed ischemia. Therefore, in patients clinically suspected of CGI, the combination of radiological imaging of the gastrointestinal arteries by CTA and TM provides a minimally invasive, reliable diagnostic approach. This approach seems very useful in clinical practice and seems to have similar outcome as the established diagnostic work-up. This is the first large cohort study describing the results of TM and the diagnostic combination using TM and CT- or MRA in patients suspected of CGI.

In **chapter 4** we proposed visible light spectroscopy (VLS) during upper endoscopy as new diagnostic technique in this particularly difficult patient group, measuring mucosal oxygenation in a resting situation. We studied the diagnostic accuracy of VLS for detection of ischemia in consecutive patients referred for evaluation of possible CGI. All patients underwent VLS next to the standard work-up consisting of evaluation of symptoms, TM and abdominal CT- or MRA. In 16 months, 121 patients were included: 80 in a trainee data set, followed by 41 patients in a validation data set. CGI was diagnosed in 89 (74%) patients. VLS cut-off values were determined based on the diagnosis CGI, and applied in the validation data set and the results compared to the gold standard, resulting in a sensitivity and specificity of VLS of 90% and 60%. Repeated VLS measurements showed improvement in 80% of CGI patients after successful treatment. This is the first large cohort study using VLS for the diagnosis of mucosal ischemia. In conclusion, VLS during upper endoscopy is a promising, minimally invasive technique to detect mucosal hypoxemia in patients clinically suspected for CGI, showing excellent correlation with the established ischemia work-up. The technique is easy to perform, and can be operated in any endoscopy unit. This could lead to a change

in approach in patients clinically suspected for CGI, which is likely to allow more institutions and gastroenterologists to consider and test for this condition.

In **chapter 5** we assessed serum markers as a non-invasive diagnostic in patients clinically suspected of CGI. Consecutive patients suspected of CGI were prospectively enrolled and underwent the standard diagnostic work-up consisting of TM and either CT- or MRA. Blood samples for analysis of intestinal fatty acid binding protein (I-FABP), D-dimer, lactate dehydrogenase (LDH), leucocyte counts, C-reactive protein (CRP), and L-lactate were drawn before and after a standard meal. Forty patients were included. Ischemia was diagnosed in 32 patients (80%). The early serum marker I-FABP and the late serum markers LDH, leucocyte counts, and CRP were not different between patients with and without ischemia, both before and after a test meal. Only L-lactate concentration showed a significant elevation in ischemia patients compared to non-ischemia patients. Furthermore, in ischemia patients postprandial D-dimer levels were significantly higher compared to the fasting state. In conclusion, I-FABP, leucocyte counts, LDH and CRP levels are not clinically useful for the diagnosis of CGI. However, postprandial rises in L-lactate and D-dimer serum levels can serve as non-invasive indicators of CGI. Future studies are necessary to investigate the use of L-lactate and D-dimer levels in the diagnosis of CGI. Furthermore we evaluated small bowel function in ischemia patients in this chapter, as assessed with glutamine, citrulline and arginine and compared to the suger absorption test (SAT), the classical small bowel function test. The levels of glutamine, citrulline and arginine and SAT were within normal range and did not differ between patients with and without ischemia. Therefore intestinal function seems unaffected in ischemia patients.

ENDOSCOPY AND HISTOPATHOLOGY

In **chapter 6** we described the upper endoscopy findings in patients with well-defined CGI. Consecutive patients suspected of CGI were prospectively enrolled and underwent the standard diagnostic work-up consisting of TM and either CT- or MRA, including upper endoscopy. Upper endoscopic findings which were scored using the Paris classification and the Sydney System. In 32 months, 148 patients were included. CGI was diagnosed in 103 (70%) patients, of which 57 (55%) had pathological endoscopic findings, compared to 20 (44%) of the patients without ischemia (p=0.28). Overall, no significant differences in prevalence and character of upper endoscopic findings were found comparing patients with single- versus multiple-vessel CGI patients. Repeated upper endoscopy after initiation of treatment showed improvement of pathological findings in majority of patients. Therefore, normal endoscopic findings on upper endoscopy have a limited negative predictive value for the presence of CGI. But, the presence of otherwise unexplained gastric or duodenal ulcerative lesions, reduced vascularity, and mucosal paleness during upper endoscopy might be related to ischemia, and

therefore CGI should be considered in patients presenting with these endoscopic features. However, the majority of CGI patients did not show these particular endoscopic findings and therefore CGI is often missed using upper endoscopy as sole diagnostic method for this disease entity.

In **chapter 7** we evaluated histopathology findings in patients with well-defined CGI. Consecutive patients suspected of CGI were prospectively included and underwent a diagnostic work-up existing of upper endoscopy, TM and CT- or MRA. Endoscopical biopsy samples were taken from the descending duodenum, gastric antrum and corpus, and scored using the Sydney, Vienna, Chiu, Marsh and OLGA classifications. Gastropathy was scored present or absent. In eight months time, 79 patients were analyzed. CGI was diagnosed in 41 patients (52%). Prevalence of gastropathy was significantly higher in patients with ischemia (p=0.025). No other differences in prevalence and character were found between patients with and without ischemia. In conclusion, histological examination of biopsy samples plays no definitive role in diagnosing CGI, but the presence of histological signs of reactive gastropathy can be used to support the clinical diagnosis of ischemia in a proper clinical setting. This implies that histology of stomach and duodenum is of little aid in the diagnosis of chronic gastrointestinal ischemia. This is in contrast to the well established criteria of lower intestinal ischemia in colonic biopsies, where histological changes vary with the duration and severity of the injury.

RISK FACTORS FOR CARDIOVASCULAR DISEASE

In **chapter 8** we conducted a prospective cohort study with the primary objective to determine whether classical risk factors of cardiovascular disease are associated with atherosclerotic CGI. In addition, we compared the patients with those in whom CGI was not confirmed (non-CGI). Therefore, consecutive patients suspected of CGI were prospectively enrolled and underwent the standard diagnostic work-up consisting of TM and either CT- or MRA. Additionally, an extensive evaluation for atherosclerotic risk factors was performed. Control subjects from the DiaGene Study population served as controls. Between 2006 and 2009 195 patients were evaluated. Atherosclerotic CGI was diagnosed in 69 patients. The prevalence of hypercholesterolemia, the personal and family history of CVD, smoking, use of statins and anti-hypertensive agents were significantly higher in atherosclerotic CGI patients compared with controls. Weight loss was reported in 74% of atherosclerotic CGI patients. Total LDL-cholesterol was lower in ath-CGI vs. controls, this can be explained by higher statin use and substantial weight loss. We did not find relevant differences between CGI and non-CGI patients. The results of our study indicate that CGI due to atherosclerotic stenosis is associated with the classical cardiovascular disease risk factors. These features advocate secondary

prevention therapy in patients with atherosclerotic CGI such as statin use. Future research is needed to observe a positive effect of the secondary prevention therapy in these patients.

PRESENTING SYMPTOMS

Postprandial pain is thought to be the typical presenting symptom for CGI. This pain causes fear of eating, which results in reduced intake and consequent weight loss. However, patients with CGI can also present with less typical symptoms as exercise-related abdominal pain, diarrhea and nausea. The 'classical triad of angine abdominal', i.e. a combination of postprandial pain, loss of weight caused by fear of eating, and an abdominal bruit, is only present in a minority of patients. In **chapter 9** we discussed two examples of uncommon presenting symptoms of patients finally diagnosed with CGI. One patient presented with unexplained diarrhea caused by an atherosclerotic stenosis of the celiac artery due to mesenteric steal phenomenon. The other patient presented with a giant antral ulceration caused by a stenosis of the celiac artery due to fibromuscular dysplasia.

CONCLUSIONS

In conclusion, the outcome of the studies as presented in this thesis, suggest that the approach to patients suspected of CGI, next to evaluation of symptoms and medical history, is the combination of VLS during upper endoscopy to measure mucosal oxygenation and radiological imaging with CTA as first choice technique to evaluate gastrointestinal arterial anatomy. MRA can be used in case of contra-indications for CTA, i.e. contrast allergy or renal function failure. VLS proved to be a minimally invasive technique to detect mucosal hypoxemia in patients clinically suspected for CGI, showing excellent correlation with the ischemia work-up including TM and CTA. The combination of TM and CTA provides a minimally invasive diagnostic approach with similar outcome as the established diagnostic work-up including DSA. By using CTA or MRA as the preferred radiological imaging of the gastrointestinal arteries a diagnostic and invasive DSA can be prevented. Additional diagnostic techniques can give an indication for further evaluation. CGI should be considered in patients presenting with otherwise unexplained gastric or duodenal ulcerative lesions, reduced vascularity, and mucosal paleness during upper endoscopy. These findings may be related to ischemia. However, normal endoscopic findings on upper endoscopy have a limited negative predictive value for the presence of CGI. Histological examination of biopsy samples does not play a significant role in diagnosing CGI, but the presence of histological signs of gastropathy can be used to support the clinical diagnosis of gastrointestinal ischemia. At last, postprandial rises in L-lactate and D-dimer serum levels can serve as non-invasive indicators of CGI.

GENERAL LIMITATIONS AND FUTURE DIRECTIONS

This thesis has several drawbacks. Firstly, a possible drawback of this thesis is the single center setting. The Erasmus MC is a large tertiary care center and one of the two referral centers in The Netherlands with a dedicated CGI working group for patients suspected of CGI. Each of these two centers has a tertiary referral function for a catchment area of approximately eight million people. To increase power and share knowledge, it will be very interesting to cooperate with the other referral center in The Netherlands. These collaboration possibilities can be explored in future.

A limitation of our studies is the possibility that mucosal ischemia is thought to be patchy and could be missed due to sampling error. In case of histological findings, assessment of the entire endoscopic field by taking multiple biopsy specimens throughout the gastric and duodenal mucosa simultaneously for focal areas of ischemia would be preferred, but the limited findings in our histological study show that more extensive biopsy sampling does not strongly increase the yield of specific histological findings in this patient category. Concerning VLS, assessment of the gastroduodenal mucosa by means of a very large number of repeated point measurements in theory increases the diagnostic yield of VLS, this remains to be established in future research. In the current setting with selected small number of measurement points, VLS performed similar to the established diagnostic approach in defining patients with or without mucosal ischemia. Furthermore, the possibility remains that ischemia only occurs in response to increased metabolic demand, such as after a meal or exercise. To evaluate endoscopic findings and assess VLS, all patients were fasting because of the nature of the tests as performed during endoscopy. In theory, in patients with less pronounced blood flow impairment, VLS measurements might show low-normal or even normal mucosal saturation measurements in the resting situation. However, we demonstrate with our findings that VLS can also detect the less pronounced mucosal blood flow reduction in this range. Postprandial VLS measurements, for example in stomach with jejunal feeding, are of great interest and will be considered for further research. This was the first large cohort study using VLS for the diagnosis of mucosal ischemia. It is very important to expand our large cohort study using VLS for the diagnosis of mucosal ischemia. Repeated upper endoscopy is useful to evaluate improvement of endoscopic, including mucosal VLS measurements, and histological pathological findings after treatment. Unfortunately, a repeated upper endoscopy after endovascular or surgical revascularization was not performed in all patients due to the invasive nature of the test. Until now, the treatment options for NOMI patients are limited. NOMI patients are currently treated with a sequence of vasodilating drugs. This treatment has never been investigated prospectively. Therefore, the treatment of NOMI patients will be of great interest for further research. At last, the use of proton pump and platelet aggregation inhibitors, non-steroidal anti-inflammatory drugs, acetylsalicylic acid or biphosphonates may be a confounding factor, as at time of the upper endoscopy most patients were using these

types of medication. At referral, medication use was scored in all patients, however we did not explicitly ask for over the counter use of non-steroidal anti-inflammatory drugs.
Although this thesis was written from a gastroenterologist point of view, we would like to give some suggestions for further radiological research concerning CGI. Future research could focus on portal vein flow measurements by magnetic resonance angiography before and after standard test meals. This might be a very promising non-invasive diagnostic technique. The main advantages of MRA over CTA are its lack of radiation exposure and the possibility to perform flow measurements. MRA measurements have shown a consistent relationship between flow in the portal or superior mesenteric vein and flow in the arteries supplying those veins. The assessment of flow velocities of the portal and superior mesenteric vein before and after oral caloric stimulation seems a promising diagnostic tool for CGI. Furthermore, the long-term efficacy of endovascular therapy is threatened by stent occlusion and displacement. In several series stent dysfunction has been reported in up to one third of cases. Therefore, the long-term patency of the current generation of stents is still inferior to the patency of surgical revascularisation. Drug-coated stents, and / or improved anti-platelet medication or medical regimens, might improve the patency of endovascular stent placement therapy.

SAMENVATTING

De bloedvoorziening van de tractus digestivus wordt verzorgd door drie vaten die ontspringen uit de aorta: de truncus coeliacus (TC), de arteria mesenterica superior (AMS) en de arteria mesenterica inferior (AMI). De TC voorziet de maag, de lever, een deel van de pancreas en het proximale deel van het duodenum van bloed. De AMS voorziet het distale deel van het duodenum, de gehele dunne darm en het proximale deel van het colon. De AMI is relatief klein en voorziet het distale deel van het colon van bloed. De anatomie van deze vaten varieert en een vernauwing (stenose) in deze abdominale arteriën komt regelmatig voor. Door de collaterale circulatie blijft een dergelijke stenose vaak asymptomatisch. Alleen patiënten met een significante arteriële stenose in combinatie met een insufficiënte collaterale circulatie ontwikkelen klinische symptomen van gastrointestinale ischemie. Veelal wordt de diagnose gemist door een gebrek aan sensitieve diagnostiek. De diagnostiek van patiënten met chronische gastrointestinale ischemie (CGI) richt zich op de identificatie van een abdominale arteriële stenose en het aantonen van mucosale ischemie.
In dit proefschrift wordt dieper ingegaan op het correct stellen van de diagnose CGI, wat een klinische uitdaging blijft in de dagelijkse praktijk voor MDL-artsen, internisten en chirurgen. Op dit moment bestaat er geen enkel- en eenvoudig onderzoek met een hoge sensitiviteit voor de correcte diagnose van CGI. In **hoofdstuk 1** worden de doelen en hoofdlijnen van dit proefschrift beschreven.

EÉNVATSLIJDEN

Hoofdstuk 2 gaat in op de langdurige discussie betreffende het bestaan van abdominale arteriële aandoeningen op basis van éénvatslijden. In de afgelopen jaren hebben verschillende cohortstudies met grotere aantallen patiënten aangetoond dat dit ziektebeeld bestaat, correct kan worden gediagnosticeerd en met succes kan worden behandeld. Er kunnen twee verschillende oorzaken van een vernauwing van de TC worden onderscheiden. Ten eerste een stenose ten gevolge van uitwendige compressie, veroorzaakt door het ligamentum arcuatum medianum (celiac artery compression syndrome (CACS)). Atherosclerose is de andere oorzaak van éénvatslijden. In zowel asymptomatische als symptomatische patiënten komt geïsoleerde atherosclerotische stenose meer voor in de TC dan in de AMS. Atherosclerose is de belangrijkste oorzaak van abdominale arteriële stenoses bij de oudere patiënt, terwijl bij de jongere patiënt CACS de meest voorkomende oorzaak is. De klinische symptomen van CGI veroorzaakt door éénvatslijden zijn vergelijkbaar met de klachten van CGI-patiënten met meervatslijden, zoals postprandiale pijn, gewichtsverlies en inspanning gerelateerde pijn. Abdominale echo duplex, computed tomography angiography (CTA) en magnetic resonance angiography (MRA) kunnen worden gebruikt als screening methode om de diagnose abdo-

minale arteriële stenose te stellen. Klassieke angiografie wordt nog steeds beschouwd als 'gouden standaard' maar met name CTA en MRA ontwikkelen zich de laatste jaren snel als niet-invasieve radiologische technieken. De gevestigde diagnostische benadering om mucosale ischemie te detecteren bij patiënten met een verdenking op CGI is gastrointestinale tonometrie. Het gebruik van gastrointestinale tonometrie heeft de detectie van mucosale ischemie verbeterd en is vooral van belang bij patiënten met verdenking op CGI op basis van éénvatslijden. Release van de TC tijdens een open chirurgische behandeling is de gevestigde benadering voor CACS. Recent werd een laparosopische release van de TC geïntroduceerd met veelbelovende resultaten. De eerste keus behandeling van een geïsoleerde atherosclerotische abdominale arteriële stenose bij een relatief jonge patiënt zonder co-morbiditeit is chirurgische revascularisatie, met name met de bekende lange termijn patency van de chirurgische in vergelijking tot de endovasculaire behandeling. Endovasculaire stentplaatsing wordt geadviseerd bij oudere patiënten, patiënten met co-morbiditeit en dient bij patiënten met ernstig gewichtsverlies als 'bridge-to-surgery'.

DIAGNOSTISCHE TECHNIEKEN

In **hoofdstuk 3** wordt een nieuwe minimaal invasieve diagnostische testmethode bij patiënten met een klinische verdenking op CGI besproken. De gebruikelijke diagnostiek bij deze patiënten bestaat uit een echo duplex van de abdominale arteriën gecombineerd met een inspanningstonometrie als functionele test. Bij gevonden afwijkingen wordt de diagnostiek gevolgd door conventionele digitale subtractie angiografie (DSA) van de abdominale arteriën. Recentelijk werden 24 uurs tonometrie (TM) en CTA geïntroduceerd als mogelijke alternatieven voor respectievelijk diagnostiek naar mucosale ischemie en stenoses van de abdominale arteriën. De waarde van de combinatie van deze relatief non-invasieve technieken werd prospectief geëvalueerd in patiënten die werden verwezen met een klinische verdenking op CGI. Alle patiënten werden besproken in een multidisciplinair team waar een consensus diagnose werd gesteld. Patiënten met de diagnose CGI werden behandeld met endovasculaire (stent) of vaatchirurgische revascularisatie, dan wel met vaatverwijdende medicatie. De definitieve diagnose CGI, de 'gouden standaard', werd gesteld indien patiënten na adequate behandeling tijdens langdurige follow-up klachtenvrij bleven. In 31 maanden werden 186 patiënten geïncludeerd. De consensus diagnose CGI werd gesteld bij 128 (69%) patiënten: 94 (73%) met occlusieve en 34 (27%) patiënten met niet-occlusieve CGI. Van de 128 CGI- patiënten kregen 66 (52%) patiënten een endovasculaire behandeling, 25 (20%) patiënten ondergingen een chirurgische revascularisatie en 25 (20%) patiënten werden behandeld met vaatverwijdende medicatie. Na een follow-up van 12 maanden of meer waren 91% van de CGI-patiënten klachtenvrij. Geen van de patiënten met een niet-CGI consensus diagnose ontwikkelde ischemie. Derhalve biedt de combinatie van TM en radiologische

afbeelding van de gastrointestinale arteriën door middel van CTA een minimaal invasieve, betrouwbare diagnostische methode. Deze methode is goed bruikbaar in de praktijk en heeft een vergelijkbaar resultaat als de gevestigde diagnostische work-up. Deze studie is de eerste grote cohortstudie die de resultaten beschrijft van de diagnostische combinatie van TM en CTA bij patiënten met een verdenking op CGI.

In **hoofdstuk 4** wordt visible light spectroscopy (VLS) tijdens gastroduodenoscopie geïntroduceerd als een mogelijk alternatieve diagnostische test in deze moeilijke patiëntenpopulatie. De diagnostische accuratesse van VLS voor de detectie van ischemie werd onderzocht in een cohort met opeenvolgende patiënten verwezen voor de evaluatie van mogelijke CGI. Naast de standaard work-up bestaande uit TM en abdominale CT- of MRA werden VLS metingen verricht tijdens een standaard gastroduodenoscopie. In 16 maanden werden 121 patiënten geïncludeerd: 80 patiënten in een 'trainee data' set, gevolgd door 41 patiënten in een 'validatie data' set. De diagnose CGI werd gesteld bij 89 (74%) patiënten. VLS cut-off waarden werden bepaald op basis van de diagnose CGI, daarna toegepast in de 'validatie data' set en de resultaten werden vergeleken met de gouden standaard, de definitieve diagnose CGI na langdurige follow-up. De VLS metingen toonden een sensitiviteit en specificiteit van VLS van respectievelijk 90% and 60% voor de diagnose CGI. Herhaalde VLS metingen na adequate therapie lieten een verbetering zien bij 80% van de CGI-patiënten. Dit is de eerste grote cohortstudie die gebruik maakt van VLS voor het stellen van de diagnose mucosale ischemie. De toepassing van VLS tijdens gastroduodenoscopie lijkt een veelbelovende, minimaal invasieve techniek om mucosale hypoxie te detecteren bij patiënten die klinisch verdacht worden van CGI, met een uitstekende correlatie met de gevestigde ischemie work-up. De techniek is gemakkelijk uit te voeren en kan in elke endoscopie unit worden toegepast. Dit zou kunnen leiden tot een verandering in de benadering van patiënten die klinisch verdacht worden van CGI en biedt meer ziekenhuizen en MDL-artsen de eenvoudige gelegenheid om dit ziektebeeld te overwegen en te onderzoeken.

In **hoofdstuk 5** zijn serum markers onderzocht als niet-invasieve diagnostische methode voor patiënten met een klinische verdenking op CGI. Opeenvolgende patiënten met een verdenking op CGI werden prospectief geïncludeerd en ondergingen een diagnostische work-up bestaande uit TM en abdominale CT- of MRA. De bloedmonsters voor de analyse van intestinal fatty acid binding protein (I-FABP), D-dimeer, lactaat dehydrogenase (LDH), leucocyten, C-reactive protein (CRP) en L-lactaat werden afgenomen voor en na een standaard testmaaltijd. Er werden 40 patiënten geïncludeerd. De diagnose CGI werd gesteld bij 32 patiënten (80%). De vroege serum marker I-FABP en de late serum markers LDH, leucocyten en CRP verschilden niet tussen patiënten met en zonder CGI, zowel voor als na de testmaaltijd. Alleen de concentratie L-lactaat liet een significante stijging zien in CGI-patiënten in vergelijking tot patiënten zonder CGI. Verder waren de postprandiale D-dimeer waarden in vergelij-

king tot voor de testmaaltijd significant hoger bij de CGI-patiënten. Concluderend zijn I-FABP, leucocyten, LDH en CRP niet bruikbaar in de praktijk voor het stellen van de diagnose CGI. Echter, de postprandiale stijging van L-lactaat en D-dimeer kan dienen als niet-invasieve indicator voor CGI. Toekomstige studies zijn nodig om de relatie tussen het gebruik van L-lactaat en D-dimeer en de diagnose CGI te onderzoeken. Daarnaast hebben we in dit hoofdstuk de dunne darm functie bij patiënten met ischemie geëvalueerd met glutamine, citrulline en arginine en vergeleken met de suiker absorptie test (SAT), de klassieke dunne darm functie test. De waarden van glutamine, citrulline, arginine en SAT blijven binnen de normale range en verschillen niet tussen patiënten met en zonder CGI. Derhalve lijkt de dunne darm functie onaangetast in patiënten met CGI.

ENDOSCOPIE AND HISTOPATHOLOGIE

In **hoofdstuk 6** zijn de bevindingen tijdens de standaard gastroduodenoscopie bij patiënten met CGI beschreven. Opeenvolgende patiënten met een verdenking op CGI werden prospectief geïncludeerd en ondergingen een diagnostische work-up, bestaande uit gastroduodenoscopie, TM en abdominale CT- of MRA. De bevindingen van gastroduodenoscopie werden gescoord met de Paris classificatie en het Sydney Systeem. In 32 maanden werden 148 patiënten geïncludeerd. De diagnose CGI werd gesteld bij 103 (70%) patiënten, waarvan bij 57 (55%) patiënten met ischemie endoscopische pathologie werd geconstateerd, in vergelijking tot 20 (44%) patiënten zonder ischemie (p=0.28). Er werden geen significante verschillen in prevalentie en karakter van de bevindingen bij gastroduodenoscopie gevonden tussen de patiënten met éénvats- versus meervatslijden. Herhaalde gastroduodenoscopie na de start van de behandeling liet een verbetering van de pathologie zien bij de meerderheid van de patiënten. Derhalve hebben normale bevindingen bij gastroduodenoscopie een beperkte negatief voorspellende waarde voor de aanwezigheid van CGI. CGI moet echter wel worden overwogen bij patiënten die zich presenteren met onverklaarbare ulceraties in de maag of het duodenum, verminderd vaatpatroon en/of mucosale bleekheid bij gastroduodenoscopie. Deze bevindingen kunnen gerelateerd zijn aan ischemie. Echter, de meerderheid van CGI-patiënten presenteren zich niet met deze typische endoscopische bevindingen en daarom wordt CGI vaak gemist indien gastroduodenoscopie als enige diagnostische methode voor dit ziektebeeld wordt gebruikt.

In **hoofdstuk 7** zijn de histopathologische bevindingen geëvalueerd bij patiënten met CGI. Opeenvolgende patiënten met een verdenking op CGI werden prospectief geïncludeerd en ondergingen een diagnostische work-up, inclusief gastroduodenoscopie, TM en abdominale CT- of MRA. Standaard biopten werden genomen in het duodenum descendens, antrum en corpus en de histopathologische bevindingen, inclusief de aan- of afwezigheid van

gastropathie, werden gescoord met de Sydney, Vienna, Chiu, Marsh and OLGA classificaties. In acht maanden tijd werden 79 patiënten geïncludeerd en geanalyseerd. De diagnose CGI werd gesteld bij 41 (52%) patiënten. De prevalentie van gastropathie was significant hoger bij patiënten met ischemie (p=0.025). Er werd geen significant verschil gevonden in de prevalentie en karakter van de resterende classificaties. Histologisch onderzoek van biopten lijkt dus geen definitieve rol te spelen bij de diagnostiek van CGI. Tekenen van anderszins onverklaarde gastropathie kunnen de diagnose CGI ondersteunen in een typische klinische setting. Al met al lijkt aanvullend histologisch onderzoek van de maag en het duodenum weinig bij te dragen aan de diagnose CGI, dit in tegenstelling tot de goed gedefinieerde criteria van ischemie voor biopten van het colon (ischemische colitis), waar de histologische afwijkingen variëren met de duur en de ernst van de aandoening.

RISICOFACTOREN VOOR HART- EN VAATZIEKTEN

In **hoofdstuk 8** is een prospectieve cohortstudie opgezet om te bepalen of de klassieke risicofactoren voor hart- en vaatziekten zijn geassocieerd met atherosclerotische CGI. Opeenvolgende patiënten met de verdenking op CGI werden prospectief geïncludeerd en ondergingen een diagnostische work-up, bestaande uit TM en abdominale CT- of MRA. Vervolgens werden de risicofactoren voor atherosclerose uitgebreid geëvalueerd. Controle proefpersonen werden verkregen uit de DiaGene Study populatie, bestaande uit proefpersonen zonder diabetes of klassieke risicofactoren voor cardiovasculaire aandoeningen. Tussen 2006 en 2009 werden 195 patiënten geïncludeerd. De diagnose atherosclerotische CGI werd bij 69 patiënten gesteld. De prevalentie van hypercholesterolemie, de persoonlijke en familiaire cardiovasculaire voorgeschiedenis, roken, statine gebruik en het gebruik van antihypertensiva waren significant hoger bij de atherosclerotische CGI-patiënten in vergelijking met de controles. Gewichtsverlies werd gerapporteerd door 74% van de atherosclerotische CGI-patiënten. Het totale LDL-cholesterol was lager bij atherosclotische CGI-patiënten versus de controle proefpersonen. Een mogelijke verklaring voor dit verschil zijn het hogere gebruik van statines en het gewichtsverlies bij de ischemie patienten. Er waren geen relevante verschillen tussen patiënten met en zonder CGI. De resultaten van dit onderzoek impliceren dat de atherosclerotische vaatafwijkingen in CGI-patiënten zijn geassocieerd met de klassieke risicofactoren voor hart- en vaatziekten. Deze uitkomsten pleiten voor secundaire preventie bij patiënten met atherosclerotische CGI, zoals het gebruik van statines. Verder onderzoek is nodig om het effect van deze secundaire preventie te observeren.

SYMPTOMEN

Postprandiale pijn is het meest voorkomende symptoom van CGI. Deze pijn veroorzaakt angst voor eten, resulterend in verminderde intake en daaruit volgend gewichtsverlies. Echter, patiënten met CGI kunnen zich ook presenteren met minder typische symptomen zoals inspanning gerelateerde pijn, diarree en misselijkheid. De klassieke trias van "angine abdominale", de combinatie van postprandiale pijn, gewichtsverlies en een abdominale souffle is slechts aanwezig in een minderheid van patiënten. In **hoofdstuk 9** worden twee voorbeelden van minder vaak voorkomende symptomen besproken van patiënten die uiteindelijk gediagnosticeerd zijn met CGI. Eén patiënt presenteerde zich met onverklaarbare diarree veroorzaakt door een atherosclerotische stenose van de TC als gevolg van het mesenteric steal phenomenon. De andere patiënt presenteerde zich met een uitgebreide ulceratie in het antrum, veroorzaakt door een stenose van de TC als gevolg van fibromusculaire dysplasie.

CONCLUSIE

Het minimaal invasieve karakter en eenvoudigheid van de VLS metingen maken deze diagnostische methode zeer geschikt als alternatief voor de meer invasieve en ingewikkelde gastrointestinale tonometrie meting. De CTA, met als alternatief bij contra-indicaties de MRA, lijkt voldoende sensitief als screenend onderzoek voor abdominale arteriële stenoses bij patiënten die klinisch verdacht worden van CGI. Op deze manier kan in een groot aantal patiënten een diagnostische DSA achterwege blijven. Anderszins onverklaarde ulceraties in de maag en/of het duodenum, een verminderd vaatpatroon en/of mucosale bleekheid bij gastroduodenoscopie kunnen gerelateerd zijn aan CGI. Echter, normale bevindingen bij gastroduodenoscopie hebben een beperkte negatief voorspellende waarde voor de diagnose CGI, met andere woorden: normale bevindingen tijdens gastroduodenoscopie sluiten CGI niet uit. Histopathologisch onderzoek van biopten lijkt geen significante rol te spelen bij het diagnosticeren van CGI, maar histologische tekenen van gastropathie kunnen wel worden gebruikt om de klinische diagnose van gastrointestinale ischemie te ondersteunen. Tenslotte kan een postprandiale stijging van serum L-lactaat en D-dimeer waarden dienen als non-invasieve indicator voor CGI.

ABBREVIATIONS

BMI	Body mass index
CA	Celiac artery
CACS	Celiac artery compression syndrome
CGI	Chronic gastrointestinal ischemia
CRP	C-reactive protein
CTA	Computed tomography angiography
CVD	Cardiovascular disease
DSA	Digital subtraction angiography
GET	Gastric exercise tonometry
H. pylori	*Helicobacter pylori*
I-FABP	Intestinal fatty acid binding protein
IMA	Inferior mesenteric artery
LDH	Lactate dehydrogenase
MRA	Magnetic resonance angiography
NOMI	Non-occlusive mesenteric ischemia
PTA	Percutaneous transluminal angioplasty
PVD	Peripheral vascular disease
SAT	Sugar absorption test
SMA	Superior mesenteric artery
TM	24-hour gastrointestinal tonometry
VLS	Visible light spectroscopy

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PhD PORTFOLIO

Oral Presentations

CT angiography and 24 hour tonometry: a novel and useful approach in the diagnosis of chronic gastrointestinal ischemia
Dutch Society of Gastroenterology, Veldhoven, the Netherlands 2008

Additional value of jejunal measurements during 24 hour tonometry in patients suspected of chronic gastrointestinal ischemia
Dutch Society of Gastroenterology, Veldhoven, the Netherlands 2008

Endoscopic visible light spectroscopy: a new minimally invasive technique for the diagnosis of chronic gastrointestinal ischemia
Dutch Society of Gastroenterology, Veldhoven, the Netherlands 2009

Poster Presentations

CT angiography and 24 hour tonometry: a novel and useful approach in the diagnosis of chronic gastrointestinal ischemia
Digestive Disease Week, San Diego, USA 2008
United European Gastroenterology Week, Wien, Austria 2008

Additional value of jejunal measurements during 24 hour tonometry in patients suspected of chronic gastrointestinal ischemia
Digestive Disease Week, Chicago, USA 2009

Endoscopic visible light spectroscopy: a new minimally invasive technique for the diagnosis of chronic gastrointestinal ischemia
Digestive Disease Week, Chicago, USA 2009
United European Gastroenterology Week, London, England 2009 (Best Poster Award)

Upper endoscopic findings in patients with chronic gastrointestinal ischemia
Digestive Disease Week, Chicago, USA 2009

Serum markers and intestinal mucosal injury in chronic gastrointestinal ischemia
Digestive Disease Week, New Orleans, USA 2010

Membership

2008 Dutch Society of Gastroenterology

Grant allocation

2008 Gastrostart, Dutch Society of Gastroenterology € 7.500
Early markers of chronic gastrointestinal ischemia

Courses

Introduction to clinical research – NIHES, Erasmus MC, Rotterdam, the Netherlands
Biostatistics for clinicians – NIHES, Erasmus MC, Rotterdam, the Netherlands
English presentation course – Erasmus MC, Rotterdam, the Netherlands

Tutoring

Supervising medical students in extracurricular research activities

DANKWOORD

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Désirée

CURRICULUM VITAE

Désirée van Noord werd geboren op 10 februari 1979 te Rotterdam. In 1997 behaalde zij haar eindexamen aan het Erasmiaans Gymnasium te Rotterdam. In afwachting van de studie geneeskunde, waarvoor zij 5 keer werd uitgeloot, studeerde zij Nederlands Recht en de studie Recht, Bestuur & Management aan de Universiteit Utrecht. Na de decentrale selectie startte zij in 2001 de studie geneeskunde aan de Erasmus Universiteit Rotterdam en na een oudste co-schap op de afdeling Maag-, darm- en leverziekten van het Sint Franciscus Gasthuis te Rotterdam werd in 2007 het arts-examen behaald. In oktober 2007 startte zij met onderzoek naar chronische gastrointestinale ischemie op de afdeling Maag-, darm- en leverziekten van het Erasmus MC te Rotterdam onder begeleiding van Prof.dr. E.J. Kuipers en Dr. P.B.F. Mensink. In september 2009 is zij begonnen met de opleiding tot Maag-, darm- en leverarts (opleider Dr. R.A. de Man). De vooropleiding interne geneeskunde wordt thans gevolgd in het IJsselland Ziekenhuis te Capelle a/d IJssel (opleider Dr. H.E. van der Wiel).