CHRONIC MESENTERIC ISCHEMIA IN THE PICTURE

NEW DIAGNOSTIC TECHNIQUES AND TREATMENT MODALITIES

LOUISA J.D. VAN DIJK

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new diagnostic techniques and treatment modalities

Louisa Josina Dorothea van Dijk

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nieuwe diagnostische technieken en behandelingsmodaliteiten

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CHAPTER
1.1

General introduction

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DEFINITION

Chronic mesenteric ischemia (CMI) is defined as insufficient blood supply to the gastro-intestinal (GI) tract causing ischemic symptoms with a duration of at least 3 months according the latest guidelines (1). CMI requires timely diagnosis and treatment to prevent the development of acute mesenteric ischemia, which is associated with high morbidity and mortality. CMI is a diagnosis that is difficult to establish as symptoms are highly variable and diagnostic tests may be inconclusive.

EPIDEMIOLOGY

The exact incidence of CMI in the general population is unknown, since population based incidence studies are lacking. However, the number of revascularization procedures for CMI is increasing. Data from the National (Nationwide) Inpatient Sample (NIS) database showed a total of 14,897 revascularization procedures performed for CMI between 2000 and 2012 in the United States of America (USA)(2). The number of patients undergoing revascularization for CMI was significantly increased from 1.8 per million in 2000 to 5.6 per million in 2012 ($p<0.01$)(2). The increase in revascularization procedures for CMI does not necessarily reflect an increase in the prevalence of CMI but may be a sign of increased recognition of this disease entity and/or the increase of minimally invasive treatment options.

ANATOMY

Three mesenteric arteries provide blood supply to the intestines: the celiac artery (CA), superior mesenteric artery (SMA) and inferior mesenteric artery (IMA) (Image 1 and Image 2). The CA supplies blood to the stomach, liver, part of the pancreas and the proximal duodenum, whereas the SMA supplies blood to the distal duodenum, small bowel and the proximal colon and the IMA provides the blood supply to the distal colon. The anatomy of the mesenteric arteries shows some inter-individual variability(3) but there is always an abundant collateral network between these arteries. The CA and SMA are anastomosed by the pancreaticoduodenal arteries named after their describers Rio Branco and Bühler(4). The SMA and IMA are proximally connected by the arcade of Riolan and the arcade of Villemin and more distal by the arcade of Drummond. The most distal end of the mesenteric arteries are the superior rectal arteries which originate from the internal iliac arteries via the middle rectal arteries.

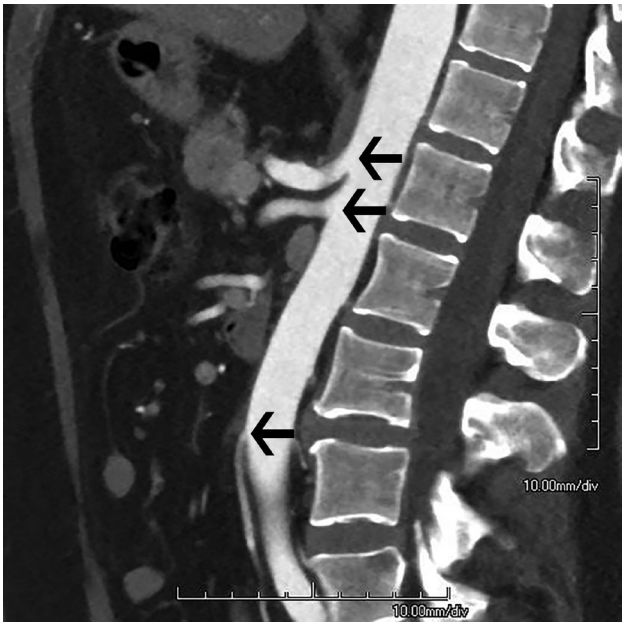

Image 1. CTA image in sagittal plane visualizing normal anatomy of the CA, SMA and IMA (top-down, respectively).

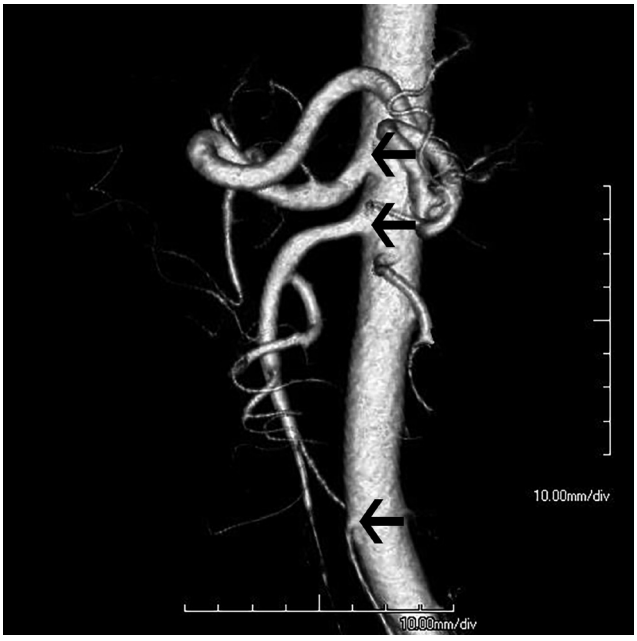

Image 2. 3D CTA image visualizing normal anatomy of the CA, SMA and IMA (top-down, respectively).

ETIOLOGY

Atherosclerotic stenosis of one or more mesenteric arteries is causing CMI in >90% of the cases(5). Less frequently, CMI is caused by vasculitis. Asymptomatic mesenteric stenoses are common in the general population and prevalence increases with age. The reported prevalence of asymptomatic CA and/or SMA stenosis is 3% in patients under 65 years and 18% in patients older than 65 years(6). Multi-vessel mesenteric stenoses causing CMI is a well-accepted conception, whereas insufficient blood supply caused by isolated mesenteric stenosis is thought to be limited because of abundant collaterals. If the collateral circulation is insufficient, however, revascularization of a single-vessel stenosis will result in symptom relief(7-10). The most common cause of isolated CA stenosis is median arcuate ligament syndrome (MALS): anatomical eccentric compression of the CA and/or celiac ganglion by the median arcuate ligament (MAL) and diaphragmatic crura(11). The degree of stenosis caused by the MAL depends on the respiratory cycle. The MAL moves caudally during inspiration, releasing the compression on the CA and increasing compression during expiration (Image 3). Also, compression that only occurs during inspiration may be observed as well. Characteristics of patients with CMI differ depending on the underlying cause being MALS or atherosclerosis(Table 1)(12-18).

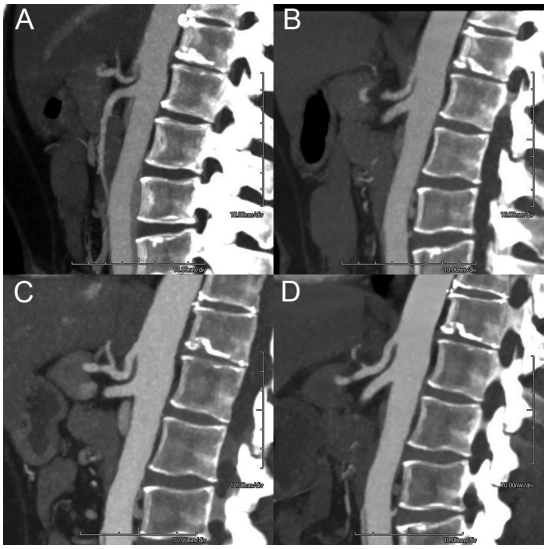

Image 3. A 48-year-old woman presented with postprandial abdominal pain and 10 kg weight loss. CTA showed compression of the CA, with increased compression in expiration (panel A) and less compression in inspiration (panel B). Patient was planned for surgical release of CA. After successful release, patient had gained weight 5 kg and was symptom free. CTA 11 months after surgery showed an open CA (panel C expiration and D inpiration).

Table 1. Reported prevalence of characteristics of patients with atherosclerotic CMI versus patients with CMI based on MALS.

	Atherosclerotic CMI(12)	MALS(13-18)
Mean age (years)	69	37-54
Female	62%	69-78%
Smoking	66%	33-63%
Hypertension	64%	33%
Hyperlipidemia	41%	13%
CVD	54%	6%

CMI =chronic mesenteric ischemia; CVD = cardiovascular disease; MALS = median arcuate ligament syndrome.

Chronic non-occlusive ischemia (NOMI) or ‘‘migraine abdominale’’(19) is characterized by symptoms of CMI in the absence of a vascular stenosis and is diagnosed in up to 13–16% of all CMI patients(10). Several pathophysiological mechanisms causing chronic NOMI have been suggested: underlying conditions such as cardiac and pulmonary insufficiency, shunts, occlusion of smaller mesenteric arteries due to spasms or micro-emboli, and autonomic dysfunction. Therapy is directed towards amelioration of adverse effects caused by the underlying pathophysiological mechanism. Vasodilating drugs are applied in case of autonomic dysfunction and optimization of oxygen supply to the GI tract is applied in case of underlying cardiac or pulmonary disease. Successful treatment of these patients, however, is challenging because the etiology of chronic NOMI is not fully unraveled yet.

CLINICAL PRESENTATION

Typical CMI symptoms are postprandial abdominal pain with food aversion and weight loss. The abdominal pain is classically located in the mid-abdomen or epigastrium and usually starts 20–30 minutes after a meal and lasts 1–2 hours. Atypical symptoms are constant abdominal discomfort, nausea, vomiting, diarrhea or constipation(1). Abdominal bruit may be present during physical examination; however, the ‘‘classic CMI triad’’ of postprandial abdominal pain, weight loss and abdominal bruit is only present in 16–22% of CMI patients(8, 20).

DIAGNOSIS

In the absence of a golden standard test, the diagnosis of CMI is established by consensus in a multidisciplinary meeting attended by vascular surgeons, gastroenterologists and (interventional) radiologists(1, 21). The consensus diagnosis is based on clinical symptoms, radiological evaluation of the mesenteric vasculature and if available, functional assessment of mucosal ischemia(22-24). The value of symptoms alone is limited for the prediction of the diagnosis of CMI(20, 25, 26).

Computed tomography angiography (CTA) is the primary imaging modality in patients with a moderate or high suspicion of CMI to assess the mesenteric arteries and to detect other intra-abdominal pathology according the European Society of Vascular Surgery (ESVS) guidelines(1). CTA depicts various atherosclerotic plaque components such as soft plaque and calcifications with a sensitivity for mesenteric artery stenosis of 100% and a specificity of 95%(27). Current magnetic resonance angiography (MRA) techniques do not seem as accurate as CTA, especially for the IMA and smaller branch vessels(28). When CTA is not feasible, i.e. in the presence of contrast allergy or renal insufficiency, MRA can be used as an alternative imaging modality according the American College of Radiology (ACR) guidelines(29). Duplex ultrasound (DUS) can be used as first screening imaging modality to identify a mesenteric artery stenosis. DUS identifies a ≥70% CA stenosis with a sensitivity of 72-100% and a specificity of 77-90% and a ≥70% SMA stenosis with a sensitivity of 72-100% and a specificity of 84-98%(30, 31). However, DUS is operator dependent, technically challenging and the flow velocities of the evaluated artery could be influenced by respiration, the presence of concomitant stenosis in other mesenteric vessels, and existing stents. Digital subtraction angiography (DSA) is reserved for treatment of occlusive mesenteric artery disease and is replaced by CTA as diagnostic modality. Plain abdominal X-ray has no role in the diagnosis of CMI.

Dynamic imaging is important to detect a CA stenosis caused by MALS since the grade of stenosis varies with respiration in contrast to atherosclerotic stenosis. CTA, MRA, DUS or DSA during both inspiration as expiration phases are sufficient.

A functional test to prove actual GI ischemia is needed since the prevalence in the asymptomatic general population is high and symptoms of CMI are largely overlapping with many other disorders. Visible light spectroscopy (VLS) performed during upper endoscopy allows measurement of the oxygen saturation of the upper GI mucosa

using a fiber-optic catheter passed through the accessory channel of the endoscope connected to the VLS oximeter (T-Stat 303 Microvascular Oximeter; Spectros, Portola Valley, California, see Image 4)(32). The sensitivity of VLS-measurements for the diagnosis of CMI is 90% and the specificity is 60% if mucosal oxygen saturation cut-off values of <63% in the antrum of the stomach, <62% in the duodenal bulb and <58% in the descending duodenum are used(33). Since VLS is relatively new, validation studies have to be performed.

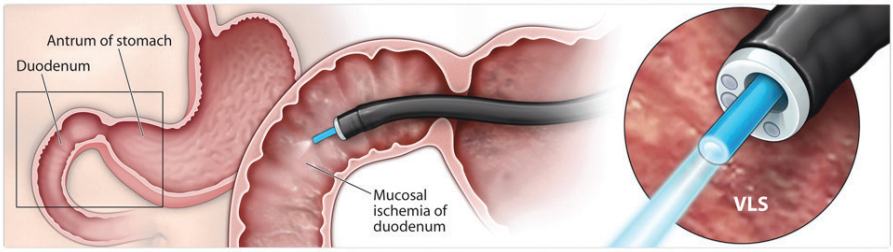

Image 4. Visible light spectroscopy (VLS) performed during upper endoscopy measures the mucosal oxygen saturation.

Tonometry is another functional test that measures luminal pressure of carbon dioxide (PCO_2) by a nasogastric and nasojejunal catheter attached to a capnography (Tonocap©). Luminal PCO_2 increases during mesenteric ischemia. Exercise tonometry is performed during a bicycle test (sensitivity 78%, specificity 92%(10)) and 24-hours tonometry is performed using test meals as provocation of ischemia (sensitivity 76%, specificity 94%(24)).

A functional test is not needed in the work-up of the most common CMI suspected patients with typical symptoms and multi-vessel disease (Figure 1). However, especially in the work-up of single vessel disease a functional test is a prerequisite. It is therefore recommended to refer these patients to a specialized center to undergo functional testing. Research is in progress to develop simple and reliable functional tests that can be widely applied.

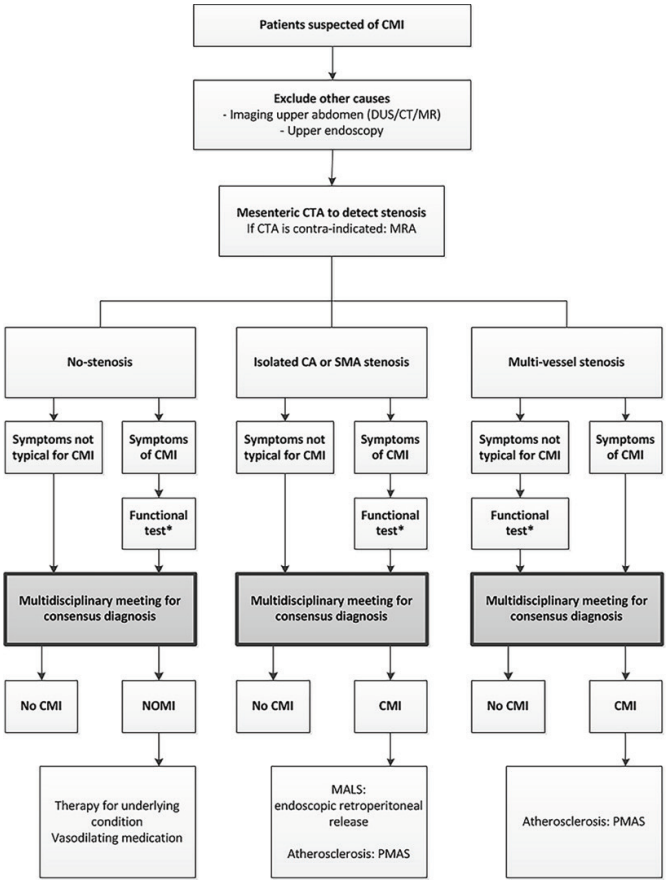

Figure 1. Algorithm for clinical management of CMI.
* refer for functional test. Suitable functional tests are upper GI endoscopy with visible light spectroscopy (VLS) or gastric-jejunal tonometry (24-hours tonometry or exercise tonometry). CA = celiac artery; CMI = chronic mesenteric ischemia; CT = computed tomography; CTA = computed tomography angiography; DUS = duplex ultrasound; MR = magnetic resonance; MRA = magnetic resonance angiography; NOMI = non-occlusive mesenteric ischemia; PMAS = percutaneous mesenteric artery stenting; SMA = superior mesenteric artery.

Laboratory tests such as leucocytes, D-dimer, lactate and C-reactive protein are not useful for detection of CMI(1, 34, 35). Since CMI is a state of transient ischemia episodes induced by eating, fasted marker levels are presumably not sufficient to indicate CMI. In a study in which several serum markers before and after a meal were determined in patients suspected of CMI, a significant increase of D-dimer was reported in 32 CMI patients after a meal in contrast with 8 patients without CMI(34). Another study in 49 CMI suspected patients reported a significant increase in intestinal fatty-acid

binding protein (I-FABP) levels in patients with positive tonometry results after a meal in contrast with patients with normal response after a meal(35). Further research and larger studies are needed to potentially identify a sensitive and specific biomarker for detecting CMI.

In contrast to a diagnosis of acute ischemic colitis, endoscopic assessment of the mucosa by visual appraisal or taking biopsies plays no crucial role in detecting CMI. In CMI patients atrophy of the duodenal mucosa and non-Helicobacter pylori/non-nonsteroidal anti-inflammatory drug gastric or duodenal ulcers are observed in a minority of cases(25). Pathology seen in CMI patients during upper GI endoscopy is shown in Image 5. Histological examination of biopsy samples are not discriminative for the diagnosis of CMI(36). Nevertheless, upper endoscopy remains indicated in CMI suspected patients to exclude alternative diagnoses, such as peptic ulcer.

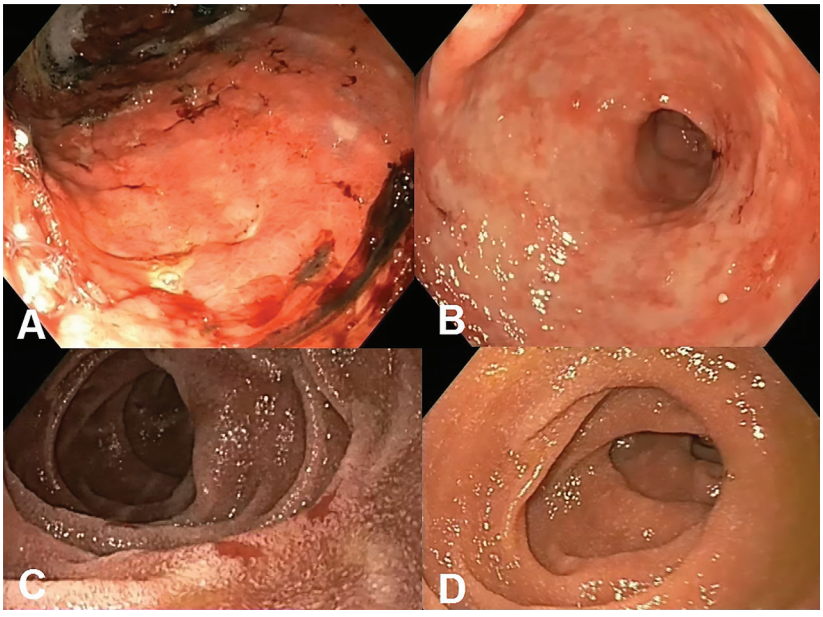

Image 5. Pathology seen in CMI patients during upper GI endoscopy. A. Ischemic ulceration in the stomach, B. patchy whitening of the gastric mucosa, C. duodenual whiteness typical on the top of the duodenal folds and D. upper GI endoscopy in the same patient as C but after successful revascularization shows normal duodenal mucosa.

Multi-vessel stenoses and classic symptoms will lead to a straightforward diagnosis of CMI. In case of single-vessel disease, careful investigation for alternative causes is warranted(1). Exclusion of other etiologies by imaging of the upper abdomen (DUS/

CT/MR) for gallstones and pancreatitis and upper endoscopy in patients suspected of CMI is important to prevent overtreatment (Figure 1). When a consensus diagnosis of occlusive CMI is established in the multidisciplinary meeting, patients are planned for revascularization therapy. A definitive diagnosis of CMI is proven when technically successful treatment results in durable symptom relief.

THERAPY

Revascularization is indicated in patients with occlusive CMI to relief symptoms, improve quality of life, restore normal weight and to improve survival by preventing bowel infarction (acute-on-chronic mesenteric ischemia)(1). The challenge is to select the patient with mesenteric stenosis who will benefit from treatment. Revascularization is accepted in case of symptomatic multi-vessel stenosis (Image 6). Since the presence of the mesenteric collateral circulation is assumed to prevent single-vessel CMI, revascularization is up for discussion in case of single-vessel stenosis (Image 3 and Image 7).

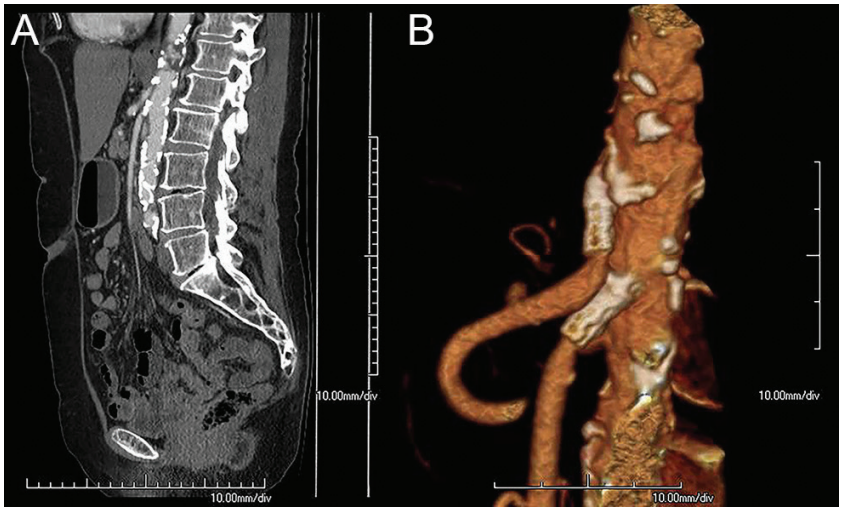

Image 6. A 69-year-old woman presented with postprandial abdominal pain and 10 kg weight loss since three months. A significant stenosis of the CA and SMA was shown on CTA (panel A). A consensus diagnosis of multi-vessel CMI was established and patient was plannend for endovascular revascularization. The CA and SMA were successfully stented. CTA 6 months after revascularization showed open stents (panel B) and the patient was free of symptoms and her weight was increased by 12 kg.

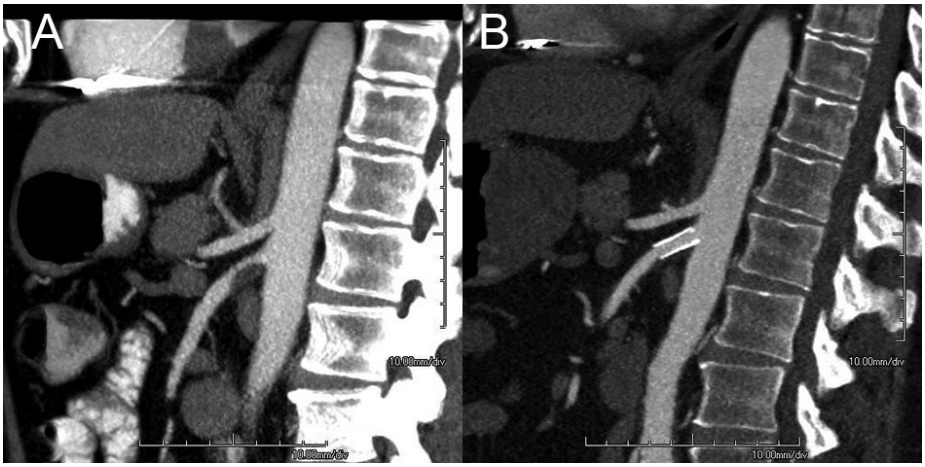

Image 7. A 50-years-old man presented with postprandial abdominal pain and 13 kg weight loss. CTA showed a significant stenosis of the SMA and <50% CA stenosis (panel A). His mucosal saturation levels were decreased as detected by visible light spectroscopy. A consensus diagnosis of single-vessel CMI was established and patient was planned for stent placement of the SMA. CTA 6 months after revascularization showed an open SMA stent (panel B). The patient was free of symptoms and his weight was increased by 7 kg.

Open surgical revascularization has been the standard therapy modality for years. However, endovascular revascularization is less invasive and has become the therapy of choice in most centers over the past two decades(1-3). The number of endovascular procedures performed for CMI in the USA has increased significantly from 0.6 in 2000 to 4.5 per million persons in 2012 ($p<0.01$)(35).

Prospective studies comparing percutaneous transluminal angioplasty (PTA) alone with primary stenting are lacking. However, in parallel to renal artery stenosis and the advantage of stent placement over PTA in this patient group, endovascular therapy for mesenteric stenosis consists of stent placement according the ESVS and Society of Interventional Radiology (SIR) guidelines(1, 3). Mesenteric stenoses are usually located at the ostium and are therefore prone to recoil after PTA(3, 36, 37). The endovascular approach for percutaneous mesenteric artery stenting (PMAS) is trans-brachial access (TBA) or trans-femoral access (TFA), however trans-radial approach (TRA) showed a decrease in major access-site complications with similar procedural and clinical outcomes in interventional cardiology. Current guidelines do not issue recommendations on TRA for PMAS since literature on TRA specific for mesenteric artery procedures is lacking(31). Bare-metal stents are standard care but retrospective

data have reported better primary patency rates when using covered stents(39). Outcome of a randomized multicenter clinical trial (the study protocol is described in **Chapter 8**) is currently awaited to confirm the superiority of covered stents for PMAS.

Open surgical revascularization can be considered if endovascular approach has failed, if endovascular revascularization is technically not possible due to extensive occlusion and calcification, contra-indications to radiation or contrast media, or if revascularization is needed in young patients with complex non-atherosclerotic lesions caused by vasculitis or mid-aortic syndrome(1). Open surgical revascularization can be performed antegrade (from the supraceliac aorta), or retrograde (from the iliac artery), or hybrid with open access to the SMA and retrograde stenting. Autogenously revascularization techniques are first choice but a prosthetic conduit can be used as bypass for one or more vessels as well. This thesis focuses on endovascular revascularization and not on open surgical revascularization.

Overall technical success rates of endovascular mesenteric revascularization varied from 85-100% versus technical success rates of surgical revascularization of 97-100%(3, 6, 40). Relative contraindications for endovascular revascularization associated with lower technical success rate and/or increased procedural complications are highly tortuous aorta-iliac arteries, long-segment occlusion, small-diameter distal vessels and heavily calcified stenosis(3). It should be emphasized that ostial occlusion does not exclude PMAS. In a study of 185 CA and SMA vessels treated with PMAS, 21% of the revascularized vessels (9 CA and 30 SMA) were occluded prior to PMAS(41).

Reported complication rates of surgical revascularization in CMI patients are 13-40%(24, 42) and reported endovascular complication rates are between 0-31% (Table 2)(2, 3). In 4-38% of the cases the complication of the endovascular intervention is access-site related, whereby access-site hematomas are most reported(3, 12).

The therapy for MALS consists of surgical release of the MAL, adjacent crus of the diaphragm and removal of the celiac plexus (Image 3). If stenosis of the CA persists after adequate surgical release, additional bypass surgery or endovascular therapy is performed(43). An endoscopic retroperitoneal release is favorable since this has been proved feasible and less invasive with comparable short-term results as the open procedure(17). PMAS is contraindicated as primary therapy for MALS, since the high risk of stent fracture resulting in re-stenosis(3).

Table 2. Reported type of complications of mesenteric endovascular revascularization versus mesenteric surgical revascularization.

Complications endovascular revascularization(29, 31)	Complications surgical revascularization(25, 37)
Hematoma	Bowel resection
Dissection access-site	Acute renal failure
Mesenteric dissection	Acute myocardial infarction
Thrombosis	Stroke
Branch perforation	Peripheral vascular disease
Stent dislodgement	Hemorrhage
Distal thromboembolization	Respiratory failure

CLINICAL OUTCOME AFTER TREATMENT

Repeated follow-up after therapy for CMI might be considered to detect symptomatic restenosis according the ESVS guidelines(1). Routine repeated imaging after therapy may show re-stenosis, but the benefit of treating asymptomatic re-stenosis is unknown. Antiplatelet therapy is recommended after revascularization and dual antiplatelet therapy may be considered for 3-12 months(1, 29, 31).

In-stent stenosis can be seen in 28-36% of endovascular treated patients within 2 years after PMAS(31). This number is lower after surgical revascularization with 0-25%(5, 38). Independent predictors of re-stenosis after mesenteric revascularization are endovascular revascularization, prior mesenteric intervention, female gender, and small (<6 mm) SMA diameter(39). Severe mesenteric calcification, occlusions, longer lesions, and small vessel diameter are associated with an increased risk of distal embolization, re-stenosis and re-interventions after endovascular revascularization(38).

Surgical revascularization is associated with a superior long-term patency rate compared to endovascular revascularization (cumulative odds ratio 3.57, 95% CI 1.82-6.87, p=0.0002)(40). Table 3 shows the 1-year and 5-years primary patency rates and primary assisted patency rates of surgical versus endovascular revascularization(31, 40-42).

Table 3. The 1-year and 5-years primary patency rates and primary assisted patency rates of surgical versus endovascular revascularization for CMI.

	Surgical revascularization (31, 40, 41)	Endovascular revascularization (31, 42)
1-year primary patency rate	91%	58-88%
1-year primary assisted patency rate	96%	90%
5-years primary patency rate	74-90%	45-52%
5-years primary assisted patency rate	96-98%	69-79%

primary patency rate = uninterrupted vessel patency after initial intervention without repeat intervention(31); primary assisted patency rate = successful restoration of vessel patency by revascularization therapy of restenosis or a newly occurring arterial stenosis of the previously treated lesion. Primary assisted patency ends with vessel occlusion(31).

A recently published meta-analysis included 100 observational studies to compare endovascular revascularization (10,679 patients) and open surgical revascularization (8047 patients)(12). Risk of in-hospital complications was significantly increased in the open surgical revascularization group (relative risk (RR) 2.19, 95% CI 1.84-2.60). The risk of 3-years recurrence was lower in the patients treated with open surgery than in the patients treated with endovascular approach (RR 0.47, 95% CI 0.34-0.66). The 3-years survival rate was not significantly different (RR 0.96, 95% CI 0.86-1.07). The ESVS guidelines recommend to offset the superior long-term results of open revascularization against the possible early benefits of endovascular revascularization in the absence of randomized controlled trials(1).

Immediate symptom relief is reported in 90-98% of surgically treated patients and remains excellent after 5 years with 89-92%(5). After endovascular revascularization, immediate symptom relief was reported in 87-95%, symptom relief after 3 years in 61-88%, and in 51% after 5 years(5).

A retrospective analysis of prospectively collected data (10,920 endovascular revascularized patients versus 4555 surgical revascularized patients) showed that endovascular revascularization is associated with a significantly lower in-hospital

mortality rate of 2.4%, shorter length of hospitalization by 10 days, and reduced costs of $25,000 for hospitalization compared to surgical revascularization(43).

CONCLUSION

Although the exact incidence of CMI is unknown, it is expected that the incidence will increase in the upcoming years due to the aging population and the increasing prevalence of cardiovascular disease (CVD) in Europe. CVD patients have an increased life expectancy due the improved diagnostics and better therapeutic opportunities but these patients are also prone to develop mesenteric atherosclerosis. Patients with CMI present usually with GI symptoms. The diagnostic work-up of the patient suspected of CMI and therapeutic management is multidisciplinary. The current clinical management of CMI is summarized in an algorithm (Figure 1). Early diagnosis is important to timely treat, improve quality of life and to prevent acute-on-chronic mesenteric ischemia.


CHAPTER
1.2

Aims and outline of the thesis

AIMS

The exact prevalence of CMI is not known and CMI is often described as a rare disease in literature. However, the incidence of revascularization procedures for CMI is increasing(2) and given the aging population and increasing prevalence of CVD with increased life expectancy due to the improved diagnostic and therapeutic opportunities, the incidence of CMI is expected to increase in the upcoming years. Therefore, it is important to put CMI in the picture. This thesis aims to provide insights in different aspects of the diagnosis and therapy of CMI to optimize the diagnostic work-up and treatment for this specific patient group. The outline of this thesis is discussed below.

OUTLINE OF THIS THESIS

This thesis is divided into four parts. **Part I** contains the introduction of this thesis. **Chapter 1.1** describes the general introduction on CMI including the definition, epidemiology, etiology, clinical presentation, diagnostic work-up, therapy and clinical outcome of CMI and the anatomy of the mesenteric vasculature followed by **Chapter 1.2** describing the aims and outline of this thesis.

Part II focusses on different aspects of the current diagnostic procedures for CMI and strategies and insights to optimize the diagnostic work-up. This part starts with an overview of the current imaging techniques for the mesenteric vasculature in **Chapter 2.**

The current diagnostic work-up for CMI is cumbersome and time-consuming with invasive diagnostic interventions in the absence of a gold standard test. All patients suspected of CMI are currently exposed to this extensive diagnostic work-up. This results in unnecessary diagnostic procedures for patients without CMI and delay in treatment for patients with CMI. An easy-to-use tool is needed to assess the risk of CMI in patients suspected of CMI and to guide clinical decision making. **Chapter 3** describes the multicenter external validation of a prediction model for CMI as previously published by our study group. Furthermore, an updated version of the score chart is presented in this chapter based on the performance of the prediction model in the combined original and validation cohort and by including the cause of CA stenosis (MALS or vascular disease).

VLS is a functional test to detect mucosal ischemia during upper GI endoscopy. VLS is currently used in clinical practice in the diagnostic work-up for CMI. Since VLS is a relatively new diagnostic test, further validation of VLS is needed. **Chapter 4** describes the interobserver and intraobserver validation of VLS measurements during upper GI endoscopy.

Upper GI endoscopy is performed in fasting state and subsequently the VLS measurements are performed in fasting state. Symptoms of CMI are usually provoked by a meal; therefore VLS performed in fasting state could potentially underdiagnose CMI. **Chapter 5** describes a study in patients suspected of CMI and healthy controls who underwent VLS measurements in both fasting state and after luminal feeding to assess the additional value of postprandial VLS measurements for the diagnosis of CMI.

Further validation of VLS is performed in a porcine model study by comparing VLS measurements and a calibrated microvascular oxygen tension ($\mu PO_{2)}$ measurement technique as described in **Chapter 6**.

The last chapter of Part II, **Chapter 7**, introduces a novel promising technique to measure oxygen-dependent signal in the cells of the GI tract during upper GI endoscopy. This chapter describes a pilot study in healthy controls to assess the feasibility and safety of this technique during upper GI endoscopy.

Part III describes various therapeutic elements of CMI. Endovascular revascularization is the therapy of choice and bare-metal stents are currently standard care for endovascular revascularization of atherosclerotic CMI. A retrospective cohort study showed better patency for covered stents in atherosclerotic CMI patients(44). The study protocol for a multicenter, randomized controlled trial of bare-metal stents versus covered stents in patients with atherosclerotic CMI is described in **Chapter 8.**

Revascularization therapy for multi-vessel mesenteric arterial disease is generally accepted. A single mesenteric arterial stenosis is seldomly symptomatic due to the existence of the abundant mesenteric collateral network. However symptomatic single vessel disease may develop when the extent of stenosis is too severe and/or the collateral network is insufficient. The challenge is to identify those patients with isolated mesenteric arterial disease and abdominal complaints who will benefit from revascularization. **Chapter 9** describes the long-term clinical success rates for single

mesenteric artery revascularization of either CA or SMA in patients with chronic GI symptoms and confirmed mucosal ischemia with VLS or tonometry.

The vascular approach for endovascular mesenteric arterial interventions is TBA or TFA according the current guidelines(31). Literature on coronary artery intervention shows less major access-site complications for TRA than for TBA and for TFA with similar procedural and clinical outcomes(45-49). Current guidelines do not issue any recommendations on the use of TRA for mesenteric arterial interventions since studies on TRA for this specific indication are lacking. **Chapter 10.1** describes a single-center cohort study of patients with an endovascular mesenteric intervention with TRA, TBA or TFA. The feasibility and safety of TRA is compared with the feasibility and safety of TFA and TBA. **Chapter 10.2** describes a severe complication of a TRA procedure for brachiocephalic stent placement.

Since the prevalence of mesenteric arterial stenosis in the general population is high, it is challenging to define the clinical significance of a mesenteric arterial stenosis, especially in case of single vessel mesenteric disease. Pressure measurements are used in interventional cardiology to define the clinical significance of a coronary artery stenosis and to guide treatment decision. Consensus on the use of pressure measurements for mesenteric arterial stenosis is lacking. A cohort study on pressure measurements in patients with mesenteric stenosis is described in **Chapter 11** to define a clinically significant CA or SMA stenosis by correlating mesenteric pressure measurements with clinical success.

Part IV starts with a summary of the main findings of this thesis in **Chapter 12.1** followed by the general discussion in **Chapter 12.2** and further directions for future research in **Chapter 12.3**. Finally, **Chapter 12.4** provides a brief conclusion of this thesis.

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PART II

Diagnosis

Chapter 2
Vascular imaging of the mesenteric vasculature

Chapter 3
Validation of a score chart to predict the risk of chronic mesenteric ischemia and development of an updated score chart

Chapter 4
Intraobserver and interobserver reliability of visible light spectroscopy during upper gastrointestinal endoscopy

Chapter 5
Detection of mesenteric ischemia by means of endoscopic visible light spectroscopy after luminal feeding

Chapter 6
Evaluation of endoscopic visible light spectroscopy: comparison with microvascular oxygen tension measurements in a porcine model

Chapter 7
Oxygen-dependent delayed fluorescence of protoporphyrin IX measured in the stomach and duodenum during upper gastrointestinal endoscopy


CHAPTER
2

Vascular imaging of the mesenteric vasculature

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ABSTRACT

Imaging of the mesenteric vasculature is crucial in diagnosing vascular disease of the gastro-intestinal tract such as acute or chronic mesenteric ischemia caused by arterial stenosis, embolism or thrombosis, mesenteric vein thrombosis and mesenteric aneurysm or dissection. The reference standard for imaging of the mesenteric vasculature is digital subtraction angiography. However, modalities as duplex ultrasonography, computed tomography angiography and magnetic resonance angiography are developing rapidly and may provide accurate imaging non-invasively. This review provides an up-to-date overview of the anatomic resolution, clinical application, emerging techniques and future perspectives of these four radiological modalities for imaging of the mesenteric vasculature.

INTRODUCTION

Imaging of the mesenteric vasculature plays a crucial role in diagnosing vascular disease of the gastro-intestinal tract such as acute or chronic mesenteric ischemia caused by arterial stenosis, embolism or thrombosis, mesenteric vein thrombosis and mesenteric aneurysm or dissection.

Three main branches of the abdominal aorta vascularize the gastro-intestinal tract: the celiac artery (CA), the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA); see Image 1 and Image 2. The CA provides blood supply to the stomach, liver, part of pancreas and the proximal part of the duodenum. The SMA provides blood supply to the distal duodenum, small bowel and the proximal colon. Blood supply to the distal colon is provided by the IMA, which is relatively small compared to the CA and SMA. Collaterals connect the three main branches and these can exist within one mesenteric artery, between two mesenteric arteries, or between mesenteric and parietal or body wall vessels.

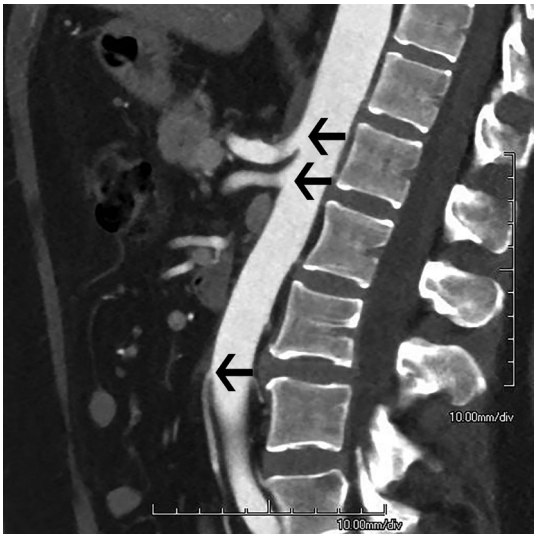

Image 1. (2D) CTA image in sagittal plane visualizing normal anatomy of the CA, SMA and IMA (top-down, respectively).

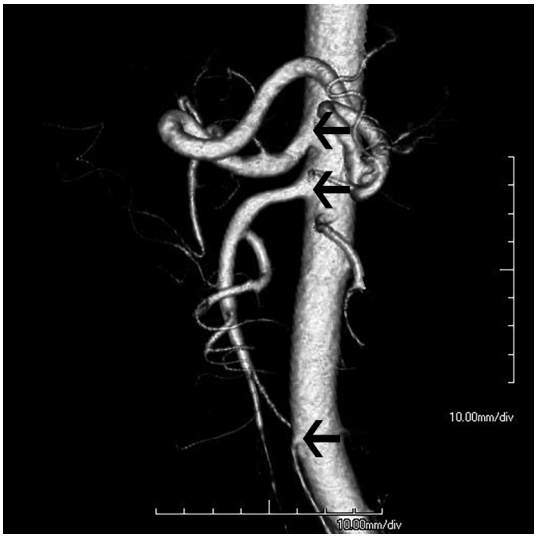

Image 2. 3D CTA image visualizing normal anatomy of the CA, SMA and IMA (top-down, respectively).

The mesenteric venous system is localized parallel to the arterial mesenteric system. The superior mesenteric vein (SMV) receives venous blood from the duodenal, pancreatic, right gastroepiploic, jejunal, ileal, right colic and middle colic veins. The inferior mesenteric vein (IMV) receives venous blood from the left colic, sigmoid and superior haemorrhoidal veins and generally drains into the splenic vein, less frequently into the SMV. In addition, the splenic vein receives venous blood from the pancreatic, left gastroepiploic and short gastric veins. The splenic vein and SMV drain into the portal vein (PV).

The reference standard for imaging of the mesenteric vasculature is digital subtraction angiography (DSA). DSA is an invasive, i.e. endovascular, procedure using X-ray and iodine contrast media, the latter being a potentially nephrotoxic contrast agent. DSA allows diagnosis and treatment of vascular mesenteric disease in one single procedure. Novel radiological techniques are being developed rapidly. Three most important non-invasive modalities for imaging of the mesenteric vasculature are US, computed tomography angiography (CTA) and magnetic resonance angiography (MRA). This review starts with a description of the most frequent mesenteric vascular diseases followed by an up-to-date overview of the anatomic resolution, clinical application, emerging

techniques and future perspectives of each of these four modalities for imaging of the mesenteric vasculature.

MESENTERIC VASCULAR PATHOLOGY

Acute mesenteric ischemia (AMI) is caused by an acute event resulting in decreased blood supply to the gastro-intestinal tract. AMI is a life-threatening condition with a high mortality and prompt diagnosis followed by treatment is of utmost importance. In most cases (approximately 40-50%), AMI is caused by acute occlusion due to an embolism in the SMA. AMI has several etiologies: 1. in 20-30% thrombosis of a mesenteric artery associated with atherosclerotic disease, 2. in 25% non-occlusive mesenteric ischemia (NOMI) and 3. in 5-15% portomesenteric venous thrombosis(1). Nowadays, a shift in the etiology of AMI from embolism towards atherosclerotic disease is appreciated in Western countries because of aging of the population, which results in higher prevalence of atherosclerosis. Furthermore, the use of anticoagulation therapy is increasing, thereby potentially reducing the incidence of embolic events. This hypothesis is not yet confirmed in a population-based study(2, 3).

Chronic mesenteric ischemia (CMI) is most frequently caused by atherosclerosis. CMI often presents with postprandial pain and weight loss. Revascularization is needed for symptom relief and may be considered to prevent acute ischemia (acute on chronic mesenteric ischemia). Other causes of CMI are median arcuate ligament syndrome ((MALS) or celiac artery compression syndrome (CACS)) or, less common, fibromuscular dysplasia (FMD) or vasculitis. Historically, surgical revascularization was therapy of first choice for atherosclerotic CMI, but minimally invasive endovascular approaches encompassing percutaneous transluminal angioplasty (PTA) and stent placement have emerged leaving surgical interventions for complex disease only.

Mesenteric artery stenosis is highly prevalent in the (asymptomatic) population. Cohort and population based duplex ultrasonography (DUS) studies in asymptomatic individuals show an overall prevalence of mesenteric artery disease of 18%, isolated CA stenosis up to 15%, isolated SMA stenosis approximately 1% and two vessel disease in up to 7% of the population(4-7). Autopsy series showed a higher prevalence of mesenteric artery disease of 29% overall and two or three vessel disease in 15%. The prevalence of mesenteric artery disease in these autopsy series is age related, 67% for the subjects aged 80 years or more compared with a prevalence of 6% among the subjects of less

than 40 years old(8). Concluding, mesenteric artery stenosis is a common finding in imaging of the mesenteric vasculature but not necessarily related to symptoms. The combination of stenosis detected with radiological imaging, clinical symptoms and a positive gastro-duodenal mucosal functional test as tonometry and visible light spectroscopy is essential for the diagnosis of mesenteric ischemia, especially in CMI(9-12).

Mesenteric vein thrombosis involves the SMV and rarely the IMV. Five to 15% of all mesenteric ischemia cases are caused by mesenteric vein thrombosis. Underlying causes of mesenteric vein thrombosis can be primary (idiopathic) or secondary. Secondary causes are underlying coagulopathy due to hereditary factors (e.g. deficiencies in Factor III, protein C, protein S or antithrombin, polycythemia vera) or acquired factors (e.g. paraneoplastic, intra-abdominal inflammatory disease, abdominal surgery, oral contraceptive use, cirrhosis and portal hypertension)(1, 13).

Aneurysms of the CA, SMA and IMA are rare, contributing an incidence of 4%, 5.5% and 1% of all visceral vessel aneurysms, respectively(14). CA aneurysms are caused by atherosclerosis, tunica media degeneration, trauma, vascular disorder or mycotic infection. Most CA aneurysms are asymptomatic and are incidentally detected with radiological imaging. Presenting symptoms of a CA aneurysm are epigastric pain, abdominal bruit, gastrointestinal haemorrhage, jaundice, haemoptysis or palpable mass. The risk of spontaneous rupture of a CA aneurysm seems to be low, however rupture is associated with high morbidity of up to 100%(15, 16). Surgical intervention or endovascular embolization are the options for therapy of a CA aneurysm to prevent rupture. Criteria for appropriate patient selection for therapy of CA aneurysms do not exist at the moment. Possible selection criteria are size of the aneurysm, symptomatic aneurysms and rapid enlargement of the aneurysm(15, 16).

SMA aneurysms are most commonly detected in the proximal 5 cm of the SMA. The prevalence of SMA aneurysm is higher compared to TC aneurysms. Atherosclerosis, infectious disease, dissection, trauma and inflammatory processes as pancreatitis or biliary tract disease are causes of SMA aneurysms. Most SMA aneurysms present symptomatic with comparable symptoms as CA aneurysms and treatment is required because of frequent spontaneous rupture, even in case of an asymptomatic SMA aneurysm. Treatment options are identical as CA aneurysms.

Dissection of mesenteric vessels is reported as involvement in aorta dissection cases and in spontaneously cases of CA or SMA dissection. Asymptomatic patients and even symptomatic patients without evidence of ischemia can be observed and followed with intermittent imaging(17). However, blood flow in these vessels can decrease or, rarely, completely obstruct if the dissection flap extends into the vessels resulting in intestinal ischemia. Therapy consists of surgical or endovascular intervention.

DUPLEX ULTRASONOGRAPHY

In 1984, Jäger et al. described a patient with symptoms of chronic gastro-intestinal ischemia as post-prandial abdominal pain, weight loss and diarrhoea with elevated blood flow velocity of the CA and SMA defined by DUS Doppler imaging. Elevated blood flow velocities indicated severe stenosis of the CA and SMA and subsequent DSA confirmed stenosis in both arteries(18). Two years later, Nicholls et al. published their results of the use of hemodynamic parameters obtained by DUS in identifying mesenteric insufficiency in a small cohort of normal subjects and patients referred for analysis of CGI(19). At the moment, DUS imaging is still used for imaging of mesenteric vasculature.

The primary clinical application of mesenteric DUS is to identify proximal stenosis of the SMA and CA appreciated from both anatomic and hemodynamic changes. The CA and SMA are relatively easy to examine. Moreover, it is feasible to examine the IMA with US, but the IMA is generally difficult to visualize with DUS due to its more distal localization and smaller size. DUS of mesenteric artery stenosis beyond the artery's origin is limited due patient's body habitus or overlying bowel gas.

DUS is observer dependent and should therefore be performed by an experienced sonographer. Interpretability of duplex ultrasound imaging of the CA and the SMA varies between 68% good and 11% moderate interpretability(20). The patient should be fasting before the examination in order to prevent postprandial flow changes and with an optimal moment of duplex scanning in the morning when bowel gas is minimal. Respiration influences duplex parameters in the CA and SMA with generally higher values during expiration(20). The head of the bed is tilted 30° and the patient is positioned in supine position. The mesenteric vessels of interest are identified with 2-dimensional grayscale imaging (B-mode) and the presence of a disease process within the lumen of the mesenteric vessels can be assessed (see Image 3). First, the presence

of blood flow will be assessed using Doppler ultrasound. Absence of any blood flow indicates complete occlusion of the selected vessel and should also be suspected when interpretability is poor(20). A potential pitfall is the presence of flow beyond an occlusion because of collateral flow from other mesenteric arteries of the abdominal wall. When blood flow is present, the waveform is analyzed and the peak systolic velocity (PSV) and end diastolic velocity (EDV) will be determined. Flow measurements should be obtained with an insonation angle between the probe and the blood vessel between 45° and 60°. An angle exceeding 60° will result in elevated and unreliable velocities.

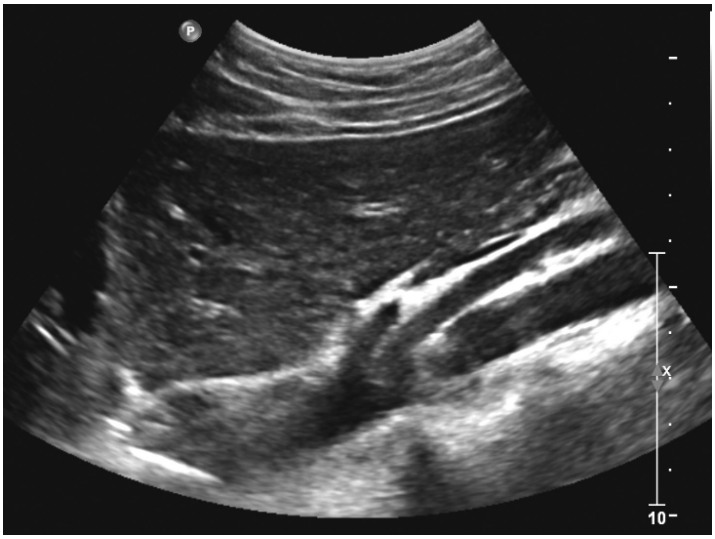

Image 3. Visualization of the CA and SMA with US.

In literature, several reports are published with different thresholds for detecting significant stenosis of the mesenteric arteries with US. At the moment, no consensus has been reached on which threshold should be used. Table 1 shows an overview of reported threshold velocities and their sensitivity and specificity in detecting significant (≥50% and ≥70%) stenosis of the SMA or CA. Respiration and the presence of concomitant stenosis influence threshold values(20, 21).

Table 1. Duplex ultrasound criteria for the diagnosis of SMA/CA stenosis.

First author (publication year)	**SMA PSV** ≥ 50% stenosis	**SMA PSV** ≥ 70% stenosis	**CA PSV** ≥ 50% stenosis	**CA PSV** ≥ 70% stenosis	**SMA EDV** ≥ 50% stenosis	**SMA EDV** ≥ 70% stenosis	**CA EDV** ≥ 50% stenosis	**CA EDV** ≥ 70% stenosis
Bowersox (61) (1991)	> 300 cm/s sens 63% spec 100%	-	-	-	> 45 cm/s sens 100% spec 92%	-	-	-
Moneta (62) (1993)	-	≥ 275 cm/s sens 92% spec 96%	-	≥ 200 cm/s sens 87% spec 80%	-	-	-	-
Perko (63) (1997)	≥ 275 cm/s sens 93% spec 80%	-	≥ 200 cm/s sens 94% spec 94%	-	≥ 50/cm/s sens 100% spec 100%	-	-	-
Zwolak (64) (1998)	≥ 300 cm/s sens 60% spec 100%	-	≥ 200 cm/s Sens 93% Spec 94%	-	≥ 45 cm/s sens 90% spec 91%	-	≥ 55 cm/s sens 93% spec 100%	-
Lim (65) (1999)	-	≥ 275 cm/s sens 100% spec 98%	-	≥ 200 cm/s sens 100% spec 87%	-	-		
AbuRahma (58) (2012)	≥ 295 cm/s sens 87% spec 89%	≥ 400 cm/s sens 72% spec 93%	≥ 240 cm/s sens 87% spec 83%	≥ 320 cm/s sens 80% spec 89%	≥ 45 cm/s sens 79% spec 79%	≥ 70 cm/s sens 65% spec 95%	≥ 40 cm/s sens 84% spec 48%	≥ 100 cm/s sens 58% spec 91%
Van Petersen (20) (2013)	≥ 220 cm/s (expiration) sens 84% spec 76% ≥ 277 cm/s (inspiration) sens 68% spec 93%	≥ 268 cm/s (expiration) sens 75% spec 86% ≥ 205 cm/s (inspiration) sens 78% spec 84%	≥ 268 cm/s (expiration) sens 66% spec 80% ≥ 243 cm/s (inspiration) sens 68% spec 71%	≥ 280 cm/s (expiration) sens 66% spec 77% ≥ 272 cm/s (inspiration) sens 72% spec 77%	≥ 62 cm/s (expiration) sens 75% spec 94% ≥ 52 cm/s (inspiration) sens 76% spec 93%	≥ 101 cm/s (expiration) sens 74% spec 96% ≥ 52 cm/s (inspiration) sens 78% spec 93%	≥ 64 cm/s (expiration) sens 78% spec 65% ≥ 83 cm/s (inspiration) sens 53% spec 81%	≥ 57 cm/s (expiration) sens 83% spec 56% ≥ 84 cm/s (inspiration) sens 66% spec 81%

SMA = Superior Mesenteric Artery, CA = Celiac Artery, PSV = Peak Systolic Velocity, EDV = End Diastolic Velocity, Sens = sensitivity, Spec = specificity.

The waveform of the CA is different compared to the waveform of the SMA in fasting state. The PSV of the SMA is higher compared to the PSV of the CA. Furthermore, the EDV of the SMA is lower compared to the EDV of the CA. The SMA often shows a short flow reversal at the end of the systole. This reverse flow component is generally not appreciated in the CA. Image 4 and Image 5 show the waveform of the CA and SMA, respectively.

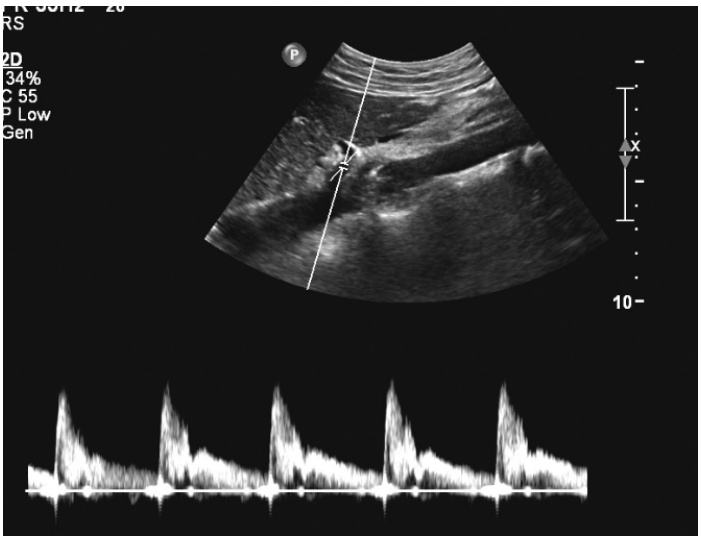

Image 4. Waveform of the CA analyzed with US-Doppler.

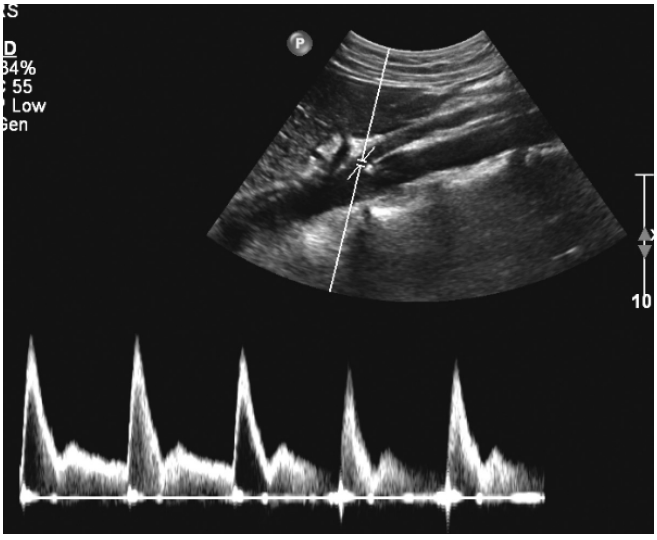

Image 5. Waveform of the SMA analyzed with US-Doppler.

The accuracy of DUS assessment of the mesenteric vessels is strongly dependent on the performer and adequate assessment can be limited in obese patients, in patients with overlying bowel gas and in patients with severe vessel calcification. In the acute setting, DUS assessment can be impossible due to the abdominal pressure by the performer in a patient with acute abdominal pain. However, Sartini et al. performed a pilot study in patients presenting at the emergency department with abdominal pain with no specific diagnosis after initial work-up. Diagnostic mesenteric DUS images were obtained in 96% of the 47 patients and sensitivity, specificity and negative predictive value of DUS for occlusive AMI were 100%, 64% and 100%, respectively. These results suggest a role of DUS in the emergency department in identifying patients who require CTA or DSA immediately, but this have to be substantiated in a larger population(22).

DUS can detect proximal stenosis of the CA and SMA, but the role of DUS after endovascular treatment in detecting in-stent stenosis is still matter of debate. Possibly, a stent decreases the compliance of the artery causing elevated PSV values resulting in overestimation of in-stent stenosis, a phenomenon also described in renal and carotid stenting(23-27). Retrospective cohort studies confirmed the overestimation of mesenteric in-stent stenosis if native duplex criteria were used(28, 29). Prospective validation studies of specific mesenteric in-stent stenosis duplex criteria are needed.

DUS surveillance is recommended in patients treated with mesenteric bypass grafts(30). The type of bypass used can differ: retrograde or antegrade and origin from the aorta, iliac vessels or other visceral arteries. Liem et al. reported no significant differences in mesenteric bypass DUS outcomes for different sorts of inflow arteries, however, graft diameter affects mesenteric bypass DUS outcome possibly(31).

DUS can also detect mesenteric aneurysms. Typical signs of an aneurysm at DUS are significant vessel wall thickening, presence of plaques and increased flow with the ‘aliasing’ phenomenon. DUS can provide information of a thrombus inside the aneurysm(32).

Concluding, DUS of the mesenteric vasculature is a non-invasive, low-cost radiological modality without radiation exposure with acceptable specificity and sensitivity in detecting mesenteric artery stenosis. DUS is therefore useful in the work-up of CMI and in the follow-up after surgical or endovascular treatment. However, the outcome of

DUS is operator dependent and DUS of the mesenteric vasculature is limited in analyzing the IMA and distal stenosis.

CTA

Multi-detector computed tomography (MDCT) technique with contrast enhancement allows fast scanning of the mesenteric vasculature with high spatial resolution enabling multi-planar image reconstruction. CTA technique produces volume data sets, which can be converted into any projection, including surface rendered 3D images (see Image 2). Both hardware and software developments in CT techniques permit fast scanning with imaging times less than 1 second for the abdomen with low radiation exposure. In additional, dual source (= the use of two x-ray sources and two x-ray detectors mounted on a single CT gantry) dual energy (= CT datasets representing 2 different X-ray energies) CT techniques may considerably reduce the amount of iodine contrast agent needed to visualize the mesenteric arteries. CTA is nowadays the first-line imaging modality for the diagnosis of AMI and CMI with high accuracy. Therefore, CTA is replacing DSA as a diagnostic tool because of its non-invasive nature(33, 34).

CTA is performed with intravenous iodine contrast agent for enhancing both vessels and parenchymatous organs. Image acquisition is performed with the contrast bolus arriving in the arterial and portal venous phase to detect mesenteric vascular pathology and associated intestinal and parenchymal changes. High-density oral positive contrast agents should not be used, because the distinction between mesenteric vessels and bowel lumen will be obscured. The use of water as a negative contrast agent has been advocated previously(34). Axial images are reconstructed to thin axial slices of 1-3 mm for further multiplanar reformatting. It is of note that slice thickness should preferably be smaller than the size of the smallest mesenteric artery, conforming the need for even thinner slices below 1 mm. Current CT systems cover the entire abdomen during a breath hold of several seconds and automated bolus timing techniques provides accurate scan timing with regard to the arrival of contrast in the mesenteric arteries. The origin of the CA, SMA and IMA are best visualized in sagittal or sagittal oblique plane and branches of the mesenteric arteries are best visualized in coronal, coronal oblique or axial oblique plane. CTA can analyze the extend and characteristics of the stenosis or occlusion and the relation with the branch vessels. If collateral pathways or more prominent vessels are present in the surrounding area of a stenosis, the suspicion

of a hemodynamically significant stenosis raises. Moreover, CTA can detect other gastrointestinal findings related to (acute) mesenteric vascular pathology: thickening of the bowel wall, bowel dilatation, bowel wall attenuation, free intra-abdominal air, mesenteric fat stranding, intestinal pneumatosis intestinalis and portal venous gas. CTA can perform anatomic mapping of the surrounding gastrointestinal structures, which is useful in preoperative planning to visualize the local anatomy. Finally, CTA visualizes the entire gastrointestinal and genitourinary tract to rule out other causes of chronic and acute abdominal pain.

The CTA images are transferred to a 3D workstation, which converts the 2D slices into 3D images. Three-dimensional CTA produces images with high spatial resolution in any possible image plane for an optimal visualization of the mesenteric vasculature, especially for the evaluation of small and distal arteries and complex anatomy. Chen et al. reviewed the records of cohort patients with significant unsuspected mesenteric arterial pathology who underwent axial CTA with 3D multiplanar reconstructions. In 66% of the patients no mesenteric arterial lesion of the CA or SMA was seen on axial CTA but definitely found on 3D CTA(35).

Arterial embolism presents on CTA as a filling defect in the lumen of the mesenteric vessel. In case of occlusion of the artery by an embolism, the ‘cut-off’ sign can be seen: abrupt termination of the affected artery. Arterial thrombus is seen as focal stenosis of the vessel often with calcified atherosclerosis. The obstruction is occlusive if the thrombus spans the complete width of the lumen and no blood flow is identified. Arterial thrombosis is often located proximal to the origin of the affected generally atherosclerotic vessel, in contrast to arterial embolism, which is located more distally. See Images 6-10 for CTA images of mesenteric arterial thrombosis. Mesenteric venous thrombosis (Image 11) is seen as a persistent, well-defined filling defect in the venous lumen with central low attenuation. The walls of the vein can be thickened due to thrombophlebitis and the vein can expand due to the clot. Furthermore, collateral circulation, engorgement of mesenteric veins upstream and mesenteric oedema can be detected with CTA. The sensitivity of CTA for venous mesenteric thrombosis is lower compared to arterial stenosis. The sensitivity can be improved with use of two-phase imaging to enhance venous drainage.

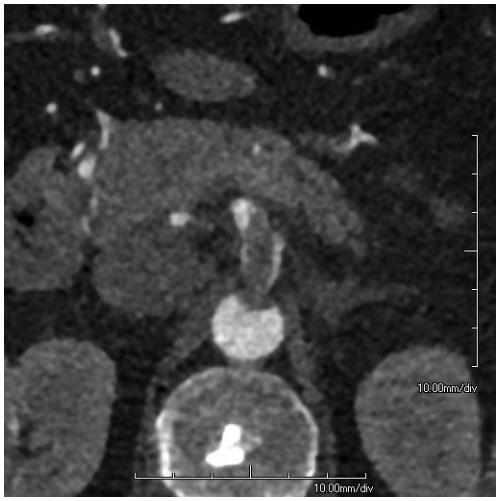

Image 6. CTA image of CA thrombosis.

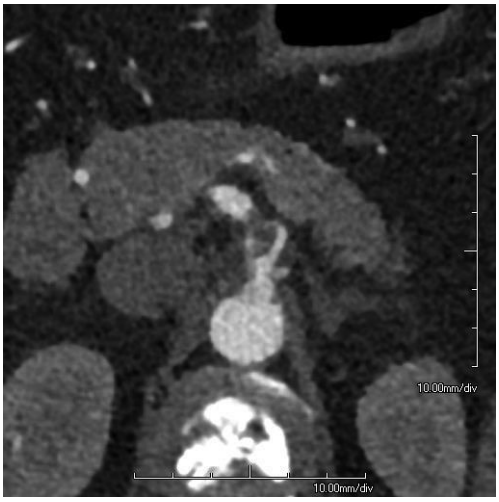

Image 7. CTA image of CA thrombosis.

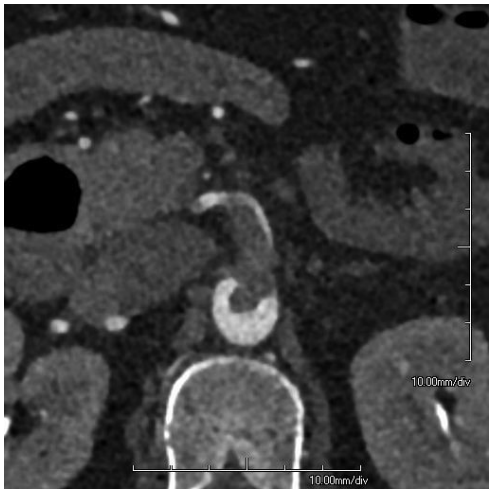

Image 8. CTA image of SMA thrombosis.

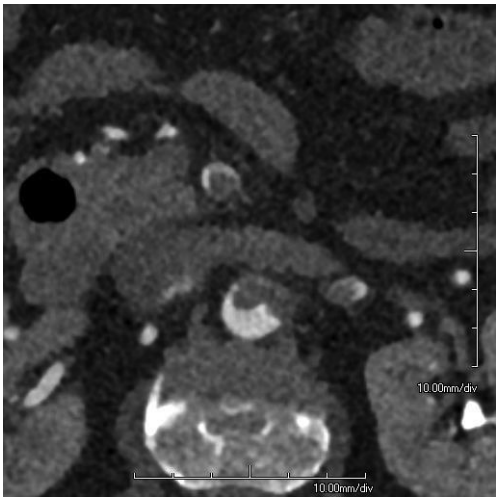

Image 9. CTA image of SMA thrombosis.

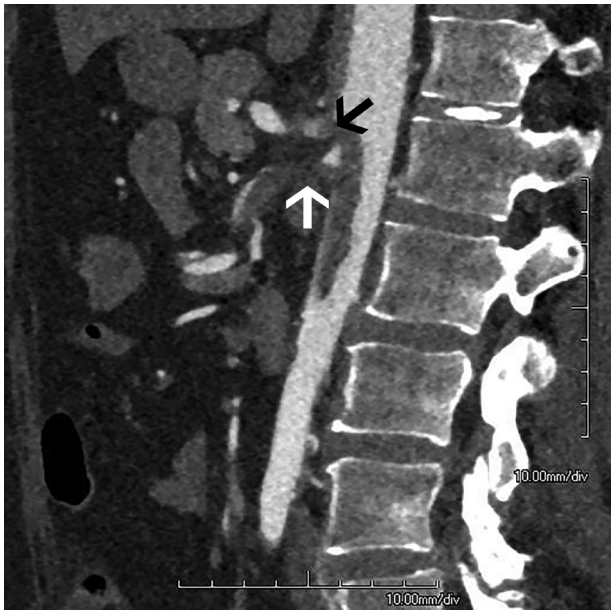

Image 10. Sagittal CTA image of aorta-mesenteric artery thrombosis (thrombosis into the CA is indicated with a black arrow and thrombosis into the SMA is indicated with a white arrow).

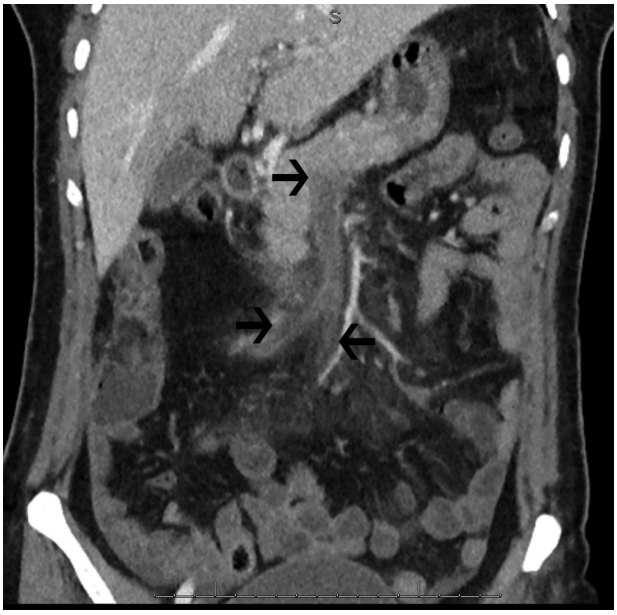

Image 11. Coronal CTA image of SMV thrombosis, the extensiveness of the SMV thrombosis is shown between the black arrows**.**

Vasculitis is difficult to differentiate from atherosclerosis and can present as vascular wall thickening, occlusion of the affected vessel, aneurysm formation and wall enhancement. If mesenteric ischemia is caused by a low-flow state, non-occlusive mesenteric ischemia (NOMI) due to heart failure, shock, hypovolemia, dehydration, chronic renal failure, CTA may show diffuse thickened bowel wall within small and pruned blood vessels(36). These signs are non-specific and can be seen in mesenteric ischemia.

CTA is superior to DUS in detecting mesenteric aneurysms (Image 12-13) because of complete visualization of the mesenteric arteries and the surrounding tissue. CTA provides information of the size and volume of the aneurysm and degree of thrombosis, but can also define collateral flow information which is important knowledge for surgical or endovascular treatment.

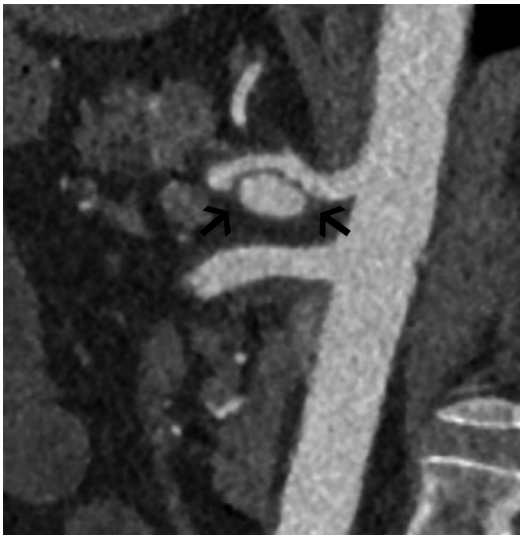

Image 12. CTA image of CA aneurysm with dissection (indicated between the black arrows).

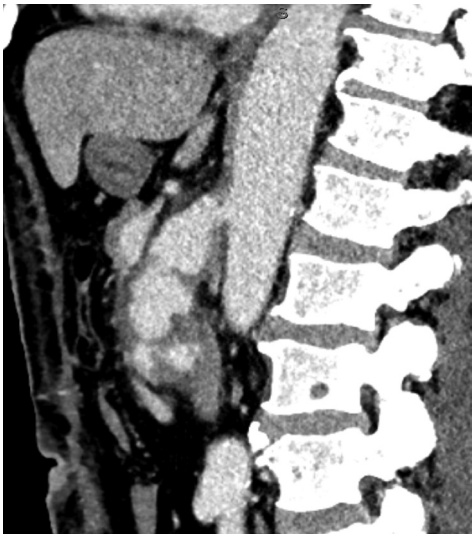

Image 13. CTA image of SMA aneurysm in a patient with Q-fever**.**

Dissection of a mesenteric vessel is well detected by CTA (Image 14). The exact location and extend of the dissection flap can be analyzed easily and this information can be used for pre-interventional planning.

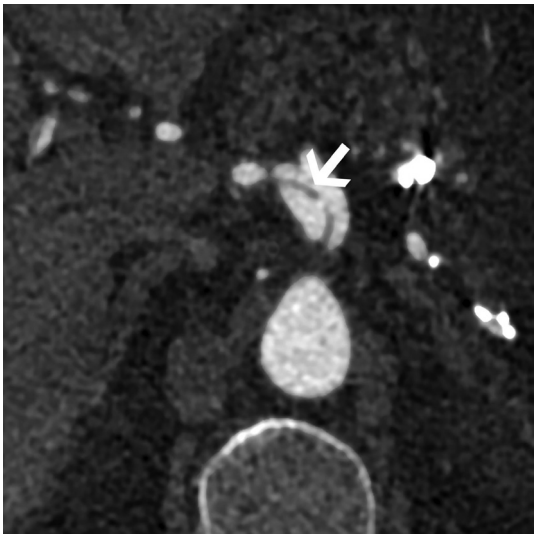

Image 14. CTA image of CA dissection, the intimal flap is indicated with a white arrow.

CTA can be used to detect in-stent stenosis after endovascular treatment (Image 15). Intimal hyperplasia presents as a hypodense rim on the inner stent surface on CTA. Stent fraction (Image 16) and migration can also be detected by CTA. Finally, CTA can visualize grafts, graft anastomoses, intimal hyperplasia of bypasses and vessel patency after PTA.

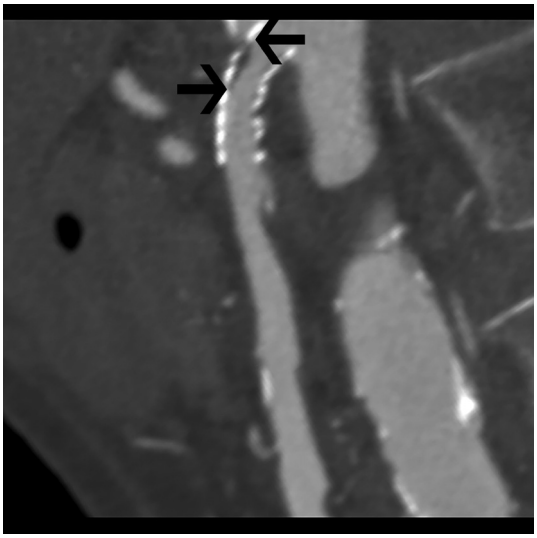

Image 15. CTA image of subtle in-stent stenosis of the SMA due to intimal hyperplasia, shown between the black arrows.

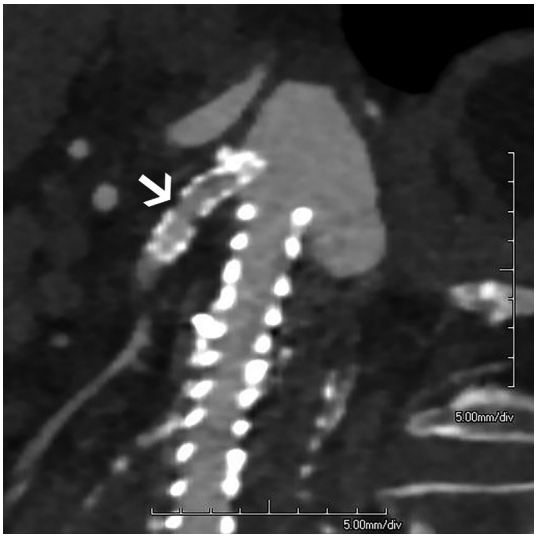

Image 16. CTA image of CA stent fracture (indicated with the white arrow) and a long uncomplicated stent in the SMA.

Table 2 shows an overview of the known sensitivity and specificity rates of CTA for diagnosing AMI and CMI. The sensitivity and specificity reported in the last decade is 93-100% and 90-100%, respectively. The sensitivity and specificity rates are increasing over time, due to the developments and advancements in CTA techniques. Though, this sensitivity and specificity rates are mostly derived from studies with patients clinically suspected of AMI. In clinical practice, AMI is often diagnosed unexpectedly after imaging for acute abdominal pain. The protocol of these acute CT-scans performed in an emergency setting is often suboptimal for the diagnosis of AMI. As a result, AMI is underdiagnosed in CT-scans performed in patients with abdominal pain without clinical suspicion of AMI(2).

Table 2. Overview of sensitivity and specificity rates of CTA in diagnosing AMI and CMI.

First author (publication year)	CTA sensitivity	CTA specificity
Taourel (66) (1996)	64%	92%
Kirkpatrick (59) (2003)	96%	94%
Wiesner (67) (2004)	80%	100%
Zandrino (68) (2006)	92%	100%
Aschoff (69) (2008)	93%	100%
Ofer (70) (2008)	89%	97%
Akyildiz (71) (2009)	93%	90%
Menke (72) (2010) Meta analysis (59, 67-71)	93%	96%
Yikilmaz (73) (2011)	100%	100%
Schaefer (48) (2013)	CA 100% SMA n.a.	CA 95% SMA 98%

CTA is a non-invasive, widely available and fast imaging modality with high sensitivity and specificity for evaluation of the mesenteric vasculature. CTA techniques are developing rapidly resulting in even faster imaging techniques, lower radiation and lower iodine contrast agent exposure. Furthermore, resolution of the CT images is still increasing. Development of 3D CTA techniques ensures higher accuracy in detecting mesenteric vascular pathology, even in the smaller vessels. Despite the radiation and intravenous nephrotoxic contrast exposure, CTA is the first-line approach for AMI and CMI.

MRA

Gadolinium contrast-enhanced MRA of the mesenteric vasculature can visualize mesenteric stenosis and occlusions. MR technique uses a strong magnetic field. The technique is based on the relaxation of protons after excitation by a radio frequency (RF) pulse. Gadolinium changes the speed of this relaxation after the RF pulse. This results in optimal contrast between the bright blood and darker stationary tissue due to the T1-shortening effect of gadolinium and tissue that has not yet been perfused by the contrast agent. Today, modern MR systems acquire high-resolution MRA images within a single breath hold. This reduces motion artefacts and artefacts from bowel peristalsis. A major shortcoming of MRI is its inability to demonstrate calcifications, which makes the differentiation between atherosclerotic disease and MALS difficult. Still, MRA is a time consuming and expensive test, which is not often promptly available. This results in a limited role for MRA, especially in the acute setting.

MRA is usually performed on an 1.5T or 3T MR field strength in the arterial and venous phase comparable to CTA contrast timing. The contrast agent used is gadolinium, which only has a few side effects such as a low incidence of allergic reactions, a minimal nephrotoxic effect compared to the contrast agent used with CTA for a similar volume and the recently described potential development of nephrogenic systemic fibrosis in patient with kidney failure(33, 37). Main limitations of MRA are the length of MRA examination up to 1 hour, claustrophobia, and contra-indications such as implanted cardiac devices and metal foreign bodies

MRA has high sensitivity and specificity for stenosis of the origin of the SMA and CA (Image 17-18), but has lower sensitivity and specificity for the smaller downstream vessels and IMA(33). Shirkhoda et al. evaluated the mesenteric circulation with MRA

and reported good visualization of the SMA in 85%, CA in 75%, IMA in 25%, first-order branching in 75%, second-order branching in 60%, third-order branching in 50%, SMV in 85% and portal vein in 85% of all performed MR angiograms(38). The inter-observer variability of MRA is reported as near perfect for proximal stenosis of the CA and SMA and moderate for the IMA(39). MRA tends to overestimate stenosis, which decreases the specificity(39). MRA is less sensitive for detection of calcification compared to CTA and secondary signs of AMI as bowel wall thickening and mesenteric fat stranding are more difficult to assess. Furthermore, the resolution of MRA is not sufficient to visualize NOMI(40). Ernst et al. reported the comparison of MRA with DSA for visualization of the mesenteric vessels specific. They concluded a good agreement for the SMA and excellent agreement for the SMV and poor agreement for the branches of the SMA(41). MRA has similar performances to CTA in detecting mesenteric aneurysms(32). Table 3 shows the sensitivity and specificity of MRA for several mesenteric vascular pathologies.

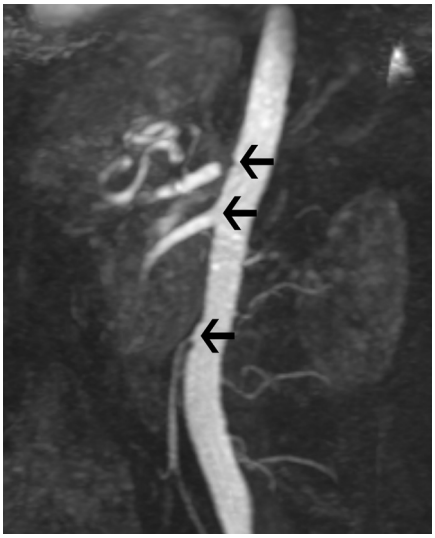

Image 17. MRA image of CA stenosis; the CA, SMA and IMA are top-down shown with the black arrows, respectively.

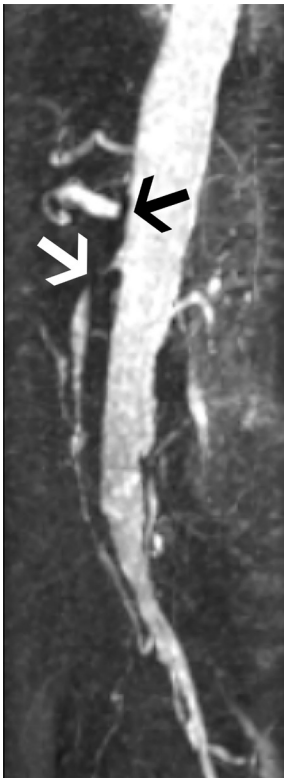

Image 18. MRA image of CA stenosis (black arrow) and SMA stenosis (white arrow).

Table 3. Overview of sensitivity and specificity rates of MRA

First author (publication year)	Pathology	MRA sensitivity	MRA specificity
Holland (74) (1996)	Mesenteric stenosis ≥ 50%	100%	100%
Meaney (60) (1997)	CMI > 75% stenosis	100%	95%
Kreft (75) (2000)	Portal venous thrombosis	100%	98%
Schaefer (48) (2013)	Mesenteric stenosis ≥ 50%	CA 92% SMA n.a.	CA 84% SMA 96%

MRA is not suitable to assess stent patency due to (metal) stent-induced artefacts. However, MRA is suitable for visualizing grafts, graft anastomoses, intimal hyperplasia of bypasses and follow up of vessel patency after PTA(42).

An advantage of MRI is the possibility to perform blood flow measurements, i.e. measurements of flow profiles, stroke volumes and peak velocities using cine phase contrast MR imaging. Cine phase contrast MR techniques enable non-invasive qualitative assessment of presence, magnitude and direction of blood flow in 2 and currently also 3 directions (4D MR flow). The retrieved dataset can be processed for estimation of blood flow velocity, volume flow rate and displaced volumes. In healthy subjects the mesenteric blood flow will increase after a meal. This increase can be measured 15 minutes postprandially with a peak velocity after 30 minutes. This postprandial blood flow increase assessed with cine phase contrast MR technique is reported in the SMA, SMV and PV(43-45). In patients with chronic mesenteric ischemia the mesenteric blood flow is suspected to increase less postprandially compared to healthy subjects, due to hemodynamically significant stenosis of one or more mesenteric vessels. Significantly less increase in postprandial blood flow of the SMV in patients with CMI compared to healthy subjects is shown with use of the MR flow technique. Although, the postprandial blood flow increase of the PV did not significantly differ in patients with CMI versus healthy subjects(45). Furthermore, the existence of a negative correlation between the degree of the SMA stenosis and the degree of postprandial blood flow increase in the SMA measured by MR has been reported(46). The cine phase contrast MR technique is a promising technique for non-invasive functional assessment of the mesenteric vasculature. More research is needed to assess the use of the technique in the diagnostic work-up for CMI and other mesenteric diseases.

Concluding, MRA is a non-radiation imaging technique that can visualize the proximal CA and SMA accurately. Due to lower resolution of MRA compared to CTA, the IMA and distal branches of CA and SMA are visualized less accurately. Cine phase contrast MR technique can assess the mesenteric blood flow pre- and postprandial non-invasively and might become a discriminatory functional test for in the diagnosis of CMI.

DSA

Catheter-based arteriography is the gold standard in diagnosing mesenteric arterial disease and still is the reference standard. Due to its invasive nature, and the technical improvements in CTA techniques, its use for diagnosis has been replaced by non-invasive CTA largely. Other less invasive modalities as DUS and MRA have been used increasingly for diagnosis as quality increased(47). Only one study compared the non-invasive modalities CTA, MRA and DUS with DSA. CTA provided the best image quality with the best diagnostic accuracy(48).

Angiography of the mesenteric vessels can be performed by a femoral, brachial or radial approach. Femoral or radial access is first choice as brachial access has a higher complication rate(49). In case of a steep angle of the mesenteric arteries with regard to the aorta, a radial approach may be more appropriate than a femoral approach. Sheath diameter should be chosen according to expected intervention and material used, but is generally 6-F or 7-F. Ultrasound guided puncture of the artery reduces the number of attempts and time required for acquiring access especially in the radial approach(50). Selective angiography is performed with 15-20ml iodine contrast medium for both the CA and the SMA. The use of low-osmolar contrast agent such as Visipaque 320 mg I/ml (GE Healthcare Inc., Medical Diagnostics, Princeton, New Jersey, USA) minimizes abdominal discomfort, but, again, has a nephrotoxic risk. The femoral access site is closed by manual hemostasis or a closure device such as Angioseal (St. Jude Medical, Austin, Texas). The radial access site is sealed using dedicated bandages.

Multiplane digital subtraction angiography of the abdominal aorta and its branches enables multiple oblique projections of the abdominal aorta and of the origin and outflow of the mesenteric arteries. At least antero-posterior and lateral views should be obtained. Selective angiography and views during ex- and inspiration are optional and of diagnostic importance in patients with MALS (Image 19 and 20). Early imaging is necessary for visualizing the origins of the CA and the SMA. Late imaging is required to evaluate the retrograde flow, delayed filling and collateral pathways(51). The dynamic imaging also provides information on flow direction, which may be valuable interpreting collateral circulation(52). Retrograde flow within the IMA, the arc of Riolan or common hepatic artery are indicative for stenosis of respectively the SMA and CA. Common collateral pathways are through the gastroduodenal arteries, arc of Riolan and Drummond. Well-established collaterals (grade 2) are clearly defined by non-selective

angiography (Image 21-23) however potential collaterals (prior to enlargement) (grade 1) may be more difficult to demonstrate but may be visible on more selective angiography (Image 24)(21, 53). Collaterals present during non-selective angiography are indicative for significant stenosis in contrast to selective angiography (grade 1)(21). A recent study shows a possible compensational role for type 2 collaterals as success rate after release of the CA in MALS was lower when type 2 collaterals were present(54).

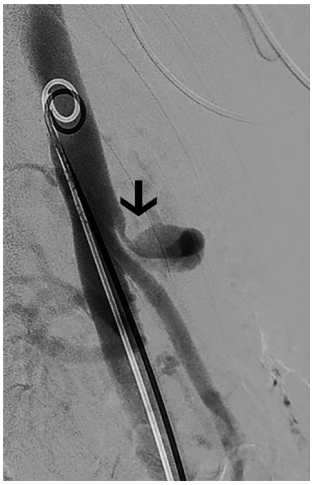

Image 19. Non-selective DSA in a patient with MALS in expiration (black arrow indicates the compression of the CA).

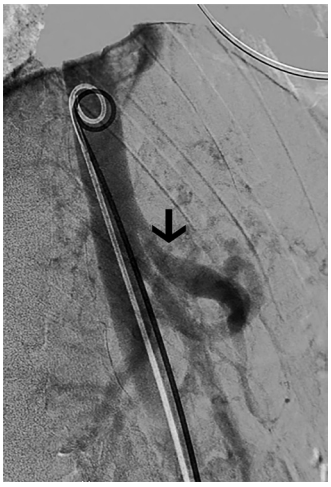

Image 20. Non-selective DSA in a patient with MALS in inspiration (black arrow indicates the CA).

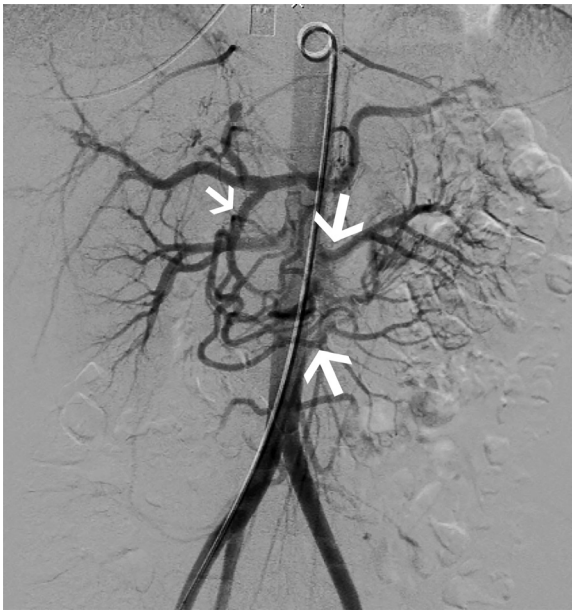

Image 21. Non-selective DSA in a patient with CA stenosis showing gastroduodenal grade 2 collaterals (white arrows indicate collaterals between SMA and CA with flow direction from large to small arrow).

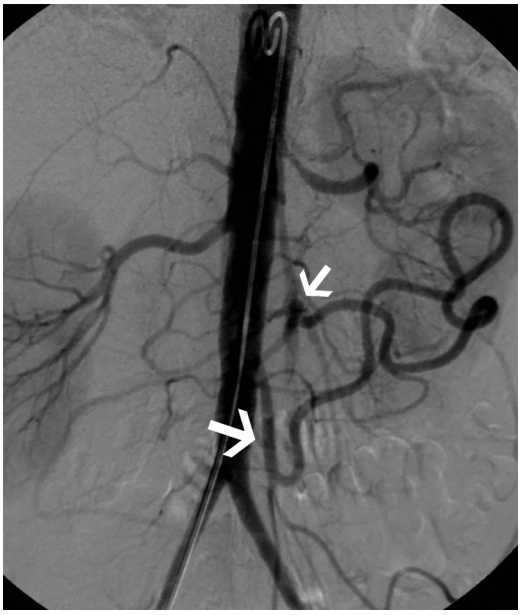

Image 22. Non-selective DSA (anterior-posterior plane) in a patient with CA and SMA stenosis showing grade 2 collateral from IMA through the arc of Riolan (white arrows indicate collateral with flow direction from large to small arrow).

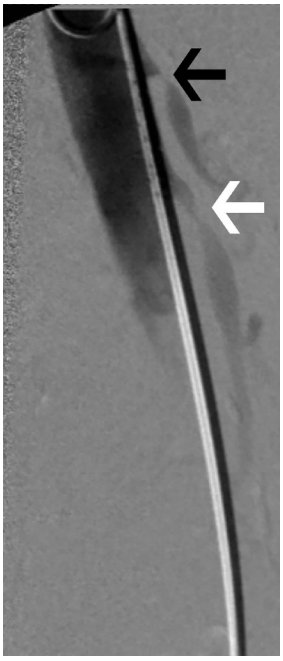

Image 23. Non-selective DSA in a patient with CA stenosis (black arrow) and SMA stenosis (white arrow) in lateral plane (same patient as image 22).

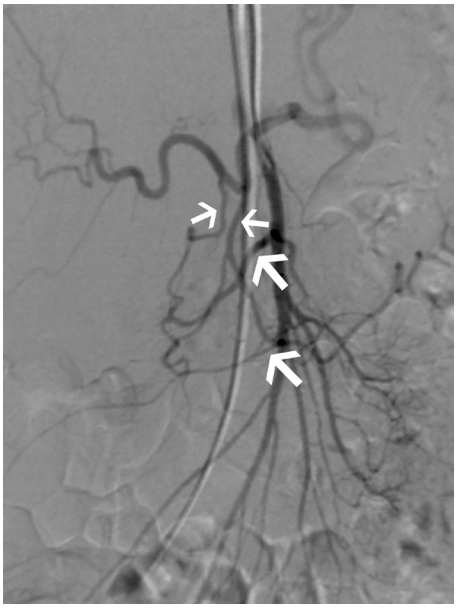

Image 24. Selective DSA of SMA showing grade 1 collaterals through the gastroduodenal pathway (from SMA to CA) in a patient with CA stenosis (white arrows indicate collaterals between SMA and CA with flow direction from large to small arrow).

Selective cannulation during angiography facilitates measurement of pressure gradients in case of doubtful stenosis(55). An alternative is fractional flow reserve (FFR) which is used for evaluation of the coronary circulation however its use in mesenteric arteries has yet to be established. Injection of a vasodilative drug such as priscoline or papaverine into the SMA may be used as a test to diagnose MALS(56). The vasodilator increases flow in the SMA, which in theory mimics a postprandial state with steal by decreasing the collateral flow to the CA bed with ischemic symptoms. Studies are needed to further determine the clinical significance of the visualization of collateral flow and FFR.

At present, angiography is mostly obtained in conjunction with a planned endovascular intervention, e.g. PTA or stent placement. Angiography however has its place in patients where other techniques provide insufficient information for example in case of extensive calcifications or presence of stents causing artefacts. Angiography also has its value in patients suspected for MALS, allowing more accurate imaging of the CA and its relation to the arcuate ligament during respiration.

CONCLUSION

Radiological imaging is essential for the diagnosis of mesenteric vascular disease. CTA and MRA are highly accurate vascular imaging modalities with high sensitivity and specificity for evaluation of the mesenteric vasculature and these imaging modalities have virtually replaced reference standard DSA as a diagnostic modality. However, DSA has a leading role in endovascular treatment of CMI and an emerging role in the treatment of AMI. CTA is the first-line approach in diagnosing acute and chronic mesenteric ischemia, because of its high spatial resolution and short acquisition time. The peripheral branches of the mesenteric vasculature and the IMA are assessed with greater accuracy compared to MRA and US. Moreover, CTA is lower in costs compared to MRA and more available in clinical practice. DUS is a non-invasive, non-radiating and non-nephrotoxic contrast agent exposing imaging modality, which is useful in the diagnosis of occlusive CMI and follow-up of revascularization therapy. Table 4 and 5 show the compared sensitivity and specificity rates of US, CTA and MRA compared with DSA as reference standard and the advantages, disadvantages and recommendations of each of these modalities are given, respectively. Because of the fast developments in imaging techniques more detailed non-invasive imaging becomes available including

functional assessment. An up-do-date comparison of the performance of the current imaging modalities for the diagnosis of mesenteric vascular pathology is needed.

Table 4. Overview of report comparing US, CTA and/or MRA in detecting of mesenteric stenosis

	US sensitivity	**US specificity**	**CTA sensitivity**	**CTA specificity**	**MRA sensitivity**	**MRA specificity**
Schaefer (48) (2013) stenosis ≥ 50%	CA 91% SMA n.a.	CA 91% SMA 96%	CA 100% SMA n.a.	CA 95% SMA 98%	CA 92% SMA n.a.	CA 84% SMA 96%

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Table 5. Overview of advantages, disadvantages and recommendations of image modalities of the mesenteric vasculature

	Advantages	Disadvantages	Recommendations
Duplex	- non-invasive - high sensitivity and specificity for proximal stenosis of CA and SMA - diagnosing of other causes of acute and chronic abdominal pain - no radiation exposure	- limited in distal stenosis - limited in visualizing IMA - operator independent - limited in obese patients, severe vessel calcification and if overlying bowel gas is present	- acute and non-acute setting - diagnosis of CMI - follow-up after revascularization
CTA	- fast - non-invasive - high sensitivity and specificity - identification of calcified plaques - visualization of entire gastrointestinal and genitourinary tract	- radiation exposure - nephrotoxic contrast agent - blooming artefacts when severe calcifications is present	- acute and non-acute setting - first line approach for AMI and CMI - follow-up after revascularization
MRA	- blood flow measurements - non-invasive - visualization of entire gastrointestinal and genitourinary tract - no radiation exposure	- increased scan time - decreased sensitivity for small vessel disease - stents causes artefacts - sensitive to motion artefacts	- non-acute setting - assessment of proximal CA and SMA - functional assessment with blood flow measurements
DSA	- both diagnosis and treatment	- invasive - radiation exposure - nephrotoxic contrast agent - procedure related complications	- acute and non-acute setting - diagnosis and treatment in one procedure

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CHAPTER
3

Validation of a score chart to predict the risk of chronic mesenteric ischemia and development of an updated score chart

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ABSTRACT

Background and objective

The objective of this article is to externally validate and update a recently published score chart for chronic mesenteric ischemia (CMI).

Methods

A multicenter prospective cohort analysis was conducted of 666 CMI-suspected patients referred to two Dutch specialized CMI centers. Multidisciplinary consultation resulted in expert-based consensus diagnosis after which CMI consensus patients were treated. A definitive diagnosis of CMI was established if successful treatment resulted in durable symptom relief. The absolute CMI risk was calculated and discriminative ability of the original chart was assessed by the *c*-statistic in the validation cohort. Thereafter the original score chart was updated based on the performance in the combined original and validation cohort with inclusion of celiac artery (CA) stenosis cause.

Results

In 8% of low-risk patients, 39% intermediate-risk of patients and 94% of high-risk patients of the validation cohort, CMI was diagnosed. Discriminative ability of the original model was acceptable (*c*-statistic 0.79). The total score of the updated chart ranged from 0 to 28 points (low risk 19% absolute CMI risk, intermediate risk 45%, and high risk 92%). Discriminative ability of the updated chart was slightly better (*c*-statistic 0.80).

Conclusion

The CMI prediction model performs and discriminates well in the validation cohort. The updated score chart has excellent discriminative ability and is useful in clinical decision making.

INTRODUCTION

Chronic Mesenteric Ischemia (CMI) is defined as ischemic symptoms caused by insufficient blood supply the gastrointestinal tract(1). The most common cause is atherosclerotic stenosis of one or more supplying gastrointestinal arteries(1, 2). Other common causes for mesenteric artery stenosis are vasculitis, and the most common cause for isolated celiac artery (CA) stenosis is compression of the CA by the median arcuate ligament (median arcuate ligament syndrome (MALS)). Chronic non-occlusive mesenteric ischemia (NOMI) is caused by hypoperfusion or hypooxygenation as can be seen in underlying conditions as cardiac or pulmonary disease, shunting, microvascular occlusion, and autonomic dysfunction(3).

The exact incidence of CMI is unknown, since population-based studies are lacking. However, the number of CMI patients undergoing revascularization procedures is increasing significantly according data from the United States (1.8 per million in 2000 to 5.6 per million in 2012 ($p<0.01$))(4). Considering the aging population and the increased prevalence of cardiovascular disease (CVD), the incidence of CMI is expected to increase in upcoming years.

Diagnosing CMI is important since untreated CMI may develop into acute-on-chronic mesenteric ischemia, which is associated with high morbidity and mortality. Since no gold-standard test for CMI is currently available, the diagnostic work-up consists of symptom assessment and radiological evaluation of the mesenteric arteries(3). Symptoms alone are associated with a low predictive value for CMI(2, 5, 6). If available, a functional test to assess mucosal ischemia as gastric-jejunal tonometry(7-9) or visible light spectroscopy (VLS)(10, 11) can enhance the diagnostic accuracy. A consensus diagnosis is established in a multidisciplinary meeting(1), an accepted method in the absence of one specific test(12). A definitive diagnosis of CMI is established when revascularization for occlusive mesenteric ischemia or medical therapy for chronic NOMI results in durable symptom relief.

The diagnostic work-up for CMI is cumbersome and time-consuming since multiple tests are required. This exposes patients to invasive diagnostic interventions and because of the need for successive investigations may lead to a delay in treatment for patients with CMI. This underlines the need for an easy-to-use tool to promptly and reliably assess the risk of CMI in patients suspected of having this diagnosis to guide clinical decision-

making: 1) patients with low risk of CMI for which a wait-and-see policy is justified to save them from unnecessary diagnostics, 2) patients with intermediate risk of CMI for which further testing to assess mucosal oxygenation such as VLS or tonometry is indicated to establish the diagnosis and 3) patients with high risk of CMI for whom no additional test is indicated and require intermediate vascular intervention.

Recently, a CMI prediction model based on a large single-center prospective cohort was published by our study group that identifies low-risk, intermediate-risk and high-risk patients(13). The score chart of this model consists of 5 predictors: female sex, presence of weight loss, presence of CVD, degree of CA stenosis, and degree of superior mesenteric artery (SMA) stenosis (Table 1). However, this CMI prediction model did not include the cause of the CA stenosis, such as MALS or atherosclerosis, which differ in patient presentation and patient characteristics(2). Since it was expected by experts in the field that the specific cause of CA stenosis would result in different predictive values for the risk of CMI, this variable was added to the updated model.

The current diagnostic work-up for CMI is extensive and cumbersome. A validated tool is much needed to stratify patients suspected of CMI in distinct risk groups to guide clinical decision making. Such a tool and corresponding strategy should result in a more optimal identification of patients with CMI whom may profit from treatment using tailored diagnostics and should lead to a decrease in patient-burden and reduced health costs. We aimed to externally validate the previously published CMI prediction model in a new multicenter cohort. Furthermore, we aimed to update the score chart based on the performance of the model by combining the original and validation cohort and by including the CA stenosis cause.

MATERIAL AND METHODS

Study design and setting validation cohort

A multicenter, prospective cohort study was conducted for all consecutive patients suspected of CMI referred to two Dutch centers specialized in functional testing for mucosal ischemia: Erasmus MC University Medical Center Rotterdam (inclusion January 2014 to July 2016) and Medisch Spectrum Twente Enschede (inclusion May 2015 to January 2016). Patients were suspected of CMI based on the criteria for the original cohort of Harki et al(13). Patients without radiological evaluation of the mesenteric

arteries with computed tomography angiography (CTA) or magnetic resonance angiography (MRA) were excluded.

The medical research ethics committee of Erasmus MC University Medical Center approved that the Medical Research Involving Human Subjects Act does not apply to this study and that no informed consent was required according to the local directives (MEC-2013-317). The study complies with the Helsinki declaration on research ethics. To enhance transparency this article is written according to the STROBE checklist for cohort studies(14).

Data sources

All data was retrieved from the hospital records in the context of standard clinical care. Follow-up of patients was by means of outpatient clinic contact or by phone. Standard protocol visits were scheduled 1, 3, 6, 12, and 24 months after revascularization during which recurrent symptoms (i.e. similar to presenting symptoms before therapy) were assessed and body weight was documented.

Participants

All included patients underwent a standardized diagnostic work-up for CMI at baseline. This work-up consists of symptom assessment, physical examination, imaging of the mesenteric arteries with either CTA and MRA, and a functional test for mucosal ischemia detection with either 24-hour gastric-jejunal tonometry, gastric exercise tonometry or VLS(6-8, 10, 15-17).

All cases were discussed in a multidisciplinary meeting attended by gastroenterologists, vascular surgeons and interventional radiologists, all specializing in CMI. An expert-based consensus diagnosis of CMI was established if two of the following three criteria were met: 1) typical clinical presentation of CMI (postprandial abdominal pain, weight loss, or diarrhea); 2) significant stenosis of at least the CA or SMA (≥ 50% diameter reduction(18-21)) on CTA or MRA and/or conventional catheter angiography; 3) mucosal ischemia as determined by 24-hour gastric-jejunal tonometry, gastric exercise tonometry or VLS(7, 10).

The degree of stenosis of the mesenteric arteries was calculated on CTA or MRA using interactive vessel segmentation software. The stenosis degree was classified in <50% stenosis, 50%-70% stenosis or ≥70% stenosis.

Definitive diagnosis of CMI

Patients with a consensus diagnosis of CMI based on occlusive disease were scheduled for either endovascular or surgical revascularization. Patients with stenosis of one or more mesenteric arteries based on vascular disease were scheduled first for endovascular revascularization: percutaneous mesenteric artery stenting (PMAS). If patients were not eligible for PMAS or if patients had recurrent episodes of restenosis, they were treated with open surgical mesenteric artery repair (OSMAR).

In patients with a CA stenosis the diagnosis of MALS was established if CTA demonstrated focal narrowing of the proximal CA ≥50% with post-stenotic dilatation and eccentric indentation on the superior aspect of the CA, creating a hook-shaped contour of the CA. This characteristic kinking dependent on the respiratory cycle in the absence of calcifications distinguishes this condition from other causes of CA stenosis such as atherosclerosis(22). When CTA did not clarify the cause of CA stenosis, an additional catheter angiography of the CA in inspiration and expiration was performed. Patients with CA stenosis based on MALS were planned for surgical release (open or endoscopic) of the median arcuate ligament.

Patients with a consensus diagnosis of chronic NOMI were treated with vasodilatory medical therapy: oral nitrates (isosorbide mononitrate or isosorbide dinitrate). First, a low dose was prescribed (10-20 mg twice per day) and if symptoms preserved with the absence of side effects the dose was increased (to 40 mg twice per day). Nitrates were replaced by Ketansarin (selective α1-receptor antagonist) if side effects occurred and/or clinical improvement was absent, starting with a 10-20 mg twice per day and increased to 40 mg twice per day.

The treated patients were evaluated during follow-up visits. A definitive diagnosis of CMI was established if the patient reported relief of initial symptoms after successful therapy. This patient-reported outcome of symptom relief was classified into two groups: no or minimal symptom relief and major or complete symptom relief. A definitive diagnosis of no CMI was established when consensus diagnosis was no CMI

or when symptom relief did not occur after technically successful treatment. Patients with a consensus diagnosis of no CMI were discharged without further follow-up.

Variables

Patient characteristics that were collected included age, sex, past medical history, presenting symptoms such as abdominal pain, postprandial pain, diarrhea, nausea, weight loss (in kg, defined as >5% loss of body weight), body mass index (BMI) at presentation, and cardiovascular risk factors. Vascular lesions were specified for localization (CA, SMA or inferior mesenteric artery (IMA)) and cause (vascular disease, MALS, NOMI).

The primary outcome was definitive diagnosis: CMI or no CMI. The definitive diagnosis was compared with the total score of the score chart to validate this score chart. Secondary outcome was the cause of CMI (vascular disease versus MALS).

Score chart

The score chart (Table 1) was applied for each included patient. Based on the total score each patient was classified in one of three risk groups: low-risk (0-2 points), intermediate-risk (3-6 points) and high-risk (≥7 points).

Table 1. Score chart for the prediction of CMI and the absolute CMI risk from Harki et al.(13).

Predictor		**Scoring points**
Sex		
	Male	0
	Female	1
Weight loss		
	No	0
	Yes	1
Cardiovascular disease		
	No	0
	Yes	1
Celiac artery		
	50-70% stenosis	1
	>70% stenosis	4
Superior mesenteric artery		
	50-70%	1
	>70% stenosis	3
Total score	**Risk group**	**Absolute CMI risk (%)**
0-2 points	Low	21%
3-6 points	Intermediate	46%
7+ -	High	79%

CMI = chronic mesenteric ischemia.

Study size

There was a requirement to include minimally 215 patients suspected of having CMI assuming a CMI diagnosis rate of 47%(13) according to literature recommendations on sample size considerations for the external validation of a multivariable prognostic model(23, 24).

Statistical methods

Baseline characteristics were described for the validation cohort either as numbers and percentages for dichotomous variables, or as means and standard deviations or medians and interquartile ranges (IQR) for continuous variables. Multiple imputation (10 times) was used to impute missing values of the predictors from the score chart and cause of CA stenosis. Univariable and multivariable associations were estimated with logistic regression analysis as odds ratios (ORs) with a 95% confidence interval (CI). The added

value of cause of the stenosis of the CA (vascular disease versus MALS) was assessed by including the variable in the multivariable logistic regression.

Performance of the original score chart was studied by comparing the definitive diagnosis with the total score of the score chart. Discriminative ability of the score chart was assessed with the *c*-statistic. This measure of concordance is identical to the area under the receiver-operating characteristics (ROC) curve. *C*-statistic of 0.5 suggests no discrimination, *c*-statistic of 0.7-0.8 is considered as acceptable discrimination, *c*-statistic of 0.8-0.9 as excellent discrimination and *c*-statistic ≥0.9 as outstanding discrimination(25). Furthermore, calibration was assessed graphically with a calibration plot: a plot with the predicted risk of CMI on the X-axis and the observed proportion of CMI on the Y-axis. After validating the score chart in the validation cohort, the data of the validation cohort was combined with the data of the original cohort described by Harki et al(13). The original score chart was updated based on the performance of the score chart in the combined original cohort and validation cohort and with inclusion of the cause of the CA stenosis based on expert view. Scores for the updated score chart were calculated by dividing the regression coefficients of the predictors by 0.17. Calibration and discriminative ability were also tested for the updated score chart.

RESULTS

Patient characteristics of validation cohort

During the study period, 246 patients suspected of CMI were included in the validation cohort. A consensus diagnosis of CMI was established in 105/246 patients (43%). After treatment for CMI a definitive diagnosis of CMI was established in 93/105 patients (89%). A flow chart is shown in Figure 1. Mean age in the validation cohort was 61 years, the majority was female (70%) with a mean symptom duration of 2 years (Table 2). Table 3 lists the consensus diagnosis, definitive diagnosis, vascular lesions, and cause of stenosis for each risk group according the original score chart in the validation cohort. The majority of patients in the low-risk group did not have significant vascular lesions (75%) whereas all patients of the high-risk group had at least one significant mesenteric stenosis, 96% being atherosclerotic. Furthermore, the majority of the patients in the high-risk group had multi-vessel disease (88%).

The follow-up period was 10.5±6.6 months for the patients with a consensus diagnosis of CMI and 3.7±6.6 months for the patients with a consensus diagnosis of no CMI.

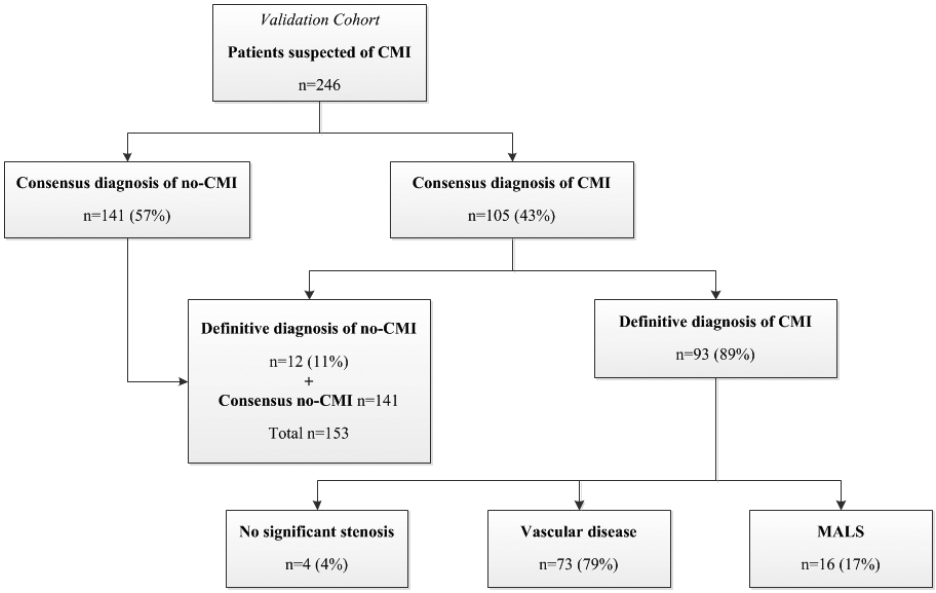

Figure 1. Flowchart of validation cohort.
CMI = chronic mesenteric ischemia; MALS = median arcuate ligament syndrome.

Table 2. Patient characteristics and presenting symptoms of validation cohort.

	All patients n=246	Definitive diagnosis of CMI n=93	No definitive diagnosis of CMI n=153
Patient characteristics			
Age (y)	60.9±16.6	65.8±14.4	57.9±17.2
Female	171 (69.5%)	58 (62.4%)	113 (73.9%)
Hypertension*	122 (49.6%)	62 (66.7%)	60 (39.2%)
Ever smoked	179 (73.7%)	79 (85.9%)	100 (66.2%)
Dyslipidemia#	123 (50.2%)	62 (67.4%)	61 (39.9%)
Diabetes	42 (17.1%)	25 (26.9%)	17 (11.1%)
BMI at presentation (kg/m^2)	23.5±4.8	23.5±5.1	23.4±4.6
History of CVD	133 (54.1%)	68 (73.1%)	65 (42.5%)
Presenting symptoms			
Symptom duration (months)	23.6±59.3	18.0±31.4	27.1±71.1
Abdominal pain	231 (93.9%)	88 (94.6%)	143 (93.5%)
Postprandial pain	166 (67.8%)	65 (70.7%)	101 (66.0%)
Exercise related pain	78 (35.0%)	23 (28.7%)	55 (38.5%)
Nausea	128 (57.9%)	51 (60.0%)	77 (56.6%)
Diarrhea	72 (30.6%)	32 (36.8%)	40 (27.0%)
Weight loss	169 (68.7%)	76 (81.7%)	93 (60.8%)

Data are presented as N (percentages) or as mean ± SD. *Hypertension was defined as a blood pressure of ≥140/90 mmHg or use of antihypertensive medication. #Dyslipidemia was defined as LDL-C >4.2 mmol/L or HDL-C <0.9 mmol/L or use of lipid lowering medication.
BMI = body mass index; CMI = chronic mesenteric ischemia; CVD = cardiovascular disease.

Table 3. Diagnosis, vascular lesion, and cause of the vascular lesion specified for each risk group according the original score chart of the validation cohort.

	Low-risk (0-2 pts) n=92	Intermediate-risk (3-6 pts) n=106	High-risk (≥7 pts) n=48
Diagnosis			
Consensus diagnosis CMI	10 (10.9%)	49 (46.2%)	46 (95.8%)
Definitive diagnosis CMI	7 (7.6%)	41 (38.7%)	45 (93.8%)
Cause of the vascular lesion			
No sign. vascular lesion[#], no ischemia	69 (75.0%)	13 (12.3%)	0 (0.0%)
Vascular disease	7 (7.6%)	57 (53.7%)	42 (87.5%)
MALS	7 (7.6%)	33 (31.1%)	2 (4.2%)
NOMI	6 (6.5%)	1 (0.9%)	0 (0.0%)
Atherosclerosis + NOMI	3 (3.3%)	0 (0.0%)	1 (2.1%)
Atherosclerosis + MALS	0 (0.0%)	1 (0.9%)	3 (6.3%)
MALS + NOMI	0 (0.0%)	1 (0.9%)	0 (0.0%)
Vascular lesion localization			
No significant vascular lesion[#]	75 (81.5%)	14 (13.2%)	0 (0.0%)
Single vessel	16 (17.4%)	70 (66.0%)	6 (12.5%)
CA stenosis	10 (62.5%)	52 (74.2%)	5 (83.3%)
SMA stenosis	0 (0.0%)	17 (24.3%)	1 (16.7%)
IMA stenosis	6 (37.5%)	1 (1.4%)	0 (0.0%)
Multi vessel	1 (1.1%)	22 (20.8%)	42 (87.5%)
CA and SMA stenosis	0 (0.0%)	9 (40.9%)	16 (38.1%)
CA and IMA stenosis	0 (0.0%)	4 (18.2%)	1 (2.4%)
SMA and IMA stenosis	1 (100%)	6 (27.3%)	0 (0.0%)
CA, SMA and IMA stenosis	0 (0.0%)	3 (13.6%)	25 (59.5%)

[#] No significant vascular lesion = no stenosis or stenosis < 50%
Data are presented as n (percentages).
CA = celiac artery; CMI = chronic mesenteric ischemia; IMA = inferior mesenteric artery; MALS = median arcuate ligament syndrome; NOMI = non-occlusive mesenteric ischemia; pts = points; SMA = superior mesenteric artery.

Performance original score chart

The original score chart performed good in the validation cohort with an absolute CMI risk of 8% in the low-risk group (original cohort: 21%(13)), 39% in the intermediate-risk group (original cohort: 46%(13)) and 94% in the high-risk group (original cohort: 79%(13)). Discriminative ability was acceptable with a *c*-statistic of 0.79 (original cohort: 0.79). Calibration results of the original model in the combined cohort are shown in

Figure 2a. Perfect prediction of CMI would show when all points are on the 45° (dashed line) because of a slope of 1 and calibration intercept of 0.

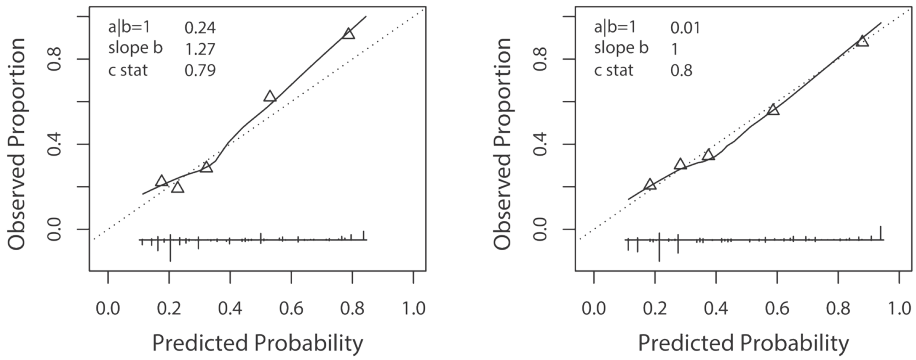

Figure 2. Performance of the original score chart (a) and the updated score chart (b) based on the combined cohort (n=666).
Alb = intercept *a,* slope b = calibration slope, c stat = *c*-statistic.

Combined cohort

The observed frequencies of CMI in the original cohort, validation cohort and combined cohort are shown in Table 4 specified per hospital. The frequency of CMI was higher in the original cohort (47%) than in the validation cohort (38%). Table 5 shows the multivariable logistic regression analyses of the combined cohort with the 5 predictors of the original score chart and with interaction of the CA stenosis cause (vascular disease versus MALS). Sex showed no effect in the combined cohort (female OR=1.01, 95% CI 0.68-1.52).

Table 4. Observed frequencies of CMI in the original, validation and combined cohort specified per hospital.

Center	Original cohort n=420	Validation cohort n=246	Combined data n=666
Erasmus MC	196/420 (46.7%)	42/136 (30.1%)	238/556 (42.8%)
Medisch Spectrum Twente	-	51/110 (46.6%)	51/110 (46.6%)
Total	196/420 (46.7%)	93/246 (37.8%)	289/666 (43.4%)

Table 5. Results of the multivariable logistic regression analyses in the combined cohort; odds ratio (95% confidence interval).

Predictors	Combined cohort n=666
Female	1.01 (0.68-1.52)
Weight loss	2.22 (1.47-3.35)
CVD	1.40 (0.95-2.07)
50-70% CA stenosis - vascular disease	1.82 (0.96-3.44)
50-70% CA stenosis - MALS	1.94 (0.77-4.91)
> 70% CA stenosis - vascular disease	6.62 (3.95-11.09)
> 70% CA stenosis - MALS	4.53 (2.43-8.44)
50-70% SMA stenosis	2.02 (0.99-4.15)
>70% SMA stenosis	5.94 (3.42-10.31)

CA = celiac artery; CMI = chronic mesenteric ischemia; CVD = cardiovascular disease; MALS = median arcuate ligament syndrome; SMA = superior mesenteric artery.

Updated score chart

Table 6 shows the updated score chart with the absolute CMI risk. We included the interaction of the CA stenosis cause based on expert view, although not statistically significant (p=0.541). The score of the updated chart ranged from 0 to 28 points, with 0 to 5 points indicating a low risk of CMI of 19% (low-risk original score chart in combined cohort: 22%), 6 to 18 points indicating an intermediate risk of 45% (intermediate-risk original score chart in combined cohort: 45%), and 19 points or more indicating a high risk of 92% (high-risk original score chart in combined cohort: 87%). The low-risk group consisted of 247 of the 666 patients of the combined cohort (37%), the intermediate-risk group of 305 (46%) patients, and the high-risk group consisted of 114 (17%) patients.

Figure 2b shows the calibration of the updated score chart. The updated model is based on the data of the combined cohort and resulted in a calibration intercept close to 0 and calibration slope *b* (slope b) close to 1. The discriminative ability of the updated model is excellent with a *c*-statistic of 0.80.

Table 6. Updated score chart for the prediction of CMI.

Predictor		**Scoring points**
Weight loss		
	No	0
	Yes	5
Cardiovascular disease		
	No	0
	Yes	2
Celiac artery		
	50-70% stenosis – vascular disease	4
	50-70% stenosis – MALS	4
	>70% stenosis – vascular disease	11
	>70% stenosis - MALS	9
Superior mesenteric artery		
	50-70% stenosis	4
	>70% stenosis	10
Total score	**Risk group**	**Absolute CMI risk (%)**
0-5 points	Low	19.4%
6-18 points	Intermediate	44.6%
19+	High	92.1%

CMI = chronic mesenteric ischemia; MALS = median arcuate ligament syndrome.

DISCUSSION

In this multicenter study, we performed an external validation of the recently developed score chart to predict the risk of CMI. Next, we developed an updated version of the score chart based on the performance of the score chart in the combined cohort and with inclusion of the CA stenosis cause. CMI predictors of the updated score chart are presence of weight loss, presence of CVD, the degree of CA stenosis combined with the cause of CA stenosis and the degree of SMA stenosis. The updated score chart is an easy-to-use and reliable tool to discriminate the risk of CMI (*c*-statistic 0.80).

The findings of our cohort analysis in 666 CMI suspected patients, the largest cohort described, correspond with the recently published clinical practice guidelines Management of the diseases of mesenteric arteries and veins(1) by the European Society of Vascular Surgery. Weight loss is an important symptom for the diagnosis of CMI according the guideline and the advice is given to perform additional analyses

for an alternative diagnosis in patients suspected of CMI without substantial weight loss. Our data confirm that weight loss is the only predictive clinical symptom in the prediction model. In accordance with the guidelines stating that patients with CMI have atherosclerotic involvement in other locations(26, 27) our score chart incorporated the presence of cardiovascular disease as a predictor of CMI. Finally, the guidelines recommends considering the diagnosis of CMI in patients with otherwise unexplained abdominal symptoms and occlusive disease of two or three mesenteric arteries. This corresponds with our findings that multi vessel disease is present in 88% of the high-risk patients as opposed to only 1% multi vessel disease in low-risk patients.

In contrast with the original score chart, female sex is not a predictor in the updated score chart. Female preponderance for CMI is reported in literature(26, 27) and we show that the majority (70%) of the patients with definitive CMI are female in the combined cohort. However, the majority of patients without CMI are also female (65%).

We recommend the updated model for clinical practice since it is based on a more heterogeneous data set from a multicenter cohort, which supports its generalizability. Its applicability is also boosted by inclusion of the cause of CA stenosis. Experts expressed reservations regarding the original score chart because it lacked the cause of CA stenosis while clinical presentation and patient characteristics differ between those with atherosclerotic CMI and CMI based on MALS. The updated score chart shows a higher predictive value for vascular disease in case of >70% CA stenosis.

Both the original and the validation cohort include patients with chronic NOMI. Patients with NOMI present with typical symptoms of CMI. Chronic NOMI patients however will not be readily identified as high risk using the score chart because of a maximum score of 7 points in the absence of mesenteric artery stenoses. Subsequently chronic NOMI patients are classified as low risk or intermediate risk. Based on symptom development they will undergo immediate or later additional testing to establish or negate the diagnosis of CMI.

We suggest a wait-and-see policy for the patients classified as low-risk by the updated score chart since the symptoms in this patient group are minor and immediate treatment is not required. According to the score chart, 19% of the patients in the low-risk group will have CMI and their CMI is caused by NOMI or single vessel disease. The delay in CMI diagnosis for the 19% patients suffering from CMI in the low-risk group can be defended

since these patients are under the control of a physician during the wait-and-see policy who may intervene when the clinical situation during follow-up worsens. With this wait-and-see strategy, on the other hand, patients without CMI in the low-risk group (81%) are spared unnecessary diagnostics procedures.

This study carries several limitations. An inevitable limitation is the absence of a gold-standard clinical test for the diagnosis of CMI. A working diagnosis is established by multidisciplinary consensus opinion and a definitive diagnosis is established when treatment results in durable symptom relief(3). Symptom relief is considered to be the most important and relevant patient related outcome. This response was noted as a dichotomous variable to limit interpretation bias. However, the patients reported symptom relief to the same team which participated in the multidisciplinary meeting reaching the consensus diagnosis of CMI, for which reason reporting bias cannot be excluded. Patients with a consensus diagnosis of no-CMI were not selected for therapy and discharged without further follow-up. The results of our prediction model can be extrapolated only to patients suspected of having CMI. Therefore, this model should not be used for patients with gastrointestinal symptoms in general, but only for those with a clear suspicion of CMI after other causes have been excluded. Incorporation bias may have possibly led to overestimation of the diagnostic accuracy of the score chart for CMI(28). Finally, the original cohort described by Harki et al. consisted of 436 patients(13). The data set used for the current combined cohort analysis consisted of 420 patients of the original cohort because of missing data. In view of the sizable number of 666 patients in the current analysis, we assume that the effect of missing data of these 16 patients is negligible.

In conclusion, we externally validated a previously published score chart to predict the risk of CMI. We also updated the original score chart and included the cause of CA stenosis based on expert view. The updated score chart shows a good performance and an excellent discriminative ability. This updated score chart is a useful-tool to be used in clinical practice to stratify CMI suspected patients in 3 groups: 1. wait-and-see policy justified, 2. additional functional testing indicated and 3. immediate vascular intervention justified.

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CHAPTER
4

Intraobserver and interobserver reliability of visible light spectroscopy during upper gastrointestinal endoscopy

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ABSTRACT

Background

Visible light spectroscopy (VLS) performed during upper gastrointestinal endoscopy allows measuring mucosal oxygen saturation levels to determine gastrointestinal ischemia. We aimed to determine the observer variability of VLS.

Research design and methods

This is a single-center prospective study of 24 patients planned for usual care upper endoscopy. To test intraobserver variability, VLS-measurements were performed in duplicate by a single endoscopist in 12 patients. For interobserver variability analysis, in another 12 patients VLS-measurements were repeatedly and independently performed by two endoscopists in the same patient during the same endoscopy session. Observer variability was assessed with intraclass correlation coefficient (ICC) and clinical disagreement defined as >5% difference between 1st and 2nd set VLS-measurements.

Results

The intraobserver reliability was excellent (ICC antrum 0.77, duodenal bulb 0.81 and duodenum 0.84) with clinical disagreement only in antrum (3% of all intraobserver measurements). The interobserver reliability was good for the duodenal bulb (ICC 0.70) without clinical disagreement, however interobserver reliability was fair for duodenum (ICC 0.49) and antrum (ICC 0.56) with clinical disagreement occurring in 11% of all interobserver measurements.

Conclusions

The observer reliability of VLS is fair to good with intraobserver reliability being better than interobserver reliability. This supports the use of VLS for detection of gastrointestinal ischemia.

INTRODUCTION

Chronic Mesenteric Ischemia (CMI) is defined as ischemic symptoms caused by insufficient blood supply to the gastrointestinal tract(1). CMI affects the upper gastrointestinal tract, while colonic ischemia affects the lower gastrointestinal tract. Patients with CMI may present with a range of symptoms, including postprandial abdominal pain and weight loss, malabsorption, villous atrophy, and gastroduodenal ulceration. These result from insufficient mesenteric blood flow, usually caused by atherosclerotic stenosis of the supplying gastrointestinal arteries. For long, a diagnosis of CMI could only be based on symptoms, physical exam, and vascular imaging. The lack of a functional test was an important shortcoming, likely leading to underdiagnosis and overdiagnosis of CMI. In recent years, substantial research efforts led to two functional tests; tonometry(2, 3) and more recently Visible light spectroscopy (VLS)(4, 5). VLS oximetry is a technique to determine the mucosal capillary hemoglobin oxygen saturation(6) by closely mimicking the widely used pulse oximetry. VLS performed during upper endoscopy allows measuring the oxygen saturation of the mucosa of the upper gastrointestinal tract. CMI is characterized by decreased mucosal saturation. Functional testing by means of VLS thus represents a tool for diagnosis of CMI and this technique is currently used in clinical practice for the diagnostic work-up of patients suspected of CMI(7).

VLS-measurements are noninvasive and performed during upper endoscopy using a fiberoptic probe passed through the accessory channel of the endoscope. This probe emits white light and detects differences in the absorption spectra of the oxygenated and deoxygenated hemoglobin molecules(6). The measured mucosal saturation reflects indirectly the adequacy of the gastro-intestinal blood flow. VLS-measurements are performed in clinical practice at three different locations during upper endoscopy: the antrum of the stomach, the duodenal bulb and the descending duodenum. Based on previously determined cut-off values (4) in CMI suspected patients, the outcomes are defined positive for ischemia if the measured saturation value is lower than 63% in the antrum, 62% in the duodenal bulb and 58% in the descending duodenum in fasting state.

The sensitivity and specificity rates for VLS for the diagnosis CMI are 90% and 60%, respectively(4). Given its ease of use, VLS has the capacity to become the standard for CMI assessment, both for initial diagnosis as well as for follow-up of patients after therapeutic intervention. Since VLS is a relatively new functional test, further validation

is needed. To validate a novel diagnostic test it is mandatory to establish its observer variability.

The rationale of this study was to determine the interobserver variability and intraobserver variability of the VLS-measurements in order to establish the reliability and reproducibility of this technique.

PATIENTS AND METHODS

Study design

A single center prospective study was performed to evaluate the intraobserver and interobserver variability of VLS. Patients, who were planned for upper endoscopy in our center from March 2017 till August 2017, were screened for eligibility for this study. The study was approved by the medical research ethics committee of the Erasmus MC University Medical Centre (NL59989.078.17) and informed consent was obtained for all participants.

Participants

All patients of 18 years or older and planned for usual care upper endoscopy were eligible. Exclusion criteria were: referral for suspicion of CMI, pregnancy, previous surgery of the upper gastro-intestinal tract including small bowel, and contra-indication for the use of butylscopolamine.

Upper endoscopy with VLS-measurements

All patients underwent an upper endoscopy for usual care with additional VLS-measurements. If sedation was administered, this consisted of midazolam intravenously (dose 2.5-5 mg) combined with fentanyl (dose 0.05 mg). Peripheral oxygen saturation and heart rate were continuous monitored. Oxygen was administered intranasally if necessary to maintain peripheral saturation level ≥ 95% during the VLS-measurements.

The VLS-measurements were performed with a fiberoptic probe (Endoscopic T-Stat Sensor; Spectros, Portola Valley, California) passed through the accessory channel of the endoscope. This probe was placed just above the mucosa (1-5 mm) of the target area, after any bile remnants were removed. The light of the endoscope was switched off and the reading of the mucosal saturation started on the monitor connected with

the probe (T-Stat 303 Microvascular Oximeter; Spectros, Portola Valley, California). The reading showed small rapid variations due to true changes in saturation and due to small changes in the position of the probe. A reading was noted if a stable measurement was obtained which is a measurement that recurrences several times during the small rapid variations of a reading. The highest saturation was noted. The probe was repositioned within the measurement site and a new measurement was performed. Three repeated readings per site were noted with fewer than 5% variation and these 3 readings were averaged reflecting the most accurate mucosal saturation at that site. These saturation measurements were performed at three different locations: the antrum of the stomach, the duodenal bulb and the descending duodenum since the cut-off values are determined for these 3 locations(4). All VLS-measurements during this study were performed before any biopsy was executed or any contrast-agent was administered. In case intestinal spasms limited obtaining proper measurements, butylscopolamine (10-20 mg) was intravenously administered. Duration of the 1st set and 2nd set of VLS-measurements was noted.

Intraobserver variability

To test intraobserver variability, VLS-measurements were performed at the three respective locations and these measurements where thereafter duplicated by a single endoscopist. The endoscopist was blinded for all VLS outcomes.

Interobserver variability

For interobserver variability analysis, in another group of patients VLS-measurements were repeatedly and independently performed by two endoscopists in the same patient during the same endoscopy session. Both endoscopists were blinded for the VLS outcomes.

Follow-up

Follow-up data were gathered in the context of usual care. All patients were seen by a physician in the weeks following upper endoscopy. Complications of the upper endoscopy and of the VLS-measurements were reported.

Variables

Baseline characteristics included age, gender, body mass index (BMI), smoking, indication of upper endoscopy and the complaints of the patient. Characteristics of the upper endoscopy included duration, administration of butylscopolamine and the aspect of gastro-intestinal mucosa. Characteristics of the endoscopists included experience, number of upper endoscopies performed, VLS experience in months, and number of VLS performed.

Primary outcome was interobserver variability and intraobserver variability quantified with the intraclass correlation coefficient (ICC) and percentage of clinical disagreement. VLS-measurements were noted in percentages. Secondary outcome were duration of VLS-measurements, procedure-related morbidity and mortality.

Statistics

Baseline characteristics and secondary outcomes were described as counts and percentages for

dichotomous variables, or means and standard deviations or medians and interquartile ranges (IQR) for continuous variables. For differences in baseline characteristics and variables $\chi 2$ test or Fisher's exact test was used for dichotomous variables and Student's t-test for continuous variables. Statistical significance was defined as $p\text{-value} < 0.05$.

First, the mean VLS-measurements of the first set of measurements were compared with the second set of measurements of the specific locations for the intraobserver and interobserver variability analysis using a paired t-test. Second, the ICC was computed for exact agreement. The ICC for the intraobserver and interobserver variability was calculated using the Two Way Random model with absolute agreement(8-10). However, the ICC did not take into account what may be viewed as clinically meaningful disagreement between individual ratings. Therefore, a value of 5% was set to define clinical disagreement and we calculated the percentage of ratings that differed at least 5%. The ICC ranges used were defined according Cicchetti et al. (11) and were less than 0.40 (poor), 0.40-0.59 (fair), 0.60-0.74 (good) and 0.75-1.00 (excellent). The range of disagreement was visualized with a Bland-Altman plot(12). Statistical analysis was performed using the SPSS Statistics 23 (IBM Inc., Chicago, IL).

Sample size

We determined an inclusion of 12 patients for the assessment of interobserver variability and another 12 patients for the intraobserver assessment to detect an acceptable ICC of 0.60-0.74 and a desirable ICC of 0.75 or larger for observer variability with an alpha of 0.05 and a power of 80%(13).

RESULTS

Twelve patients planned for upper endoscopy were included for the intraobserver analysis and another 12 patients planned for upper endoscopy were included for the interobserver analysis. Patient characteristics, indication of upper endoscopy and complaints of the included patients are specified in Table 1 and the characteristics of the upper endoscopy with VLS-measurements are specified in Table 2. Table 3 shows the characteristics of the endoscopist for the intraobserver analysis and the characteristics of the two endoscopists for the interobserver analysis.

Table 1. Patient characteristics, indication of upper endoscopy and complaints.

	All (n=24)	**Intra-observer** (n=12)	**Inter-observer** (n=12)
Patient characteristics			
Male	12 (50%)	8 (66.7%)	4 (33.3%)
Age (y)	61.1 ± 12.5	63.3 ± 10.8	58.8 ± 14.0
BMI (kg/m^2)	27.4 ± 5.7	24.9 ± 4.0	29.1 ± 6.9
Ever smoked	17 (70.8%)	7 (58.3%)	10 (83.3%)
Indication of upper endoscopy			
Surveillance Barrett	4 (16.7%)	3 (25%)	1 (8.3%)
Surveillance varices	3 (12.5%)	1 (8.3%)	2 (16.7%)
Dysphagia/achalasia	5 (20.8%)	3 (25%)	2 (16.7%)
Unintentional weight loss	2 (8.3%)	1 (8.3%)	1 (8.3%)
GERD	3 (12.5%)	2 (16.7%)	1 (8.3%)
Suspicion of malignancy	2 (8.3%)	2 (16.7%)	0 (0.0%)
Helicobacter pylori	4 (16.7%)	0 (0%)	4 (33.3%)
Iron deficiency anemia	1 (4.2%)	0 (0%)	1 (8.3%)

Table 1. Continued

	All (n=24)	Intra-observer (n=12)	Inter-observer (n=12)
Complaints			
No complaints	8 (33.3%)	5 (41.7%)	3 (25.0%)
Dysphagia	3 (12.5%)	2 (16.7%)	1 (8.3%)
GERD complaints	6 (25.0%)	3 (25%)	3 (25.0%)
Epigastric pain	5 (20.8%)	1 (8.3%)	4 (33.3%)
Weight loss	2 (8.3%)	1 (8.3%)	1 (8.3%)

Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation. BMI=body mass index, GERD=gastro-esophageal reflux disease.

Table 2. Characteristics of upper endoscopy.

	All (n=24)	Intra-observer (n=12)	Inter-observer (n=12)	p-value intra versus inter
Duration of upper endoscopy (min)	23.4 ± 5.7	21.1 ± 3.7	25.7 ± 6.5	0.05
Normal mucosa	23 (95.8%)*	11 (91.7%)	12 (100%)	0.31
Butylscopalamin administered	4 (16.7%)	0 (0%)	4 (33.3%)	0.09

Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation. * Mild antral gastritis.

Table 3. Endoscopist characteristics.

	Intra-observer	Inter-observer	
	VLS 1 & VLS 2	VLS 1	VLS 2
Endoscopy experience (months)	24	32	240
Upper endoscopies performed (n)	350	455	10.000
VLS experience (months)	3	0	19
VLS performed (n)	9	0	5

VLS = visible light spectroscopy

Intraobserver variability

The mean VLS values for each specific location (descending duodenum, duodenal bulb or antrum) were not significantly different between the first set and second set of intraobserver measurements. Furthermore, the ICC was excellent for all locations (ICC antrum 0.77, ICC duodenal bulb 0.81 and ICC descending duodenum 0.84). Clinical disagreement between the first set and the second set of intraobserver measurements occurred only for the measurements of the antrum (descending duodenum 0.0%, duodenal bulb 0.0% and antrum 8.3%, overall intraobserver measurements 2.8%.). See Table 4 and see Figure 1A, B and C for the visualization of the range of disagreement.

The mean duration of the VLS-measurements differed not significantly between first set and second set of intraobserver measurements (duration first set of VLS-measurements 6.4±1.3 minutes versus duration second set of VLS-measurements 5.7±1.0 minutes, p=0.074).

Table 4. Intraobserver VLS-measurements.

	Mean VLS 1	Mean VLS 2	p-value	Mean difference	ICC	Clinical disagreement (>5%)
Descending duodenum (%)	54.0 ± 3.4	54.2 ± 4.8	0.786	-0.19 ± 2.42	0.84 (0.53-0.95)	0 (0.0%)
Duodenal bulb (%)	57.2 ± 4.2	57.9 ± 3.7	0.370	-0.67 ± 2.47	0.81 (0.48-0.94)	0 (0.0%)
Antrum (%)	60.6 ± 3.4	61.8 ± 4.0	0.101	-1.22 ± 2.36	0.77 (0.38-0.93)	1 (8.3%)

Categoric variable are presented as number (%). Continuous variables are presented as mean ± standard deviation or median (interquartile range).
ICC = intraclass correlation coefficient; VLS = visible light spectroscopy.

Table 5. Interobserver VLS-measurements.

	Mean VLS 1	Mean VLS 2	p-value	Mean difference	ICC	Clinical disagreement (>5%)
Descending duodenum (%)	51.8 ± 2.7	52.0 ± 4.3	0.800	-0.27 ± 3.71	0.49 (-0.12-0.82)	2 (16.7%)
Duodenal bulb (%)	54.1 ± 4.2	54.9 ± 3.2	0.321	-0.86 ± 2.87	0.70 (0.27-0.90)	0 (0.0%)
Antrum (%)	60.1 ± 3.6	60.6 ± 3.4	0.616	-0.50 ± 3.36	0.56 (-0.01-085)	2 (16.7%)

ICC = intraclass correlation coefficient; VLS = visible light spectroscopy.

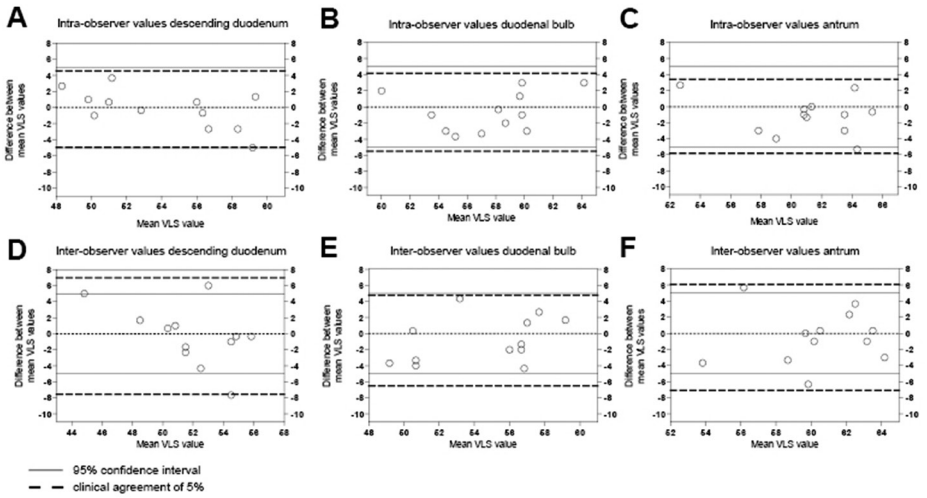

Figure 1. Bland-Altman plots for the intraobserver variability of the A) descending duodenum, B) duodenal bulb and C) antrum and Bland-Altman plots for the interobserver variability of the D) descending duodenum, E) duodenal bulb and F) antrum.

Interobserver variability

The mean VLS values for each specific location (descending duodenum, duodenal bulb or antrum) were not significantly different between the first set and second set of interobserver measurements. Furthermore, the ICC was good for the duodenal bulb (ICC 0.70), the ICC was fair for the descending duodenum (ICC 0.49) and antrum (ICC 0.56). Clinical disagreement between the first set and second set of interobserver measurements occurred in 16.7% of the measurements of descending duodenum and antrum and 0.0% in all measurements of the duodenal bulb (clinical disagreement all interobserver measurements 11.1%). See Table 5 and see Figure 1D, E and F for the visualization of the range of disagreement.

The mean duration of the VLS-measurements differed not significantly between first set and second set of interobserver measurements (duration first set of VLS-measurements 8.2±2.2 minutes versus duration second set of VLS-measurements 6.3±1.7 minutes, p=0.062).

Time between the end of the first set of VLS-measurements and the start of the second set of VLS-measurements was significantly longer for the interobserver measurements (intraobserver 0.71±0.36 minutes versus interobserver 4.53±4.52 minutes, p=0.014).

Follow-up

At the outpatient clinic visit after the upper endoscopy, no complications of the upper endoscopy or of the VLS-measurements were reported. All 24 patients were alive at the end of the follow-up period (mean follow-up duration 4.3±1.6 months).

DISCUSSION

The present study shows a fair to good observer reliability of endoscopic VLS-measurements. The intraobserver reliability is, as expected, better than the interobserver reliability. VLS-measurements, currently used in the diagnostic work-up of CMI, are reproducible.

The diagnosis of CMI is challenging as chronic abdominal pain due to other causes is common and stenosis of the mesenteric arteries are often asymptomatic due to extensive collateral circulation(14, 15). Radiological imaging modalities as CT-angiography can sufficiently detect the presence of a mesenteric artery stenosis, however the presence of a stenosis is not necessarily related with symptomatic disease. The European Society of Vascular Surgery (ESVS) recently published guidelines about 'Management of the Diseases of Mesenteric Arteries and Veins'(1). These guidelines underline the need of a functional test that indicates ischemia. Current available methods of functional testing need validation for widespread use in clinical practice. Therefore, we performed this study to determine the observer validity of endoscopic VLS-measurements.

To our knowledge, this is the first study assessing both the interobserver as intraobserver variability of endoscopic VLS-measurements. Others assessed the interobserver variability of an endoscopist experienced in VLS (>200 cases) versus an endoscopist with limited VLS-experience (<10 cases). Their study showed a good interobserver reliability with an average absolute difference of 2%(5). Their results suggest that endoscopic VLS-measurements are easy to perform without a steep learning curve.

Our results show no significant difference between repeated VLS-measurements, neither by the same endoscopist nor between different endoscopists. The intraobserver reliability was excellent for all locations and clinical disagreement was seen in 3% of all intraobserver measurements. Possibly the intraobserver variation is partly probe-related variation, however probe-related variation for VLS-measurements has never been described before. The interobserver reliability was fair to good. Subsequently, clinical disagreement was seen in 11% of all interobserver measurements. The time between the end of the first set of VLS-measurements and the start of the second set of VLS-measurements was significantly longer for the interobserver measurements due to the change for endoscopist in this group. It is not expected that mucosal saturation values change in this time period in these fasted patients. Although the interobserver reliability is less than the intraobserver reliability, we conclude that overall endoscopic VLS-measurements are reproducible with fair to good results.

VLS is a useful and minimally invasive tool to assess mucosal ischemia of the upper gastrointestinal tract. However, VLS is underutilized since the technique is not yet validated and widespread enough. This underlines the importance of this study of the observer validation of endoscopic VLS measurements. Directions for further research on the use of VLS for the diagnosis of CMI are VLS measurements after feeding in patients suspected of CMI and VLS measurements under various oxygenation levels.

This study carries several limitations. The endoscopists were blinded for the VLS-measurements during endoscopy; however, the observer noting the VLS values was not blinded. We checked all noted values with the digital output of the VLS oximeter and all noted VLS values agreed with the (blinded) VLS values from the digital output. Furthermore, upper endoscopy experience differed between the endoscopists of the interobserver variability analysis. The influence of the endoscopy experience on the VLS measurements is unknown. We assume that upper endoscopy experience has no clinically significant influence on the VLS values and this is supported by the fact that the mean values of VLS 1 and VLS 2 were not significantly different.

CONCLUSION

The observer reliability of endoscopic VLS-measurements is fair to good with intraobserver reliability being better than interobserver reliability. Endoscopic VLS-measurements are reproducible in clinical practice, which supports the use of VLS as functional test for assessment of CMI.

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CHAPTER
5

Detection of mesenteric ischemia by means of endoscopic visible light spectroscopy after luminal feeding

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ABSTRACT

Background

Endoscopic visible light spectroscopy (VLS) enables measurement of mucosal oxygen saturation during upper gastro-intestinal endoscopy and is used in the diagnostic work-up of chronic mesenteric ischemia (CMI). Currently, VLS is performed while the patient has fasted. We aimed to determine whether food challenge improves the diagnostic performance of VLS measurements for the diagnosis of CMI.

Methods

Single center prospective study in healthy controls and consecutive patients suspected of CMI and referred to a Dutch specialized CMI center for standardized diagnostic CMI work-up. Immediately after performance of conventional fasted VLS measurements, luminal feeding was administered and 45 minutes thereafter VLS measurements were performed again. Patients were classified as CMI if a multidisciplinary expert based consensus diagnosis of CMI was established and successful revascularization therapy resulted in symptom relief. Patients were classified as no-CMI when consensus diagnosis was not reached or when symptom relief did not occur after technically successful treatment.

Results

We included 60 CMI-suspected patients and 16 healthy controls. Duodenal oxygen saturation was significantly higher postprandially compared to fasting state in healthy controls (median (IQR) pre 54% (49-56), post 56% (53-58), p=0.02), no-CMI patients (pre 55% (51-57), post 57% (53-59), p>0.01), as well as CMI patients (pre 51% (48-53), post 54% (50-58), p=0.01). Mucosal oxygen saturations did not significantly increase postprandially in the duodenal bulb or antrum of the stomach. Neither absolute postprandial oxygen measurements nor the absolute or relative difference between preprandial versus postprandial oxygen measurements provided additional discriminative ability for the diagnosis of CMI.

Conclusion

Postprandial VLS measurements have no added benefit for the diagnosis of CMI.

INTRODUCTION

Endoscopic visible light spectroscopy (VLS)(1) enables targeted non-invasive catheter-based measurement of mucosal oxygen saturation of the upper gastro-intestinal (GI) tract during upper GI endoscopy. VLS determines the microvascular hemoglobin oxygen saturation using a small catheter that is passed through the accessory channel of the endoscope. The oximeter probe tip is positioned just above the GI mucosa and emits white light. Any light returning from the GI mucosa is collected by the probe and reflects the differences in the absorption spectra of oxygenated and deoxygenated hemoglobin.

VLS is currently used in the diagnostic work-up of chronic mesenteric ischemia (CMI), adding functional measurements to radiological imaging and presenting symptoms(2). CMI is the result of insufficient blood supply to the GI tract and is mostly caused by atherosclerotic stenosis of one or more supplying mesenteric arteries(3, 4). Other causes of occlusive CMI are vasculitis or compression of the celiac artery (CA) by the median arcuate ligament (median arcuate ligament syndrome (MALS)). Chronic non-occlusive CMI (NOMI) is caused by hypo-perfusion or hypo-oxygenation due to, for example, underlying cardiac or pulmonary disease.

The mucosal oxygen saturation measured by VLS during upper endoscopy is significantly lower in CMI patients than in patients without CMI(2). VLS measurements are performed in the antrum of the stomach, the duodenal bulb and the descending duodenum. The sensitivity of VLS measurements for the diagnosis of CMI is 90% with a specificity of 60%(2).

Typical symptoms of CMI are postprandial abdominal pain and weight loss due to fear of eating. VLS measurements are however performed during upper GI endoscopy in fasting state. Since CMI is mostly provoked by a meal, VLS measurements performed during fasting could potentially underdiagnose CMI.

The aim of the current study therefore was to determine whether non-fasting VLS measurements increase the discriminative ability of the test to diagnose CMI. We hypothesized that VLS measurements in healthy controls and patients without CMI will increase after a food challenge due to postprandial hyperemia and that VLS measurements in CMI patients will decrease after a food challenge.

PATIENTS AND METHODS

Study design and setting

A single center prospective study included healthy controls and consecutive patients suspected of CMI. Patients were referred to our tertiary referral center between September 2014 and March 2017 for a standardized diagnostic CMI work-up. This center is one of the two Dutch CMI referral centers that perform functional tests to detect mucosal ischemia.

Patients were suspected of CMI if at least two of the following criteria were fulfilled: 1) presence of postprandial pain, 2) otherwise unexplained weight loss, and 3) significant stenosis of >50% of at least one of the mesenteric arteries. Patients were excluded if they were known with cardiac arrhythmias or cardiac conduction disorders and/or if they had undergone gastric (bypass) surgery.

Healthy controls without GI complaints and without comorbidity, with an unremarkable medical history, not using acid-suppressive medication, and without cardiovascular or pulmonary disease were also included. Abdominal duplex ultrasound was performed to ensure patent mesenteric arteries.

The medical research ethics committee of Erasmus MC University Medical Center approved this study (NL43008.078.12). The study complies with the Helsinki declaration on research ethics. To enhance transparency, this article is written according to the STROBE checklist for cohort studies(5).

Participants

All patients underwent a standardized diagnostic work-up for CMI consisting of obtaining medical history and physical examination, imaging of the mesenteric arteries with either computer tomography (CTA), magnetic resonance angiography (MRA) and/or conventional catheter angiography, and VLS(2, 6). Thereafter, patients were discussed in our multidisciplinary CMI team of vascular surgeons, interventional radiologists, and gastroenterologists, all specialized in CMI, leading to an expert-based consensus diagnosis. This consensus diagnosis was established if at least two of the three following criteria were met: 1) typical presentation of CMI (symptoms as postprandial pain, otherwise unexplained weight loss, diarrhea) 2) significant stenosis of at least the CA

or superior mesenteric artery (SMA) (≥50% diameter reduction(7-10)) on CTA or MRA and/or conventional catheter angiography, 3) mucosal hypo-oxygenation detected by VLS (fasted). Based on previous experience, hypo-oxygenation was defined as a mucosal oxygen saturation in the antrum <63%, and/or in the duodenal bulb <62%, and/or in the descending duodenum <58%(2). Patients with chronic NOMI were excluded in this study.

VLS measurements in healthy controls and patients were performed during upper endoscopy. If sedation was administered, this consisted of midazolam intravenously (dose 2.5-5 mg) combined with fentanyl (dose 0.05 mg). Peripheral oxygen saturation and heart rate were continuously monitored. Oxygen was administered intranasally <1 minute before the introduction of the endoscope to maintain a peripheral saturation level ≥95% during the VLS-measurements. The VLS measurements were performed using a fiberoptic catheter-based VLS oximeter (T-Stat 303 Microvascular Oximeter; Spectros, Portola Valley, California) passed through the accessory channel of the endoscope. Mucosal saturation measurements were performed at three different locations: the antrum of the stomach, the duodenal bulb and the descending duodenum. After removal of any bile remnants at the target area, the catheter tip was positioned approximately 1-5 mm above the mucosa. The light of the endoscope was turned off and continuous readings of mucosal saturation were shown on the monitor. This reading showed small rapid variations due to true changes in saturation and due to small changes in the position of the probe. A study reading was started if a stable measurement was obtained. The highest value was noted. Three repeated readings per site were obtained with fewer than 5% variation and these 3 readings were averaged. All VLS-measurements were performed before any biopsy was taken or any stain was applied. When intestinal spasms prohibited obtaining proper VLS-measurements, butylscopolamine (10-20 mg) was administered intravenously.

For standardized work-up, VLS measurements are performed during upper endoscopy in persons who have fasted for at least 6 hours. The study subjects underwent additional VLS measurements after luminal feeding. For this, a guidewire was endoscopically placed in the antrum after conventional preprandial VLS measurements. The guidewire was used to insert a 10-F nasogastric tube (Wilson-Cook Medical, Cook Ireland Ltd, Limerick, Ireland) in the stomach. The study subject was placed in an upright position to prevent aspiration and 300 ml (1.5 kcal/ml) compound liquid food (Nutrison Energy©, Nutricia Koninklijke Numico N.V., WTC Schiphol, The Netherlands) was given by bolus

feeding using a 50cc syringe. Erythromycin 250 mg was given intravenously 15 minutes after the luminal feeding to stimulate motility and clear gastric contents. Forty-five minutes after luminal feeding a second upper endoscopy was performed. Redundant liquid food was aspirated. Postprandial VLS measurements were performed in the same manner as preprandial VLS measurements.

Follow-up and data sources

Patients with a consensus diagnosis of CMI based on occlusive disease were planned for either endovascular or surgical revascularization. Patients with stenosis of one or more mesenteric arteries based on atherosclerosis were primarily planned for endovascular revascularization: percutaneous transluminal angioplasty (PTA) combined with stent placement (percutaneous mesenteric artery stenting (PMAS)). If patients were not eligible for endovascular intervention or if patients had recurrent episodes of restenosis, they were treated with open surgical mesenteric artery repair (OSMAR). In patients with a stenosis of the CA the diagnosis of MALS was established if CTA demonstrated focal narrowing of the proximal CA ≥50% with post-stenotic dilatation and indentation on the superior aspect of the CA, creating a hook-shaped contour of the CA. This characteristic kinking in the absence of atherosclerotic plaques distinguishes this condition from other causes of CA stenosis such as atherosclerosis(11). Since these imaging features are dependent on the respiratory cycle, an additional catheter angiography of the CA in inspiration and expiration was performed in unclear cases. Patients with stenosis of the CA based on MALS were planned for surgical release (open or laparoscopic) of the median arcuate ligament.

Patients were evaluated during standard protocol visits at 1, 3, 6, 12, and 24 months after therapy. These visits were mostly in-clinic follow-up. All patients were minimally followed for a period of 6 months. A definitive diagnosis of CMI was established if the patient reported relief of presenting symptoms. This patient reported outcome of symptom relief was classified in two groups: no or minimal symptom relief and major or complete symptom relief. Standard protocol contains questions about recurrent symptoms (i.e. similar to presenting symptoms before revascularization therapy) and actual weight. No standard questionnaire was used.

Patients with a consensus diagnosis of no-CMI were discharged without further follow-up. The healthy controls were not followed after the preprandial and postprandial VLS measurement.

Variables

Baseline characteristics included age, gender, past medical history, presenting symptoms such as abdominal pain, diarrhea, nausea, and weight loss (kg), body mass index (BMI), smoking, and cardiovascular risk factors. Hypertension was defined as a blood pressure of ≥140/90 mmHg or use of antihypertensive medication. Dyslipidemia was defined as LDL-C >4.2 mmol/L or HDL-C <0.9 mmol/L or use of lipid lowering medication. Smoking status was defined as ever smoked or never smoked. Vascular lesions were specified for localization (CA, SMA or inferior mesenteric artery (IMA)) and cause (atherosclerosis, MALS, vasculitis).

The primary outcomes were the absolute postprandial VLS-measurements and the absolute and relative differences in preprandial and postprandial VLS-measurements in patients with CMI, patients without CMI and healthy controls. Secondary outcomes were complications and mortality.

Study size

We determined that 50 patients suspected of CMI needed to be included to detect a relative decrease of 10-15% in mucosal saturation per location with an alpha of 0.01, a power of 90% and with assumption of a CMI diagnosis rate of 50%.

Statistical methods

Baseline characteristics and secondary outcomes were described either as numbers and percentages for dichotomous variables, or as means and standard deviations or medians and interquartile ranges (IQR) for continuous variables. Differences in baseline characteristics and clinical response to treatment were determined by the χ^2 test or Student's t-test. Difference in BMI during follow-up was determined with the paired samples t-test.

Differences in absolute preprandial and postprandial VLS-measurements between CMI patients, no-CMI patients and healthy controls were determined with the Mann Whitney U-test. Differences between preprandial and postprandial VLS-measurements within

a patient group were determined with the Wilcoxon signed rank test. However, the normal VLS-measurements differ per location, as distal VLS-measurements are lower than proximal VLS-measurements. Therefore, relative differences between preprandial and postprandial measurements were calculated in percentages of the baseline VLS-measurements. Differences in relative preprandial versus postprandial VLS differences between CMI patients, no-CMI patients and healthy controls were determined with the Mann Whitney U-test. Statistical significance was defined as a two-sided $p<0.05$. Statistical analysis was performed using the SPSS Statistics 23 (IBM Inc., Chicago, IL).

RESULTS

Patient characteristics

During the study period, 136 patients suspected of CMI were referred to our center of which 75 were eligible for inclusion. Of these 75 patients, 60 patients were eligible for analysis (Figure 1). Furthermore, 16 healthy controls were included. All patients and controls gave informed consent. Baseline characteristics, presenting symptoms and vascular lesions are presented in Table 1.

Treatment

In 28 patients (39%) a consensus diagnosis of CMI was established. All patients with a consensus diagnosis of occlusive CMI were treated with revascularization therapy. The 16 patients with CMI based on atherosclerosis were all treated with endovascular revascularization (15 patients stent placement, 1 patient PTA). Of the 7 patients with CMI based on MALS, 4 underwent laparoscopic surgical decompression and 3 underwent open surgical decompression.

Endovascular revascularization was initially technically successful in 15/16 patients (94%). A re-procedure in one patient resulted in technical success for all 16 endovascular treated patients. Endovascular approach was established in 9 procedures (56%) via the radial artery, in 5 procedures via the femoral artery (31%) and in 2 procedures (13%) via the brachial artery. Of the 7 surgical celiac artery release procedures, 6 procedures were technically successful (86%). One patient needed additional mesenteric bypass surgery for successful revascularization.

After successful endovascular revascularization, 3 of the 16 patients (19%) developed symptomatic in-stent stenosis. Successful re-intervention was performed in all 3 cases resulting in relief of symptoms.

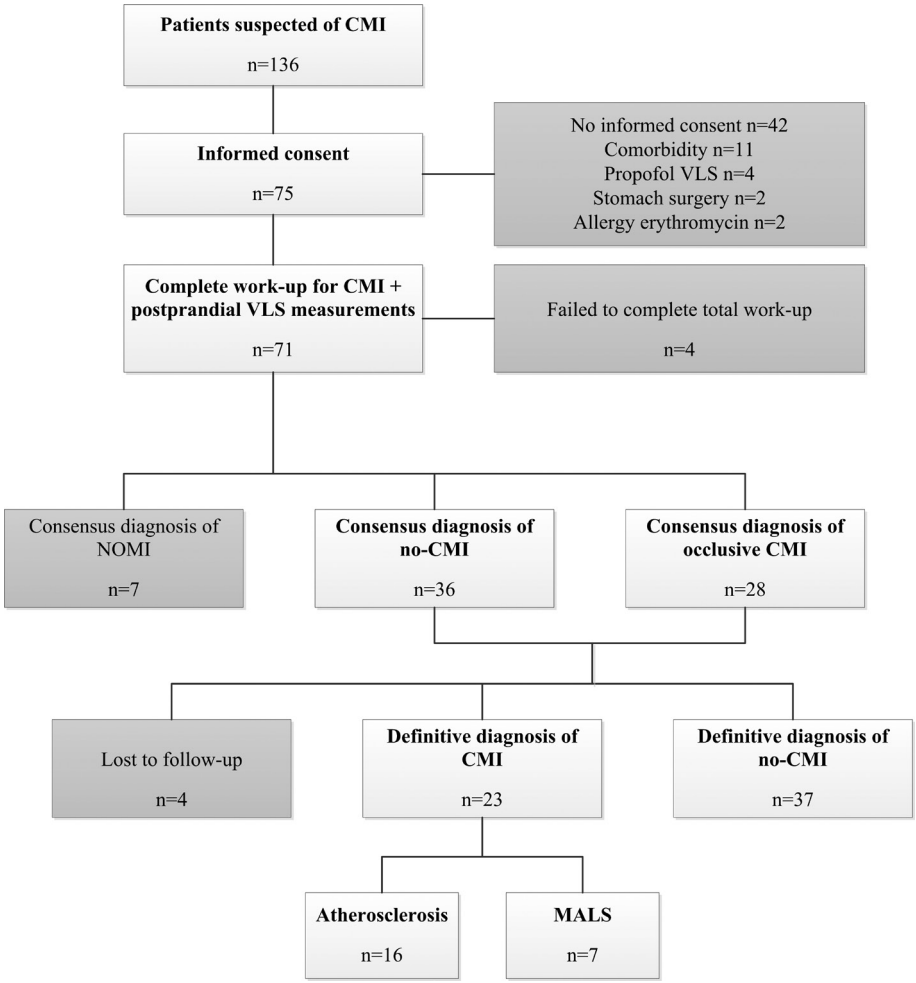

Figure 1. Flowchart.
CMI = chronic mesenteric ischemia; MALS = median arcuate ligament syndrome; NOMI = non-occlusive mesenteric ischemia; VLS = visible light spectroscopy.

Table 1. Baseline characteristics, presenting symptoms and vascular lesions.

	All patients (n=60)	**CMI patients** (n=23)	**no-CMI patients** (n=37)	**Healthy controls** (n=16)
Patient characteristics				
Age (y)	59.7±14.1	60.7±15.6	59.1±13.2	35.2 ± 8.1
Female	53.3%	47.8%	56.8%	43.8%
Caucasian	100%	100%	100%	93.8%
Hypertension	51.7%	65.2%	43.2%	6.3%
Smoking	80.0%	78.3%	81.1%	43.8%
Dyslipidemia	47.5%	59.1%	40.5%	0.0%
Diabetes	18.3%	26.1%	13.5%	0.0%
BMI at presentation (kg/m^2)	24.0±4.5	24.0±4.6	23.9±4.5	23.3 ± 2.8
History of CVD	45.0%	60.9%	35.1%	0.0%
Presenting symptoms				
Abdominal pain	88.3%	91.3%	86.5%	0.0%
Postprandial abdominal pain	83.3%	91.3%	78.4%	0.0%
Exercise related abdominal pain	33.9%	36.4%	32.4%	0.0%
Nausea	43.3%	39.1%	45.9%	0.0%
Diarrhea	16.7%	17.4%	16.2%	0.0%
Weight loss	61.7%	56.5%	64.9%	0.0%
Abdominal bruit	18.4%	31.3%	12.1%	0.0%
Classic triad of CMI	3.3%	5.3%	2.8%	0.0%
Gastric ulcer	3.3%	8.7%	0.0%	0.0%
Duration of symptoms (months)	18.1±26.0	21.3±36.8	16.0±16.0	0.0±0.0
Vascular lesions				
No stenosis	41.7%	0.0%	67.6%	100.0%
Single vessel stenosis#	36.7%	47.8%	29.7%	0.0%
Multivessel stenosis	21.7%	52.2%	2.7%	0.0%
CA stenosis	30.0%	39.1%	21.6%	0.0%
SMA stenosis	6.7%	8.7%	5.4%	0.0%
IMA stenosis	1.7%	0.0%	2.7%	0.0%
CA and IMA stenosis	3.3%	13.0%	0.0%	0.0%
CA and SMA stenosis	5.0%	13.0%	0.0%	0.0%
SMA and IMA stenosis	1.7%	0.0%	2.7%	0.0%
CA, SMA and IMA stenosis	10.0%	26.1%	0.0%	0.0%

Data are presented as percentages or as mean ± SD.
# solitary stenosis of CA, SMA or IMA.
BMI = body mass index; CMI = chronic mesenteric ischemia; CVD = cardiovascular disease; Classic triad of CMI is postprandial abdominal pain, bruit and weight loss; CA = celiac artery, SMA = superior mesenteric artery, IMA = inferior mesenteric artery.

Definitive diagnosis

A definitive diagnosis of CMI was established in 23 patients. Nine patients had a significant solitary CA stenosis, 2 patients a significant solitary SMA stenosis, 3 patients a significant stenosis of both CA and SMA, 3 patients a significant stenosis of both SMA and IMA and 6 patients a significant stenosis of CA and SMA as well as IMA. Solitary CA stenosis was caused by MALS in 7 patients. All other stenoses were caused by atherosclerosis (Table 1). BMI 6 months after revascularization was significantly higher than BMI before revascularization in CMI patients (BMI at diagnosis 24.0±4.6 versus BMI 6 months after revascularization 26.0±5.2 kg/m^2, p=0.008).

Alternative diagnoses were established in 22 of 37 patients (59%) without a definitive diagnosis of CMI: alcohol abuse, radiation damage, chronic pancreatitis, polycystic kidney disease with hepatic involvement, diarrhea after chemotherapy, tuberculosis, gastroparesis, Anterior Cutaneous Nerve Entrapment Syndrome (ACNES), obstipation, lung cancer with peritoneal and mesenteric metastases, proctitis, primary sclerosing cholangitis (PSC), sliding hiatal hernia, and diverticulosis. In 6 patients the presenting symptoms spontaneously resolved.

None of the patient characteristics or presenting symptoms differed significantly between patients with CMI and patients without CMI (Table 1). The healthy volunteers were significantly younger (p<0.01), were less often smokers (p<0.01), had less hypertension (p<0.01), dyslipidemia (p<0.01), and cardiovascular disease (p<0.01) than the patients suspected of CMI. BMI did not significantly differ between the healthy volunteers and the CMI suspected patients.

Preprandial mucosal oxygen saturations

Sedation was administered at the start of the upper GI endoscopy in 56 of the 60 (93%) patients suspected of CMI and in 2 of the 16 (12.5%) healthy controls. Preprandial mucosal oxygen saturations were significantly lower in CMI patients than in no-CMI patients in all three locations. Furthermore, preprandial mucosal oxygen saturations were significantly lower in CMI patients than in healthy controls for the antrum of the stomach and for the duodenal bulb. Preprandial mucosal oxygen saturations did not significantly differ between no-CMI patients and healthy controls in all three locations (antrum of the stomach p=0.35, duodenal bulb p=0.50 and descending duodenum p=0.14 (Figure 2)).

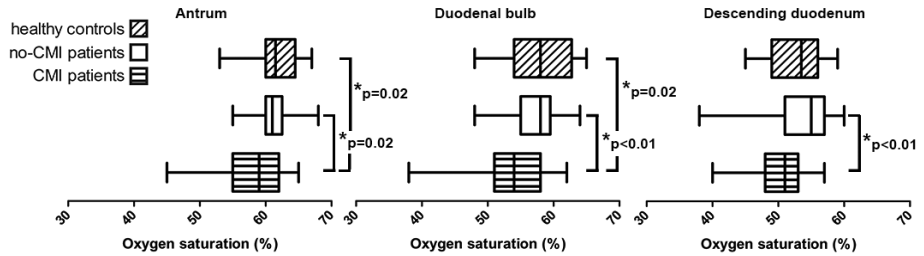

Figure 2. Preprandial oxygen saturations antrum, duodenal bulb and descending duodenum for CMI patients, no-CMI patients and healthy controls. Preprandial oxygen saturations of CMI patients were significantly lower than preprandial oxygens saturations of no-CMI patients in all three locations. Preprandial oxygen saturations of CMI patients were significantly lower than preprandial oxygens saturations of healthy controls in antrum and duodenal bulb. CMI = chronic mesenteric ischemia. * = p<0.05 Mann Whitney U-test

Postprandial mucosal oxygen saturations

Postprandial duodenal bulb mucosal oxygen saturations were significantly lower in CMI patients than in no-CMI patients. Postprandial antral mucosal oxygen saturations were significantly lower in both CMI patients and no-CMI patients compared to healthy controls. Postprandial antral and duodenal mucosal oxygen saturations were not significantly different between CMI patients and no-CMI patients (Tabel 2 and Figure 3).

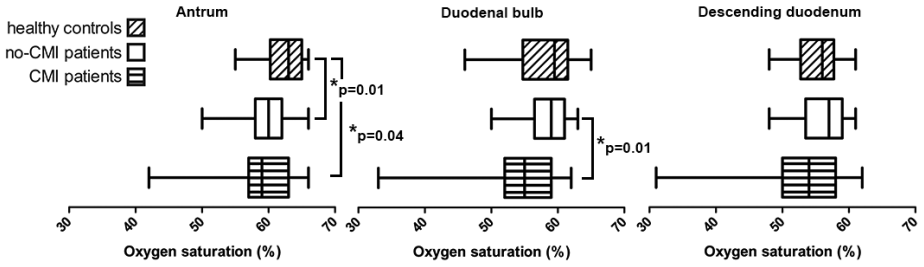

Figure 3. Postprandial oxygen saturations in antrum, duodenal bulb and descending duodenum for CMI patients, no-CMI patients and healthy controls. The postprandial oxygen saturation was only significantly decreased in CMI patients compared to no-CMI patients in the duodenal bulb. In the antrum of the stomach the postprandial oxygen saturation was significantly decreased in both the CMI patients and no-CMI patients compared to the healthy controls. CMI = chronic mesenteric ischemia. * = p<0.05 Mann Whitney U-test.

Table 2. Preprandial and postprandial oxygen saturations.

	CMI patients (n=23)	**no-CMI patients** (n=37)	**Healthy controls** (n=16)
Antrum preprandial (%)	59 (55-62)	61 (60-63)	62 (60-65)
Antrum postprandial (%)	59 (57-63)	60 (58-62)	63 (60-65)
p-value	0.10	0.03*	0.86
Duodenal bulb preprandial(%)	54 (51-58)	58 (55-60)	58 (54-63)
Duodenal bulb postprandial(%)	55 (52-59)	59 (57-61)	60 (55-62)
p-value	0.16	0.30	0.93
Descending duodenum preprandial (%)	51 (48-53)	55 (51-57)	54 (49-56)
Descending duodenum postprandial (%)	54 (50-58)	57 (53-59)	56 (53-58)
p-value	0.01*	<0.01*	0.02*

Data are presented as median (IQR).
* $p < 0.05$ pre-prandial versus post-prandial oxygen saturations .
CMI = chronic mesenteric ischemia.

Preprandial versus postprandial mucosal oxygen saturations

Enteral feeding was associated with a significant increase in duodenal mucosal oxygen saturations in all CMI and no-CMI patients, as well as healthy controls (Table 2). Furthermore, the absolute difference of preprandial versus postprandial antral mucosal oxygen saturations differed significantly between CMI patients and no-CMI patients (CMI patients absolute difference median (IQR) 0.00 (-1.0-3.0) versus no-CMI patients -0.5 (-3.0-1.0) p=0.02). However, the absolute difference of preprandial versus postprandial mucosal oxygen saturations did not significantly differ in the duodenal bulb or descending duodenum between CMI patients and no-CMI patients. In addition, there was no significant difference between CMI patients and healthy controls in any of the three locations.

The relative difference in preprandial and postprandial mucosal oxygen saturations was only significantly different between no-CMI patients and CMI patients in the antrum of the stomach, but not in the duodenal bulb or descending duodenum (Table 3 and Figure 4). The relative difference in preprandial and postprandial mucosal oxygen saturations did not differ significantly between CMI patients and healthy controls.

Table 3. Relative differences in preprandial and postprandial oxygen saturations.

	CMI patients (n=23)	**no-CMI patients** (n=37)	**Healthy controls** (n=16)
Antrum (%)	0.00 (-1.67-5.26)	0.00 (-4.05-1.65)	-0.77 (-3.05-4.42)
Duodenal bulb (%)	1.72 (-1.85-7.41)	1.67 (-3.36-5.46)	0.86 (-5.61-3.42)
Descending duodenum (%)	6.67 (0.00-12.72)	3.64 (0.86-6.29)	6.39 (-1.32-12.57)

Data are presented as median (IQR).
CMI = chronic mesenteric ischemia.

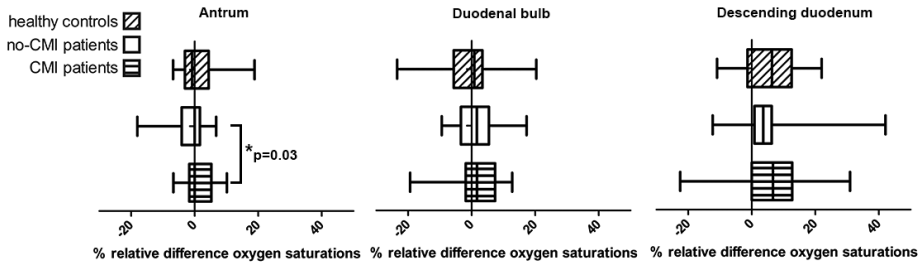

Figure 4. Relative differences in preprandial versus postprandial oxygen saturations in antrum, duodenal bulb and descending duodenum for CMI patients, no-CMI patients and healthy controls. The relative differences in preprandial versus postprandial oxygen saturations were not significantly different in any of the three locations and between any of the three groups except for CMI patients versus no-CMI patients in the antrum of the stomach. CMI = chronic mesenteric ischemia. * = p<0.05 Mann Whitney U-test.

Complications & mortality

No complications related to the preprandial or postprandial VLS measurements or the upper endoscopy were observed. Mean follow-up was 15.3±10.3 months for CMI patients and 6.7±7.1 months for no-CMI patients. Overall, 1 patient (CMI, 1/60=2%) died during follow-up due to liver failure unrelated to mesenteric ischemia. All 16 healthy controls were alive at the end of the study.

DISCUSSION

Our study shows that food administration is associated with an increase in duodenal mucosal oxygen saturation in CMI patients, no-CMI patients and healthy controls. However, neither postprandial oxygen saturation levels nor their absolute or relative

difference with preprandial levels provide additional discriminative ability for the diagnosis of CMI.

The diagnosis of CMI is a clinical challenge since a gold standard test is absent. Symptoms alone are not specific predictors for CMI(3, 12, 13). The prevalence of mesenteric artery stenosis ranges between 7-18% in the asymptomatic general population, increasing with age(14-17). Additional functional testing may increase the likelihood of the diagnosis, especially in those patients with significant solitary mesenteric artery stenosis(18). Therefore, diagnosis is generally based on the combination of symptoms, imaging of the mesenteric vasculature and a functional test to assess mucosal ischemia as VLS or gastric-jejunal tonometry(19, 20). Such a consensus approach is an accepted method in the absence of one specific test(21). A definitive diagnosis of CMI is established if symptom relief is reported after technically successful treatment. Functional assessment with VLS is performed during upper GI endoscopy. VLS has a sensitivity of 90% and a specificity of 60%, which leaves room for optimization. Furthermore, VLS requires that the mucosal surface is free of bile or food remnants since these can disturb the light reflectance.

In this study, the diagnostic value of fasted VLS measurements for the diagnosis of CMI as reported by van Noord et al.(2) is confirmed by showing significant decreased mucosal oxygen saturations in CMI patients versus no-CMI patients. Endoscopic VLS measurements in healthy controls have not been reported in literature before. We showed that fasted mucosal oxygen saturations did not significantly differ between no-CMI patients and healthy controls.

Mesenteric blood flow increases after a meal. Duplex ultrasound of the SMA in healthy volunteers has been shown to significantly increase in blood flow after a food challenge, whereas after water ingestion no significant increase of the SMA blood flow was demonstrated(22). In another duplex study blood flow measurements in the SMA in patients with a 70-99% SMA stenosis significantly less increased after a meal than the SMA blood flow in healthy volunteers and patients with SMA stenosis <70%(23). This suggests a lack of postprandial blood flow increase in patients with occlusive CMI. A decrease in blood flow to the GI tract results in decreased oxygen delivering. VLS could therefore potentially discriminate the patients with CMI from the patients without CMI based on the difference of preprandial versus postprandial mucosal oxygen saturation measurements.

Blood flow in the CA increases less than the blood flow in the SMA after a meal(3). The CA provides blood to the stomach, liver, part of the pancreas and the proximal part of the duodenum. The SMA provides blood to the distal part of the duodenum, the small bowel and the proximal part of the colon. Our results confirm the large postprandial blood flow increase in the SMA, since the largest relative increase of preprandial versus postprandial blood flow in CMI patients, no-CMI patients as well as in healthy controls is demonstrated in the descending duodenum.

This study has some limitations. First, the study was designed to simulate the natural digestion process and metabolic challenge of food ingestion. To ensure the intake of the same amount of calories in every patient, luminal feeding was given over a feeding tube. Needless to say that this is only an approximation of the natural digestion process as the physiological process of digestion normally starts with smelling, seeing and chewing food including the production of saliva. Moreover, postprandial hyperemia starts about 10 minutes after food ingestion to reach a maximum after 30 minutes(24). In this study, the second upper endoscopy started 45 minutes after the food challenge to minimize the risk of aspiration. Furthermore, postprandial VLS measurements could be hampered by liquid food remnants. To minimize the risk of aspiration and faulty measurements the delay of 45 minutes was chosen to allow for passage of the liquid food. As extra safety precaution measures we administered erythromycin intravenously to stimulate gastric food evacuation and also aspirated remnant liquid food via the gastric tube and the endoscope. As a result of this 45 minute delay in the administration of the caloric challenge and the VLS-measurements the possibility exist that we missed the peak postprandial increase in mucosal oxygenation, especially in antrum of the stomach and duodenal bulb.

Second, the sample size was calculated assuming a CMI diagnosis rate of 50%. The CMI diagnosis rate in this cohort was 38%. As a result, we included 2 CMI patients less than the 25 CMI patients determined by sample size calculation. Even if two more included patients would have the most extreme outcomes, they would not change the outcome of this study.

Assessment of the presence and time of onset of CMI symptoms after luminal feeding would be of interest. However, this was not performed, since the upper GI endoscopies

are often performed under conscious sedation which would influence the reliability and interpretation of abdominal pain scores.

In conclusion, this is the first study of VLS measurements after a food challenge. Duodenal mucosal saturation values of the upper GI tract increase after food administration in healthy controls, no-CMI patients, as well as in CMI patients. However, postprandial VLS-measurements do not provide additional discriminative ability for the diagnosis of CMI. Postprandial VLS measurements have no added benefit for the diagnosis of CMI.

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CHAPTER

6

Evaluation of endoscopic visible light spectroscopy: comparison with microvascular oxygen tension measurements in a porcine model

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ABSTRACT

Background

Visible light spectroscopy (VLS) is a technique used to measure the mucosal oxygen saturation during upper gastrointestinal endoscopy to evaluate mucosal ischemia, however in vivo validation is lacking. We aimed to compare VLS measurements with a validated quantitative microvascular oxygen tension (μPO_2) measurement technique.

Methods

Simultaneous VLS measurements and μPO_2 measurements were performed on the small intestine of five pigs. First, simultaneous measurements were performed at different FiO_2 values (18%-100%). Thereafter, the influence of bile was assessed by comparing VLS measurements in the presence of bile and without bile. Finally, simultaneous VLS and μPO_2 measurements were performed from the moment a lethal dose potassium chloride intravenously was injected.

Results

In contrast to μPO_2 values that increased with increasing FiO_2, VLS values decreased. Both measurements correlated poorly with R^2= 0.39, intercept 18.5, slope 0.41 and a bias of -16%. Furthermore, the presence of bile influenced VLS values significantly (median (IQR)) before bile application 57.5% (54.8-59.0%) versus median with bile mixture of the stomach 73.5% (66.8-85.8), p=<2.2*10^{-16}; median with bile mixture of small bowel 47.6% (41.8-50.8) versus median after bile removal 57.0% (54.7-58.6%), p=<2.2*10^{-16}). Finally, the VLS mucosal oxygen saturation values did not decrease towards a value of 0 in the first 25 minutes of asystole in contrast to the μPO_2 values.

Conclusions

These results suggest that VLS measures the mixed venous oxygen saturation rather than mucosal capillary hemoglobin oxygen saturation. Further research is needed to establish if the mixed venous compartment is optimal to assess gastrointestinal ischemia.

BACKGROUND

Visible light spectroscopy (VLS) is a technique used to measure the mucosal capillary hemoglobin oxygen saturation based on reflectance spectrophotometry(1). The mucosal oxygen saturation can be calculated by the marked difference in the absorption spectra of oxygenated and deoxygenated hemoglobin. Endoscopic VLS measurements are performed during upper GI endoscopy(2-4). As determined previously by van Noord et al., measurements are defined positive for ischemia if the measured saturation is lower than 63% in the antrum of the stomach, lower than 62% in the duodenal bulb and 58% in the descending duodenum(4).

VLS is used in clinical practice in the work-up of the diagnosis of chronic mesenteric ischemia (CMI). CMI is defined as ischemic symptoms caused by insufficient blood supply to the gastrointestinal (GI) tract(5). The main cause of CMI is stenosis of one or more mesenteric arteries due to atherosclerosis(6). Other occlusive causes are external compression of the celiac artery and/or celiac ganglion by the median arcuate ligament and diaphragmatic crura (median arcuate ligament syndrome (MALS)) and mesenteric artery stenosis due to vasculitis. However, CMI can exist in the absence of mesenteric artery stenosis. Non-occlusive mesenteric ischemia (NOMI) is caused by hypo-oxygenation due to underlying conditions such as cardiac and pulmonic insufficiency, spasms of small arteries, shunts, occlusion of smaller arteries e.g. by micro-emboli, and autonomic dysfunction(7).

The diagnosis of CMI is a clinical challenge because of the diverse presentation of CMI. Symptoms overlap largely with many other disorders and the high prevalence of asymptomatic mesenteric artery stenosis in the general population of (3-29%(8, 9)) due to the existence of an extensive collateral circulation. However, mesenteric artery stenosis can become symptomatic if this collateral circulation is not sufficient and/or the extent of the stenosis becomes significant. Accurate identification of patients with CMI is important to select those patients who will benefit of therapy, but to withhold invasive therapy from those who will not. Treatment consists of endovascular revascularization with expandable metal stents or surgical revascularization of obstructed vessels, both methods that are invasive, costly and not without side-effects. A functional test to determine mucosal ischemia of the GI tract is therefore essential.

In the absence of one specific test for the diagnosis of CMI(10), the diagnosis is established by consensus in a multidisciplinary meeting attended by gastroenterologists, vascular surgeons and interventional radiologists. Symptoms alone do not accurately predict the diagnosis of CMI(7, 11, 12). Therefore, consensus diagnosis is based on the combination of symptoms, imaging of the mesenteric vasculature and functional assessment of mucosal ischemia with gastric-jejunal tonometry(13, 14) or VLS(1, 4). The diagnosis is confirmed if successful therapy results in symptom relief. This method for the diagnosis of CMI has an acceptable diagnostic yield(15) and this method is excepted in absence of a gold standard test(10).

Endoscopic mucosal oxygen saturation measurements with VLS are already used in clinical practice to evaluate CMI, however no extensive validation studies have been performed for this intended use. In the current study, VLS mucosal oxygen saturation is compared with a validated microvascular oxygen tension (μPO_2) measurement technique(16, 17)

The microvascular oxygen tension technique used in this study is a Palladium (Pd) porphyrin phosphorescence lifetime technique that measures oxygen tension, introduced by Van der Kooi at the end of the 1980s(18). Palladium porphine (Pd-porphyrin) bound to albumin, has become a standard phosphorescent dye for μPO_2 measurements in vivo(16, 17). This quantitative measurement is also located in the microcirculation making it a convenient comparison to mucosal oxygen saturations measured with VLS.

The objective of this study was to validate the VLS technique. This validation consisted of 3 experiments in a porcine model: 1) comparison of VLS mucosal oxygen saturation and μPO_2 measurements at different levels of FiO_2, 2) VLS mucosal oxygen saturation measurements in the presence of bile and 3) comparison of VLS mucosal oxygen saturation and μPO_2 measurements during asystole.

METHODS

Ethical statement

This study was approved by the local Animal Research Committee of the Erasmus MC University Medical Center in accordance with the National Guidelines for Animal Care

and Handling (protocol number DEC 129-13-06 EMC3185). To enhance transparency this article is written according to the ARRIVE guidelines for animal research(19).

Experimental animals

In total, 5 female crossbred Landrace x Yorkshire pigs, with mean body weights of 28.1±0.6 kg (mean±standard error of mean), age 2-3 months were used for the experiments. Sample size calculation determined that 5 animals were sufficient to detect a difference of at least 5% in mucosal saturation measured with VLS before and after bile per location with an alpha of 0.05 and a power of 90%(20).

Experimental procedures

After an overnight fast with free access to water, the animals were sedated with an intramuscular injection of tilatamine/zolazepam (6/6 mg/kg; Virbac Laboratories, Carros, France), xylazine (2 mg/kg; AST Farma B.V., The Netherlands) and atropine sulfate (0.5 mg/animal; Centrafarm Services BV, Etten-Leur, The Netherlands). After a 15 min induction period, anesthesia was induced with tilatamine/zolazepam (50-100 mg/animal) through a cannula (20G Venflon (Becton, Dickinson and Company, USA) in an auricular vein. Tracheal intubation was performed with a size 7.0 Portex® endotracheal tube (Smiths Medical International Ltd., United Kingdom). For maintenance of anesthesia, the animals received continuous infusion of ketamine (5 mg kg^{-1} h^{-1}; Alfasan Nederland B.V., The Netherlands), midazolam (1.5 mg kg^{-1} h^{-1}; Atavis Group PCT, Iceland), sufentanil (4 µg kg^{-1} h^{-1}; Janssen-Cilag B.V., The Netherlands), and rocuroniumbromide (4 mg kg^{-1} h^{-1}; Fresenius Kabi Austria GmbH, Austria). All animals received 500 ml of colloid solution (Voluven®; Fresenius Kabi AG, Germany) at start and a continuous infusion of crystalloid (Sterofundin® ISO 10 ml kg^{-1} h^{-1}; B. Braun, Germany). Each pig received a bolus of magnesium sulfate (500 mg; Pharmachemie BV, Haarlem, The Netherlands), as arrhythmia prophylaxis, added to the first bag of crystalloid solution. To prevent infections during the experiment, Cefazolin (1000 mg/animal; Kefzol ® EuroCept BV, Ankeveen, The Netherlands), an antibiotic used for the treatment of a widespread of bacteria was given intravenous.

Pressure-controlled mechanical ventilation (Servo 300; Siemens-Elema, Solna, Sweden) was performed with a FiO_2 between 24% and a positive end-expiratory pressure of 5 cmH_2O while no intervention was done. Normothermia, measured nasal, was maintained between 38° and 39°C, with two heating pads underneath and an electric

heating blanket above the animal. Furthermore, hearth rate, mean arterial pressure, SpO_2 and temperature were monitored continuously throughout the entire experiment. Arterial blood samples were collected to determine the arterial oxygen pressure and arterial oxygen saturation (ABL 800Flex (Radiometer, Denmark)).

A 4F thermodilution catheter (Pulsion Medical Systems AG München, Germany) was placed in the left femoral artery for arterial blood sampling. An 9Fr introducer sheath (Arrow International Inc., USA) was placed in the right jugular vein for infusion of palladium porphyrin. Both catheters were placed using the Seldinger technique. A lower midline abdominal incision was made to insert a cystostomy tube into the urinary bladder with purse-string sutures for urine collection.

The animals were placed in supine position and an incision was made to open the abdomen. A small intestinal loop was dissected and a small incision was made at the non-vascularized side to expose the intestinal mucosa (Figure 1). Mucosal oxygen saturation measurements were performed with a fiberoptic probe (Endoscopic T-Stat Sensor; Spectros, Portola Valley, California, USA) connected to the VLS oximeter (T-Stat 303 Microvascular Oximeter, Spectros, Portola Valley, California).

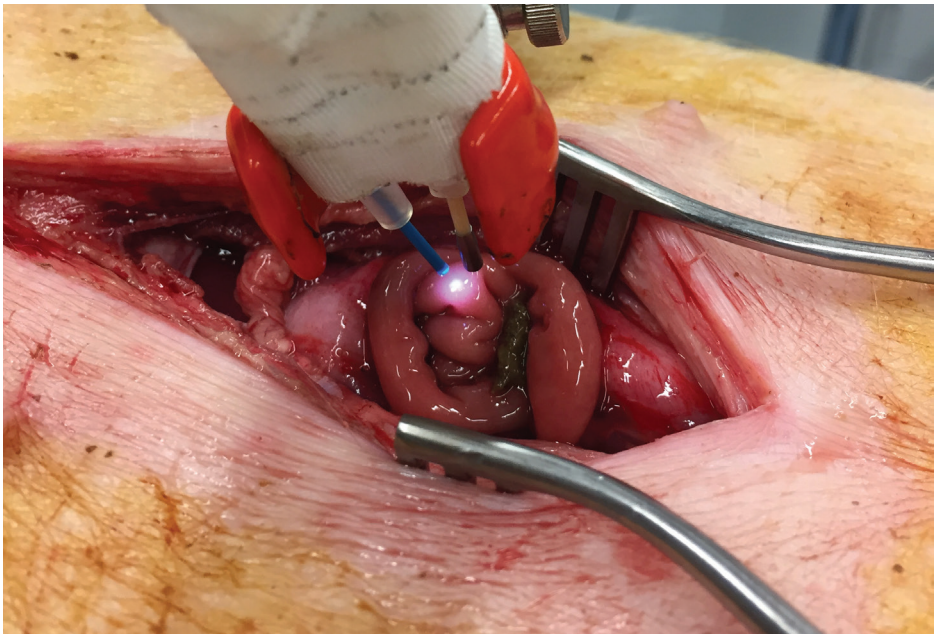

Figure 1. Set-up of the experiment of the VLS-probe (blue) and the μPO_2 probe fixated together positioned 1 to 5 mm above the mucosa of the small intestinal loop.

Microvascular oxygen tension measurements were done with oxygen dependent phosphorescent dye palladium porphine (Pd-porphyrin). Palladium porphyrin is a large molecule with optical properties that can absorb energy and react with oxygen. In the absence of oxygen it will release the absorbed energy from an excitation source via phosphorescent light with a specific decay time, i.e. lifetime. The lifetime is related to the amount of oxygen surrounding the Pd-porphyrin described by the Stern-Volmer relation(18). It has been tested for pH, temperature and diffusivity dependency(17). Calibration experiments are done and determine the O_2 accuracy of 5% independent of phosphorescence intensity itself(17).

For the laboratory experimental setup of the μPO_2 measurements the excitation source was an Opolette 355-I tunable laser (Opotek, Carlsbad, CA, USA) set to a wavelength of 524nm. An optical fiber developed by TNO and produced by Light Guide Optics was used that would fit through the working channel of a gastroduodenal endoscope. It has one central located excitation fiber with several surrounding detection fibers.

The phosphorescence was collected with a gated micro channel plate photomultiplier tube (MCP-PMT R5916U series, Hamamatsu Photonics, Hamamatsu, Japan). Phosphorescence lifetime analysis was done with a self-written software program in Labview (version 13.0, National Instruments, Austin, TX, USA). For the detailed setup description we refer elsewhere(21).

The probe palladium porphyrin was Pd(II) meso-Tetra (4-carboxyphenyl)porphine (80 mg/animal) (Frontier Scientific, Logan, USA) dissolved in 1ml DMSO and TRIS Trisma® Base (Sigma, St. Louis, MO) was combined with a 4% bovine serum albumin solution solved in phosphate buffered saline. This method has been validated *in vitro* and *in vivo*(17). Pd-porphyrin bound to albumin, forms a high-molecular-weight complex, confining it mainly to the vascular compartment when infused intravenously.

Both optical fibers were fixated together to perform stable simultaneous mucosal oxygen saturation and μPO_2 measurements of the same mucosal spot of the small intestine (Figure 1).

Mucosal oxygen saturation versus µPO2 measurements at different FiO2 values

Simultaneous VLS mucosal oxygen saturation and μPO_2 measurements were performed at different FiO_2 values ranging from 18%-100%. The mucosal oxygen saturation and μPO_2 measurements were simultaneously performed for two minutes at a specific FiO_2 value. When a new FiO_2 value was set, the start of a set of new measurements was awaited for the first two minutes. To compare the two measurement techniques the μPO_2 was converted into a corresponding saturation. For the μPO_2 conversion, for every measured value in mmHg the corresponding % was calculated called micro-vascular oxygen saturation converted (μSO_2.converted). The conversion can be found in Figure 2.

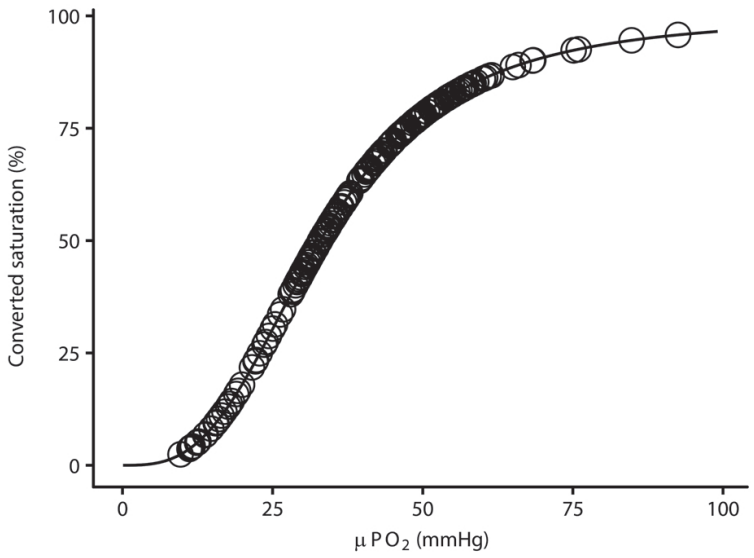

Figure 2. Conversion of μPO_2 into saturation according to the found relationship by Serianni et al.(22).

Influence of bile on mucosal oxygen saturation

Furthermore, the influence of bile on mucosal oxygen saturation values measured with VLS was assessed. Mucosal oxygen saturation measurements were performed of the small intestine mucosa in presence of bile. Two different types of bile were used: fluid obtained during upper GI endoscopy from the stomach of the animal and fluid obtained from the small intestine of the animal. The sticky viscosity of the bile ensured

the fixation of the bile on the measurement area and continuous visual confirmation ensured that the bile measurements were performed on surface covered with bile. The amount of bile applied to the mucosa, the thickness of the bile applied and the exact content of the bile applied were not controlled. The mucosal oxygen saturations in presence of bile were compared with the mucosal oxygen saturations before the bile was applied to the mucosa (baseline) and the mucosal oxygen saturations every time after the bile was removed with saline fluid as control. For every step approximately 30 measurements were done.

Mucosal oxygen saturation versus µPO2 during asystole

Finally, simultaneous mucosal oxygen saturation and μPO_2 measurements were performed from the moment a lethal dose potassium chloride was intravenously injected. A measurement period of 25 minutes after injection was considered long enough to ensure a steady state since Benaron. et al. showed detection of local ischemia with VLS within 120 seconds(23).

Experimental outcomes

Mucosal oxygen saturation values were defined in percentage tissue hemoglobin saturation. The μPO_2 measurements were defined in mmHg.

Analytical and Statistical methods

Statistical analysis was performed with R Statistics software (v3.2.4). Normal distribution was assessed visually and with the Shapiro-Wilk normality test. Normal distributed data is presented as mean±standard deviation (SD) and abnormally distributed data is presented as median with interquartile range (IQR). A linear regression model was used for the FiO_2, mucosal oxygen saturations, and μPO_2. A scatter plot was used to show the mucosal oxygen saturation versus the μPO_2 measurements at different FiO_2 values. To compare the two measurement techniques, the μPO_2 was converted from mmHg to % porcine hemoglobin saturation. To determine the saturation a porcine-specific hemoglobin saturation formula published by R. Serianni et al. was used(22): $(\%/100) = (0.13534 \cdot P_{O2})^{3.02}/[(0.13534 \_ P_{O2})^{3.02} + 91.2]$. The formula was derived from 213 data point at pH7.4 and 37 degrees with an excellent fit.

To compare the saturation, the difference in measurement frequency had to be overcome. The mucosal oxygen saturation has a fixed measurement interval whereas

the μPO_2 is measured on demand. To equally compare the two measurements the mucosal oxygen saturation was averaged over same period as one μPO_2 was done. Thereafter these results were visualized with linear regression and with a Bland-Altman comparison plot(24).

The Wilcoxon signed-rank test was used to compare the measurement before, with and after application of bile. A two-tailed p value of <0.05 was considered significant. After the potassium chloride injection mucosal oxygen saturation measurements were compared with μPO_2. Because VLS measures every second, a symmetrical moving average of 20 samples was taken to smooth the data, for example the eleventh sample is an average of sample [1-21].

RESULTS

Baseline data

All 5 animals were in good clinical condition before the start of the experiment.

Mucosal oxygen saturation versus µPO2 measurements at different FiO2 values

The mucosal oxygen saturation levels versus the μPO_2 levels different values of FiO_2 in 5 animals were measured. The mucosal oxygen saturation decreased with increasing FiO_2 in contrast to the μPO_2 values that increased with increasing FiO_2. The spread of the mucosal oxygen saturation levels and the FiO_2 levels was large, shown in Figure 3.

Figure 4a shows the correlation between mucosal oxygen saturation and the converted μPO_2 saturation. There is a poor linear correlation with an r^2=0.39, an interception of 18.5% and a slope of 0.41. In the Bland-Altman plot (Figure 4b) also a poor correlation is seen with a mean difference of -16%. If the saturation increases the mucosal oxygen saturation undervalues the saturation even more.

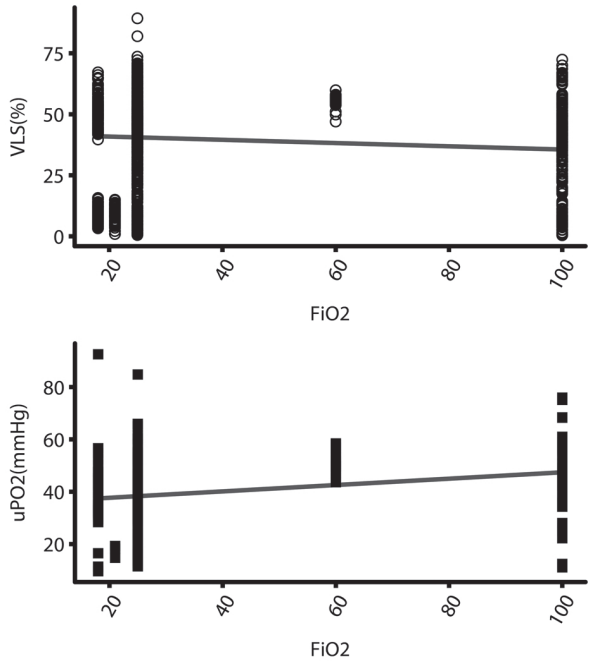

Figure 3. Scatter plot n=5 of mucosal oxygen saturation versus μPO_2 measurements at different FiO_2 values. VLS (R^2 =-0.01, Intersect=42.19, Slope=-0.07), μPO_2 (R^2=0.06, intersect=35.56, slope=0.14).

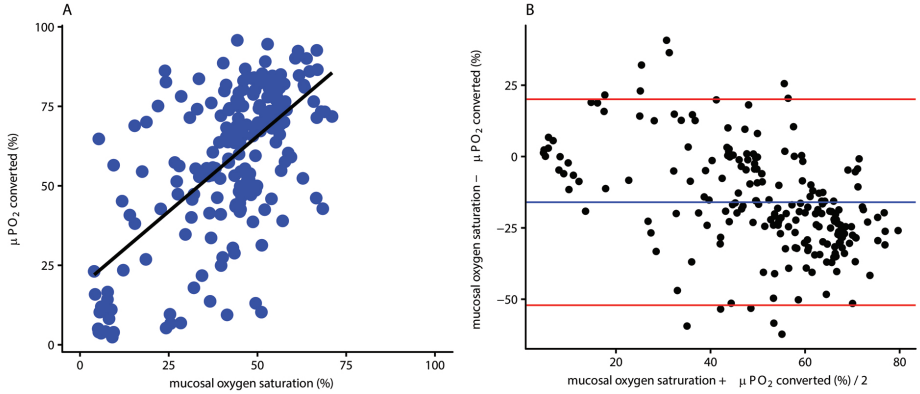

Figure 4. A) Correlation between mucosal oxygen saturation and the converted μPO_2 saturation. R^2= 0.39, intercept 18.5 slope 0.41. B) Blant-Altman plot of the mucosal oxygen saturation and the converted μPO_2 saturation. VLS – μPO_2–saturation: -16.00974, 2.5% limit: -52.83358 , 97.5% limit: 20.81410, SD(diff): 18.41192

Influence of bile on mucosal oxygen saturation

Figure 5 shows the mucosal oxygen saturation measurements without the presence of bile, with the presence of a bile mixture from the stomach and with the presence of a bile mixture from the small bowel and measurements without any of the bile mixtures measured in a total of 2 animals. The mucosal oxygen saturation measurements before application of the bile mixtures and after the bile mixtures were removed were not significantly different (mucosal oxygen saturation before application of bile mixture median (IQR) 57.5% (54.8-59.0%) versus mucosal oxygen saturation after removal bile mixture 57.0% (54.7-58.6%), p= 0.2743). However, a significant increase of the mucosal oxygen saturation was seen when the bile mixture from the stomach was applied compared to the mucosal oxygen saturation before application of the bile mixtures (median mucosal oxygen saturation with mixture of the stomach (IQR) 73.5% (66.8-85.8) p= $<2.2*10^{-16}$). When the bile mixture from the small bowel was applied, the mucosal oxygen saturation was significantly lower with a median (IQR) 47.6% (41.8-50.8), p=$<2.2*10^{-16}$ compared to mucosal oxygen saturation measurements with bile mixture form the stomach and the mucosal oxygen saturation increased significantly after the bile mixtures had been removed (p=$<2.2*10^{-16}$).

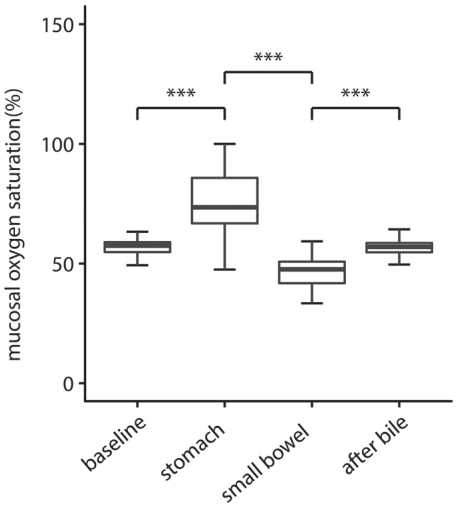

Figure 5. Mucosal oxygen saturation measurements without the presence of bile, with the presence of a bile mixture from the stomach, with a bile mixture from the small bowel and measurements without any of the bile mixtures. The baseline mucosal oxygen saturations did not significantly differ from the mucosal oxygen saturations after the bile had been removed shown as “after bile”. *** = p $<2.2*10^{-16}$

Mucosal oxygen saturation versus µPO2 during asystole

The mucosal oxygen saturation measurements and μPO_2 measurements during the minimally first 25 minutes of asystole in 5 animals are shown in Figure 6. In all 5 animals the μPO_2 measurements decreased towards a value of 0. The mucosal oxygen saturation measured with VLS decreased and increased variably during the measurement period and the mucosal oxygen saturation never reached a stable state around 0%.

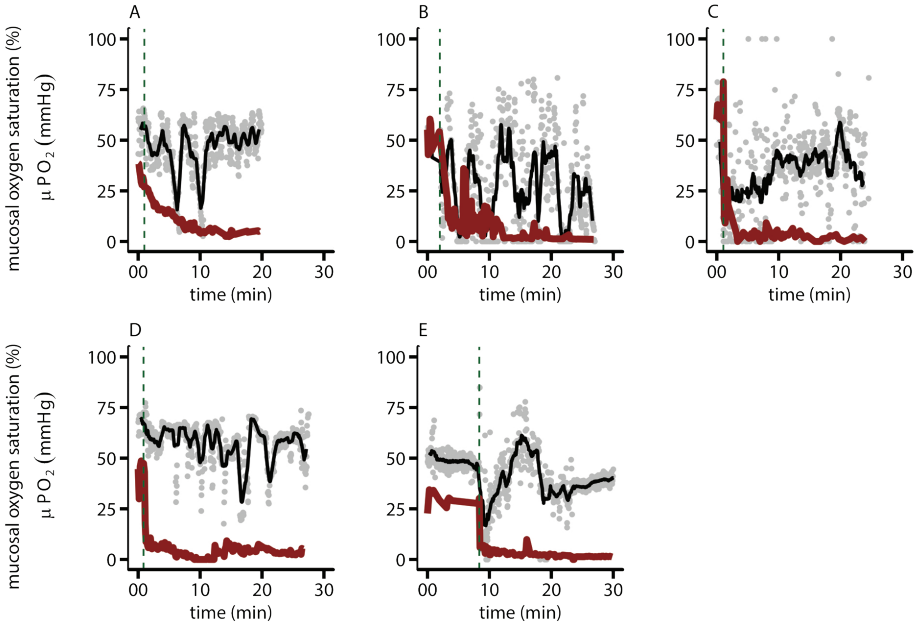

Figure 6. Average mucosal oxygen saturation measurements measured by VLS (black) over 21 data points (gray) and μPO_2 measurements (red) during the minimally first 20 minutes of asystole in 5 pigs. Green vertical dashed line represents the time a lethal potassium dose was injected.

Adverse events

No adverse events occurred during the 5 porcine experiments.

DISCUSSION

In this study we validated mucosal oxygen saturation measurements by comparing VLS with calibrated μPO_2 measurements. This study showed that the mucosal oxygen saturation values decreased with increasing FiO_2 in contrast to the μPO_2 values that increased with increasing FiO_2 with a large spread of the measured mucosal oxygen

saturation levels and FiO_2 levels and a poor linear correlation. Furthermore, a significant influence of bile on the mucosal oxygen saturation values was shown. Finally, this study showed that the mucosal oxygen saturation values, in contrast to the μPO_2 values, did not decrease towards a value of 0 in the first 25 minutes of asystole.

The found inverse relationship of the mucosal oxygen saturation measurements by VLS with FiO_2 is remarkable. Mucosal oxygen saturations measured with VLS are expected to increase with increasing FiO_2 if VLS measures the capillary oxygen saturation level. However, VLS measures not only arterial saturation but also a large venous compartment. If a large mixed venous saturation determines the overall saturation value the influence of FiO_2 is expected to be minimal. Potentially due to hyperoxic vasoconstriction the actual venous saturation can decrease more compared to normoxic situations. The high FiO_2 values will be measured by the μPO_2. Furthermore, the measured values, both VLS as μPO_2 values, have a great spread. Possibly, the oxygen tension was very variable in the gastrointestinal vessels as intestinal ischemia is also patchy and heterogenic distributed(5). During the experiment the hemodynamic state of the animals worsened by all experimental handlings, also contributing to a great spread of measured values.

Significant influence of bile on the mucosal oxygen saturation values measured with VLS was confirmed. Therefore it is advised and mentioned in the prescription to remove any bile remnants before the start of the VLS measurements. The bile has its own absorption spectrum of light. It also absorbs light in the same wavelengths as oxyhemoglobin and deoxyhemoglobin(25), and influences the result to determine the mucosal oxygen saturation. The amount of bile applied to the mucosa, the thickness of the bile applied and the exact content of the bile applied were not controlled in this experiment. However, these factors contribute to the light absorption by the bile and thus influence its effects on the VLS signal. Therefore, we advise to remove any fluid on the measuring area of the GI mucosa before the VLS measurements.

The idea that VLS measures mixed venous oxygen saturation is further confirmed by the fact that VLS measured still a reasonable oxygen saturation 25 minutes after asystole. The saturation in the capillaries is decreased towards zero over time due to diffusion of oxygen towards the still oxygen consuming cells. However, in the venous compartment the oxygen will desaturate slowly by the large buffer capacity. Therefore, the oxygen

saturation will not decrease towards zero immediately after asystole. Dips in oxygen saturation are seen in the mixed venous compartment measured by VLS as shown in Figure 6 due to spasm in the supplying arteries. After such a peristaltic contraction the blood flow stabilizes and no decrease in saturation is seen.

VLS is a powerful technique to measure oxygen saturation at a microvascular level. In the microvasculature oxyhemoglobin/deoxyhemoglobin is proportional mainly located in the venous compartment of the microvasculature. Therefore the saturation measured by the VLS is mainly represented by the venous compartment. For detection of an oxygen transport problem that results in ischemia, the microvascular arterial saturation is of importance, a part that is underexposed by VLS. This is endorsed by the fact that after a lethal potassium chloride the saturation does not drop in comparison to μPO_2, which is an exaggerated model of instant ischemia.

This study has some limitations. First, the experiments performed in this study were designed to enable generalizability in humans. However, to enable stable oxygen saturation measurements with VLS and μPO_2 of the mucosa of the small intestine of a pig, the abdomen had to be opened to open the small intestinal loop. The mucosa of this small intestinal loop was exposed to room air and room temperature. This will result in oxygen diffusion into the tissue and rapid decrease in temperature for the exposed tissue. Furthermore, the abdominal anatomy of a pig is different from the human abdominal anatomy. The GI tract of a pig is monogastric like the human GI tract, however the colon lies in a spiral. The mesenteric vascularization in humans consists of individual variable, mesenteric vessel formations with arcades, lateral branches and anastomoses in the bowel wall(26). The mesenteric vascularization in pigs consists of bundles of vessel branched of the main stem arising from the mesentery and passing directly into the bowel wall without any branching of arcades(26).

CONCLUSION

This study showed that VLS measures the mixed venous hemoglobin oxygen saturation and not the mucosal capillary hemoglobin oxygen saturation. The presence of bile significantly influences the oxygen saturation levels measured with VLS. VLS is currently used in clinical practice in the clinical work-up of CMI. Further research is needed to establish if the mixed venous compartment is optimal for mucosal hemoglobin saturation measurements to assess GI ischemia.

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CHAPTER

7

Oxygen-dependent delayed fluorescence of protoporphyrin IX measured in the stomach and duodenum during upper gastrointestinal endoscopy

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ABSTRACT

Protoporphyrin IX-triplet state lifetime technique (PpIX-TSLT) is a method used to measure oxygen (PO_2) in human cells. The aim of this study was to assess the technical feasibility and safety of measuring oxygen-dependent delayed fluorescence of 5-aminolevulinic acid (ALA)-induced PpIX during upper gastrointestinal (GI) endoscopy.

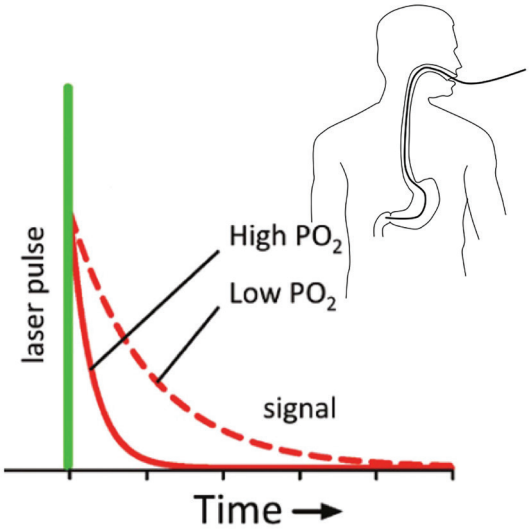
Endoscopic delayed fluorescence measurements were performed 4 hours after oral administration of ALA in healthy volunteers. The ALA dose administered was 0,1,5 or 20mg/kg. Measurements were performed at three mucosal spots in the gastric antrum, duodenal bulb and descending duodenum with the catheter above the mucosa and while applying pressure to induce local ischemia and monitor mitochondrial respiration. During two endoscopies, measurements were performed both before and after intravenous administration of butylscopolamine.

Delayed fluorescence measurements were successfully performed during all 10 upper GI endoscopies. ALA dose of 5 mg/kg showed adequate signal-to-noise ratio (SNR) values >20 without side effects. All pressure measurements showed significant prolongation of delayed fluorescence lifetime compared to measurements performed without pressure ($p<0.001$). Measurements before and after administration of butylscopolamine did not differ significantly in the duodenal bulb and descending duodenum.

Measurements of oxygen-dependent delayed fluorescence of ALA-induced PpIX in the GI tract during upper GI endoscopy are technically feasible and safe.

GRAPHICAL ABSTRACT AND TEXT

Oxygen tension (PO_2) can be measured in human cells by delayed fluorescence lifetime quenching of 5-aminolevulinic acid-induced protoporphyrin IX. This study aimed to assess the technical feasibility and safety of this technique during upper gastrointestinal endoscopy in the gastrointestinal (GI) tract. The endoscopic delayed fluorescence lifetime measurements in the GI tract were technically feasible and safe. Local mucosal ischemia was introduced temporarily by applying pressure with the probe on the mucosa. The lifetime prolongation demonstrated the oxygen-dependence of the signal.



INTRODUCTION

Protoporphyrin IX (PpIX) is an endogenous compound synthesized in active mitochondria which can be induced by administration of its precursor 5-aminolevulinic acid (ALA). PpIX exhibits oxygen-dependent delayed fluorescence after photoexcitation(1). The fluorescence lifetime depends directly on oxygen concentration, since oxygen acts as a quencher of excited PpIX molecules. In other words, upon collision of oxygen with an excited PpIX molecule energy transfer to oxygen will relax PpIX to the ground state without emission of a photon. More oxygen leads to more collisions and quenching, thereby shortening the delayed fluorescence lifetime. This phenomenon is described quantitatively by the Stern-Volmer relationship(2), relating the lifetime to the amount of oxygen (e.g. oxygen concentration or oxygen tension). A detailed description of the principles of the PpIX-triplet state lifetime technique (PpIX-TSLT) can be found in the article written by Harms et al.(3). Introduction of the COMET monitor (Photonics Healthcare BV, Utrecht, The Netherlands) made PpIX-TSLT clinically available for measurements on the skin(4). The main goal of this study was to investigate the technical feasibility of delayed fluorescence measurements in the gastrointestinal (GI) tract during endoscopy.

Oxygen tension (PO_2) measurements in cells of the GI tract during endoscopy could be of great value, e.g. for the diagnostic work-up of patients suspected to be suffering from chronic mesenteric ischemia (CMI). CMI is the result of insufficient blood supply to the GI tract caused by obstruction of mesenteric arteries and/or veins(5). CMI is in >90% caused by atherosclerosis of minimally one mesenteric artery. Typical symptoms of CMI are postprandial abdominal pain and weight loss, however more atypical symptoms as nausea, constant abdominal discomfort, vomiting, diarrhea or constipation are also reported(5). Symptoms alone are of limited value for the diagnosis of CMI(6). Mesenteric artery stenosis can be detected by CT-angiography, however the presence of mesenteric artery stenosis will not necessarily result in symptomatic disease (CMI) due to an abundant collateral mesenteric network. The prevalence of mesenteric artery stenosis in the asymptomatic general population is high (3-29%), increasing with age(7, 8). CMI occurs when extensive mesenteric artery stenosis and/or an insufficient collateral network is present. Therefore, a functional test detecting GI ischemia is highly desired. Currently, visible light spectroscopy (VLS) and tonometry are used as functional tests for the diagnostic work-up of patients suspected to be suffering from CMI.

VLS measures the mucosal capillary hemoglobin oxygen saturation during upper GI endoscopy(9, 10) and is less invasive than tonometry measuring luminal pCO_2 with a nasogastric and nasojejunal catheter connected to a capnography(10, 11). However, the sensitivity of VLS for CMI is 90% and the specificity is 60%(12), indicating the need to improve the accuracy of the diagnostic workup. Since in the original reports of PpIX-TSLT the lifetimes were shown to be related to mitochondrial oxygen levels(1, 13) this technique shows promise for diagnosing CMI. The COMET monitoring device was designed for cutaneous measurements and has been adapted for endoscopic delayed fluorescence lifetime measurements. Therefore the primary aim of this study was to assess the technical feasibility of delayed fluorescence measurements of the GI tract during upper GI endoscopy. Secondary aims were: 1. to determine the dose of 5-aminolevulinic acid (ALA) needed for endoscopic measurements; 2. to determine the specific measurements locations; 3. to demonstrate oxygen-dependent signal and, 4. to determine the influence of butylscopolamine on the measurements.

METHODS

Study design and setting

This work describes a single center study in healthy volunteers. The institutional review board of the Erasmus MC University Medical Center approved this study (NL59177.078.16, NL63050.078.17). The study complies with the Helsinki declaration on research ethics.

Participants

Healthy volunteers were recruited by distributing information leaflets. Before inclusion the medical history and existence of GI complaints were evaluated. Blood samples were taken to detect impaired renal function, and liver test abnormalities, defined as eGFR <90 ml/min/m3 or liver test abnormalities >1.5 times upper limit of normal. Healthy volunteers were eligible if they were able to give written informed consent, had an unremarkable medical history, and had no GI complaints. Volunteers were excluded in case of pregnancy, acute or chronic porphyria, and a known ALA or porphyrin hypersensitivity.

Study procedures and setup

The healthy volunteers were fasted for at least 6 hours and ALA (Gliolan, Medac GmbH, Wedel, Germany) was administered orally 4 hours before the upper GI endoscopy. The volunteers were discharged after the endoscopy. They were instructed to report any side effects. Furthermore, they were instructed to avoid exposure to sunlight as much as possible, and take precautions (e.g. sunglasses, long sleeves) during the first 24 hours after administration of ALA, since phototoxicity after sunlight exposure is a known side effect of ALA. Adverse events were collected during 7 days.

A probe that could be passed safely through the accessory channel of the endoscope was used for endoscopic detection of fluorescence light (designed by TNO, produced and CE-marked by LightGuideOptics, Mechenheim, Germany). The diameter of the accessory channel of the endoscope is 3.2 to 4.2 mm and therefore the tip of the probe is slightly smaller than 3.2 mm. The probe is a fiber optic assembly with one excitation fiber in the middle directly surrounded by seven detection fibers. The used detection fibers all have a diameter of 365 µm, and the excitation fiber is 470 µm in diameter. The fibers have a numerical aperture (NA) of 0.22±0.2. The tips of the fibers are fixed together in a ferrule. The position of the fiber tips within the ferrule and distance compared to each other is fixed and does not change when pressure is applied on the mucosa with the probe tip or while passing the probe tip through the accessory channel of the endoscope. The excitation fiber of the probe was connected to the light source in the COMET, a pulsed 515nm laser. The detection fiber was connected to the photomultiplier detection system of the COMET. To protect the highly sensitive detection system from indirect laser light a long pass filter (575nm with OD 4, Edmund Optics, Barrington, NJ, USA) was introduced in the optical path of the detection branch. During endoscopy peripheral saturation was continuously monitored and oxygen was administered intranasally to maintain a saturation level ≥95%. See Figure 1 for the setup.

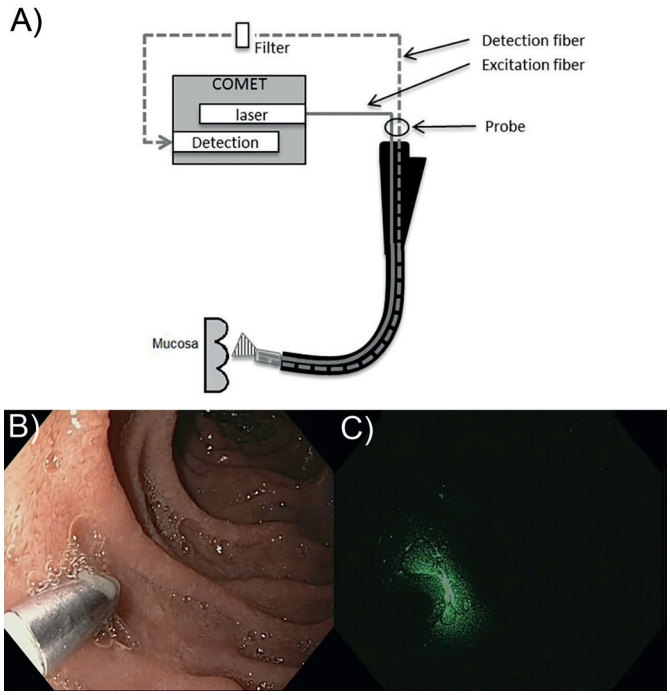


Figure 1. The setup for upper GI endoscopic delayed fluorescence measurements: A) Schematic setup, B) Probe in the descending duodenum during upper GI endoscopy, and C) Probe in the descending duodenum during endoscopic measurement (endoscopic light is switched off).

Delayed fluorescence lifetime measurements were performed similar to VLS measurements at three anatomical locations in the descending duodenum, duodenal bulb, and antrum of the stomach(12). The fiber was positioned approximately 1-5 mm above the mucosa of the target area. A perpendicular angle of the fiber tip and the target area is optimal for the signal quality, however this is not an important parameter for the outcome of the lifetime measurements. To minimize interference by background noise the light of the endoscope was switched off during the measurements. Raw delayed fluorescent traces were stored with an external computer connected via the serial (rs-232) port. A python script written to store the raw data in a comma-separated file was used to read the serial buffer. The raw data was analyzed with software written in LabVIEW (version 13.0, National Instruments, Austin, TX, USA). Lifetimes were calculated using a rectangular distribution fit, taking into account the heterogeneity in lifetimes underlying the measured delayed fluorescence signal(13) unless stated otherwise. The mitochondrial oxygen tension (mitoPO_2) reading by COMET was not used since COMET

is developed and tested for measurement on skin and links the measured lifetimes to the calibration constants for skin cells. Because this is the first report on delayed fluorescence measurements via an endoscope, we judged to exercise some restraint in reporting absolute values of PO_2. Therefore all delayed fluorescence measurements are represented as reciprocal lifetimes $1/\tau$ (with t in microseconds) in order to obtain a positive association between oxygen and lifetime. According to the Stern-Volmer relationship the reciprocal lifetime is linearly related to the actual oxygen tension. Based on our current understanding of the technology, PO_2 measurements with a reciprocal lifetime >0.1 μs^{-1} should be considered as non-physiological in humans with a normal arterial oxygen tension(1).

Determination necessary ALA dose

The appropriate dose of ALA was determined by performing delayed fluorescence lifetime measurements with different doses of ALA. Since PpIX is endogenously present and accumulates in metabolic active cells, such as mucosal cells, measurements were performed during one upper GI endoscopy without administration of ALA. In neurosurgery 20mg/kg ALA is used to induce enough PpIX to visually determine the tumor fluorescence under blue light(14). This was expected to be an abundant dose for detection of delayed fluorescence in the duodenal region because of the high cellular turnover and metabolic rate compared to neurological tissue. Therefore, five upper GI endoscopies were performed using a dose of 20mg/kg, two upper GI endoscopies were performed after administration of 1mg/kg ALA and two using a dose of 5mg/kg. Optimal dosage was based on signal quality and adverse events. Quality is expressed as signal-to-noise ratio (SNR). A SNR >20 is considered adequate(4).

Determining measurement locations and demonstrating oxygen-dependent signal

Measurements were obtained at each anatomical location with the probe hovering 1-5 mm above the mucosal surface. In order to confirm that the measured delayed fluorescence lifetimes depend on the oxygen concentration, measurements were performed while inducing local mucosal ischemia. Temporary ischemia was achieved by applying pressure to the mucosa with the probe. The oxygen supply to the tissue under the probe is compromised by compression of the capillaries. Because the oxygen is used within the cells, and the supply compromised, a prolongation of lifetime was expected due to the decrease in PO_2 during application of pressure. After minimally

two seconds of pressure, three consecutive measurements were taken while pressure was applied. This process was repeated at two more sites within each anatomical location. In the situation without pressure the tip of the probe was positioned under view in close proximity of the tissue or just on the tissue without visible deformation of the mucosa. While providing pressure the probe is pushed on the tissue and caused tissue deformation similar to the procedure performed when obtaining tissue biopsies for diagnostic purposes. The exact amount of pressure applied was not controlled or measured. Measurements started in the descending duodenum and subsequently measurements with and without applying pressure were performed in the duodenal bulb and gastric antrum.

An oxygen consumption curve was made in two volunteers who received 5mg/kg ALA by taking repeated measurements with an interval of one second. Measurements were performed without applying pressure for minimally five seconds; the next 20 seconds measurements were performed while applying pressure to visualize mitochondrial respiration(15). SNR and reciprocal lifetime were used to determine appropriate locations for measurements.

It is known that local oxygen tension will be heterogeneously distributed within the tissue(16). Further analysis was done on the raw fluorescent traces to determine the effect of local applied pressure on the reciprocal lifetime and its distribution, caused by e.g. oxygen heterogeneity. By assuming the PpIX to be homogenous distributed among the GI tract the underlying lifetime distribution can be obtained with a method described by Golub et al.(17). The trace can be described by a sum of rectangular distributions and the fractional contribution per reciprocal lifetime can be recovered. This method was successfully used by our group to recover oxygen distribution histograms (16, 18, 19) and is used on specific traces in this study to determine the distribution of (reciprocal) lifetimes in the signal as a measure of heterogeneity in the tissue. The fractional distribution within a trace describes the heterogeneity on a microvascular and cellular scale. To investigate the heterogeneity on a larger tissue scale all data recorded above the tissue is combined in a histogram and the individual contributions are visualized by color.

Determining influence of butylscopolamine

Intravenous administration of butylscopolamine is commonly used during upper GI endoscopy to reduce intestinal contractions. Since butylscopolamine is known to induce tachycardia causing increased cardiac output, GI tract tissue oxygen levels could be influenced. This possible influence was evaluated in two volunteers receiving 5mg/kg ALA. All measurements mentioned before were performed in the descending duodenum, duodenal bulb and gastric antrum. After intravenous administration of 20 mg butylscopolamine the measurements were repeated in exactly the same manner.

Statistical analyses

The SNR and reciprocal lifetime were not normally distributed and therefore described as medians and interquartile ranges (IQR). Differences in reciprocal lifetimes with and without pressure and before and after administration of butylscopolamine were determined using the Wilcoxon-Mann-Whitney Test. A two-tailed p value of <0.05 was considered significant. Statistical analysis was performed using R (version 3.4.2) (20).

RESULTS

Participants

Ten upper GI endoscopies were performed in six healthy volunteers. Nine out of ten upper GI endoscopies were performed in females, with a median age of 30.0 years (IQR 28.5-34.0 years). All endoscopies were performed in non-smokers and all healthy volunteers gave informed consent. No oxygen or sedatives were administered during endoscopy. Delayed fluorescence lifetime measurements were successfully performed during all ten endoscopies.

Determining necessary ALA dose

The SNR for each specific location and dose of ALA are presented in Table 1 and Figure 2. The endogenous amount of PpIX showed to be insufficient to measure delayed fluorescence, since SNR was below 20 at all locations. The dose of 1mg/kg ALA also showed to be insufficient with SNR values of the first quartile reaching maximal 18 in the descending duodenum and a median SNR of 29 just above the lower limit of 20.

Table 1. Signal-to-noise ratio (SNR) for measurements with probe position 1-5mm above tissue, data presented as median [IQR], total of 10 upper GI endoscopies.

Dose	0 mg/kg	1 mg/kg	5 mg/kg	20 mg/kg
SNR Antrum	2 [1-3]	4 [3-6]	6 [4-13]	19 [8-37]
SNR Duodenal bulb	3 [2-7]	233 [165-533]	702 [179-900]	617 [269-921]
SNR Descending duodenum	6 [5-6]	29 [18-56]	215 [156-684]	110 [77-248]
Adverse Events	0/1	0/2	0/2	3/5 phototoxicity

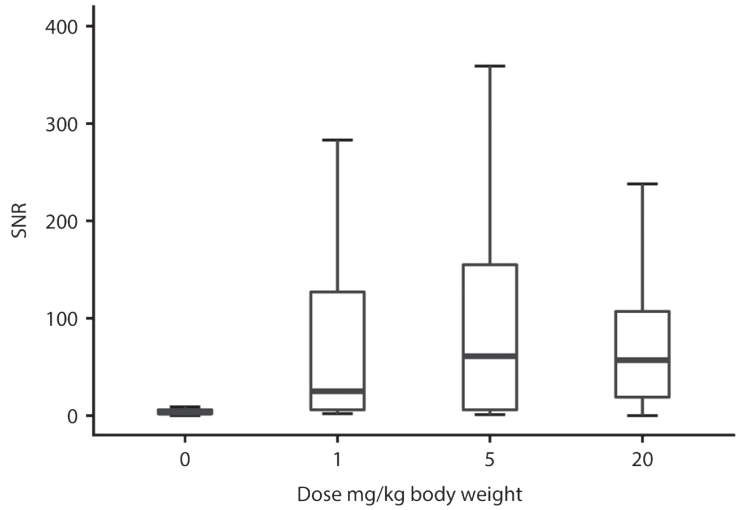


Figure 2. Signal-to-noise ratio (SNR) sorted by oral dose ALA combined for all measurement locations (gastric antrum, duodenal bulb, descending duodenum). Measurements are performed without pressure applied. Outliers are not presented since SNRs in 5 and 20mg/kg go up to 6000.

SNR in duodenal bulb and descending duodenum were adequate in the 5 and 20mg/kg group, however phototoxic side effects occurred in three out of five volunteers in the 20mg/kg group (Table 1). The phototoxicity was observed on the skin of the face exposed to sunlight after the experiment in all three volunteers with phototoxicity and looked similar to a sunburned like reaction. Side effects resolved within 24 hours in all volunteers. Phototoxicity was not observed in the GI tract and volunteers did not experience abdominal complaints.

It was concluded that 5mg/kg was the best dose with sufficient SNR values and without reported side effects. This dose leaves a margin for suboptimal circumstances, for

example less conversion of PpIX in patients and losses in the detection system due to the use of adaptors needed to couple the measuring probe to the COMET system.

Determining measurement locations

The SNR at the gastric antrum location was low compared to the SNR of the duodenal bulb and descending duodenum. Only in the 20mg/kg group the upper quartile of the values reached a SNR >20 in the gastric antrum, therefore the signal quality in the gastric antrum showed insufficient for reliable measurements. The lifetime calculation became more inaccurate if the SNR dropped below 20, resulting in a scatter of lifetimes with a tendency to non-physiological lifetimes, see Figure 3. Since the SNR values in the gastric antrum were too low and caused non-physiological lifetimes, measurements in gastric antrum were not included in the analysis of the influence of butylscopolamine.

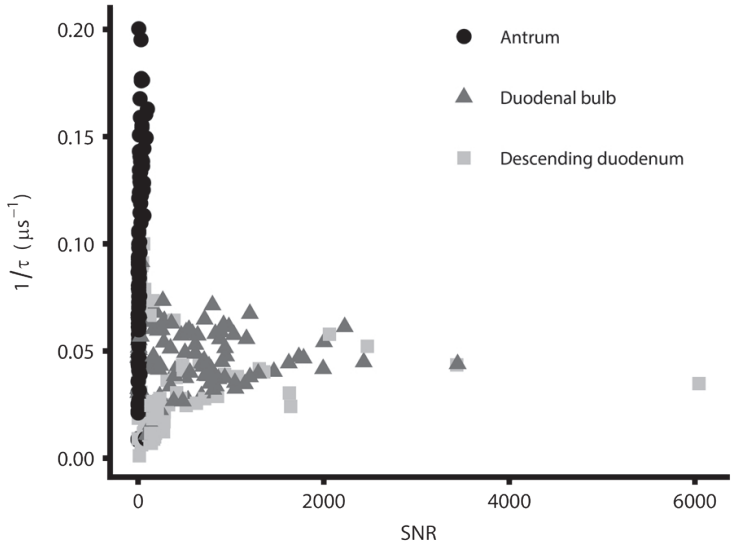


Figure 3. Reciprocal lifetimes (with lifetime $1/\tau$ tau in microseconds) versus signal-to-noise ratio (SNR) of all measurements without pressure applied specified for each measurement location.

Demonstrating oxygen-dependent signal

Raw delayed fluorescence lifetime traces were recorded. When the probe was “loose” hovering above the GI tissue short lifetimes were measured. While pressure was applied the lifetime increased, shown in the Bulbus in Figure 4.

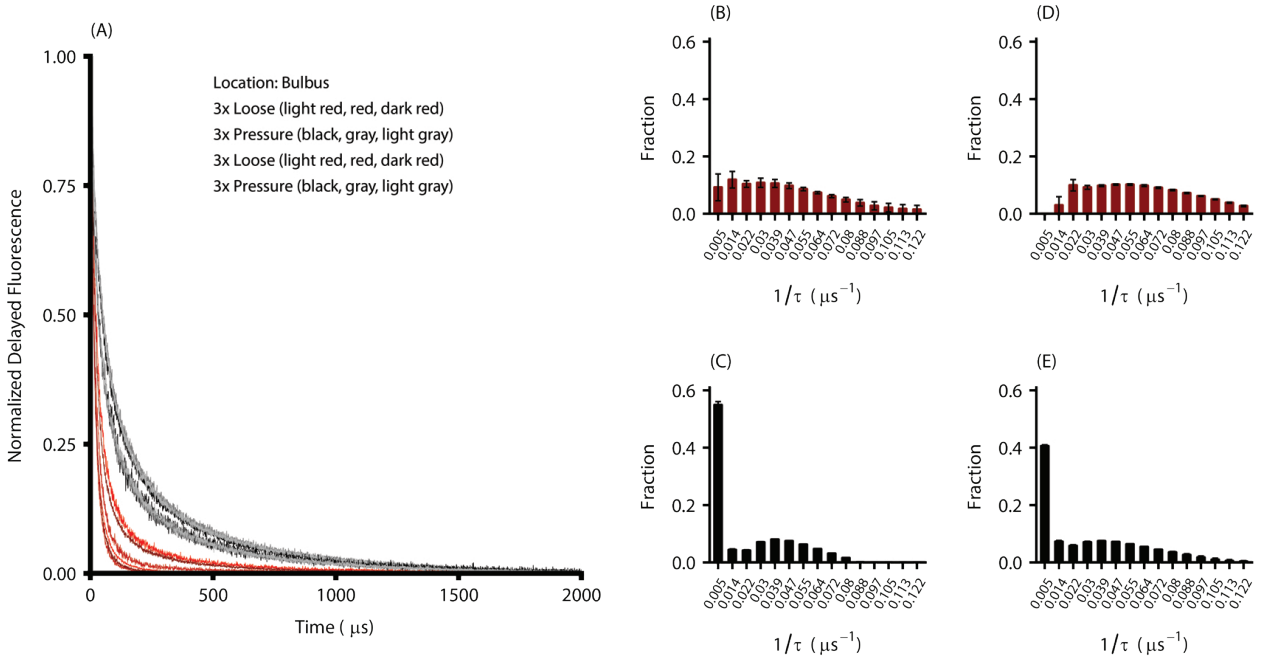


Figure 4. A) The normalized delayed fluorescence traces recorded in the Bulbus with 5mg/kg ALA. The traces represent 3 loose followed by 3 measurements while pressure was given with the probe on the tissue to induce local ischemia. This sequence was repeated for a second time. For the distribution analysis (histograms) a base of 15 reciprocal lifetimes equally distributed over a corresponding physiological PO_2 range (0-150 mmHg) assuming a quenching constant of 830 $mmHgs^{-1}$ and lifetime of spontaneous relaxation of 800 microseconds was taken(1). Histograms show reciprocal lifetime distributions of traces of the first panel. B and D) Average of 3 loose measurements. C and E) Average of 3 measurements while pressure was applied on the tissue with the optical probe. Histogram data presented as mean±SEM.

For the lifetime distribution analysis a base of 15 reciprocal lifetimes equally distributed over a corresponding physiological PO_2 range (0-150 mmHg) assuming a quenching constant of 830 $mmHgs^{-1}$ and lifetime of spontaneous relaxation of 800 microseconds was taken(1). The distribution analysis was done on the 2 times 3 loose and 2 times 3 pressure traces. The averaged distributions of both the loose and pressure measurements are shown in Figure 4. While pressure was applied a fraction of 0.55 of the signal fell in the bin with central reciprocal lifetime 0.005 μs^{-1}. Such lifetimes around 200 µs and even longer, as in this bin, indicate that a large part in the measurement volume is ischemic. The decrease in oxygen resulted in a distribution that has shifted to the left (lower PO_2) compared to the loose situation(3). To analyze the heterogeneity between different spots of mucosal tissue, all "loose" data was combined into a histogram. To visualize the contribution of individual volunteers the data is color categorized per subject, shown in Figure 5.

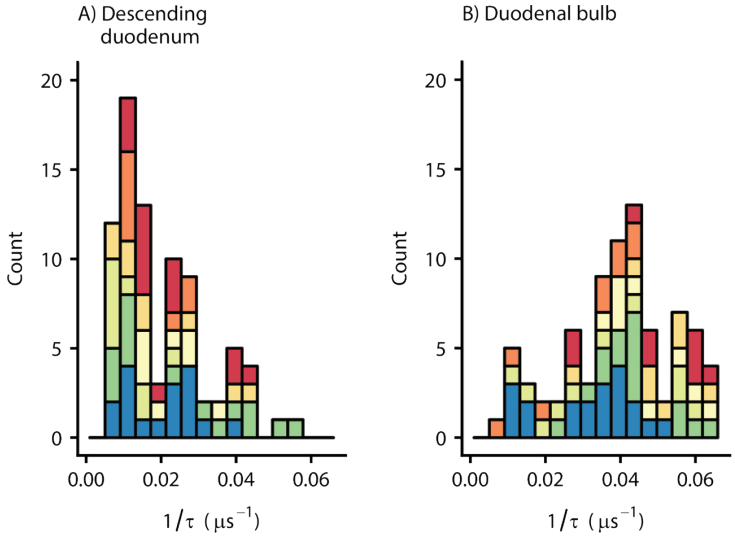


Figure 5. Histogram, 16 bins distributed over physiological reciprocal lifetimes, of the two measurement locations, included data is 5 and 20mg/kg ALA administration. The presented data is from two measurement location, a) Descending duodenum, b) Duodenal bulb, with the measurement probe hovering 5mm above the tissue. The colors indicate the individual measurement subjects.

All measurements performed while applying pressure on the mucosa were significantly lower compared to measurements performed without pressure at all measurements

locations (Table 2). Figure 6 displays a decrease of reciprocal lifetime when pressure is applied with values decreasing further when pressure is maintained for a longer period of time. The oxygen disappearance curve (Figure 7) supports this finding and shows a decrease of reciprocal lifetime over time, demonstrating disappearance of oxygen due to ongoing oxygen consumption, while temporary ischemia is induced.

Table 2. Reciprocal lifetime (in units, $1/\tau$ ms^{-1}) of GI tissue PO_2 measurements with and without pressure applied for each measurement location. ALA dose is 5mg/kg and 20mg/kg, total of seven upper GI endoscopies.

Location	1/τ loose median [IQR]	1/τ pressure median [IQR]	p-value
Antrum	0.092 [0.061-0.132]	0.052 [0.032-0.069]	<0.001
Duodenal bulb	0.041 [0.032-0.049]	0.013 [0.010-.0.022]	<0.001
Descending duodenum	0.016 [0.011-0.026]	0.009 [0.008-0.011]	<0.001

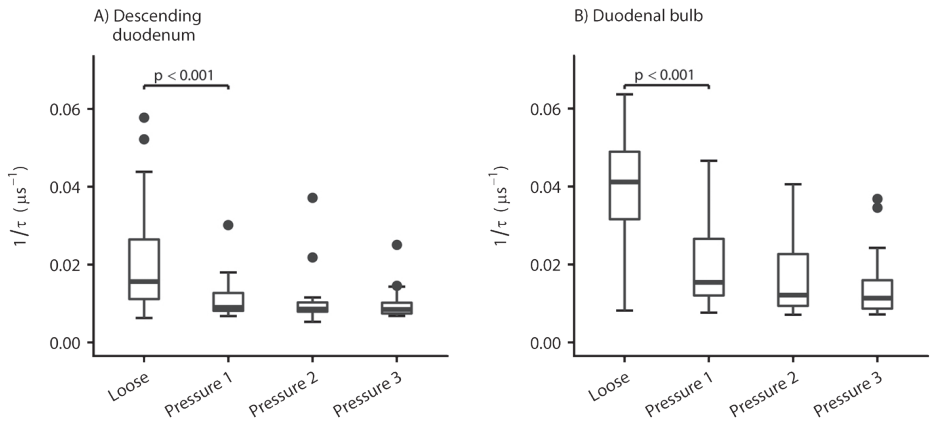


Figure 6. A) Measurements in the descending duodenum. X-axis shows measurements just above tissue (loose) and three consecutive measurements during pressure application (pressure 1, pressure 2, pressure 3). B) Measurements in the duodenal bulb. X-axis shows measurements just above tissue (loose) and three consecutive measurements during pressure application (pressure 1, pressure 2, pressure 3).

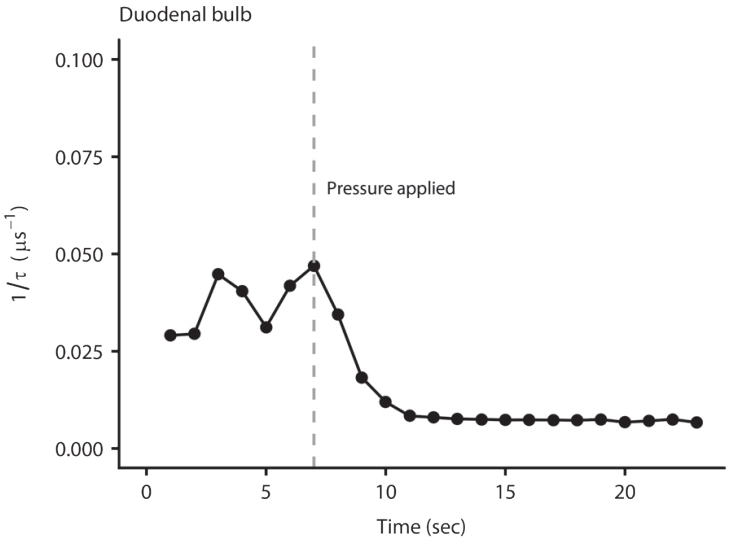


Figure 7. Oxygen consumption curve performed in the duodenal bulb.

Determining influence of butylscopolamine

Delayed fluorescence before and after administration of butylscopolamine did not differ significantly in the duodenal bulb (Figure 8). In the descending duodenum, reciprocal lifetimes before administration of butylscopolamine were significantly lower than after administration of butylscopolamine (Figure 8). Measurements before and after administration of butylscopolamine did no longer differ significantly (p=0.281) when the lowest duodenal values before administration of butylscopolamine are excluded. These measurements were performed while unintended pressure was applied to the mucosa due to intestinal contractions.

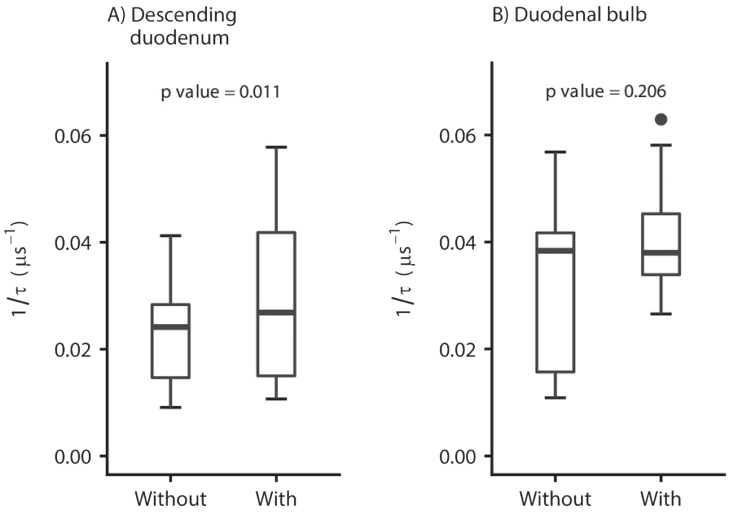


Figure 8. A) measurements with 5mg/kg ALA in duodenal bulb without butylscopolamine versus measurements with butylscopolamine and B) measurements with 5mg/kg ALA in descending duodenum without butylscopolamine versus measurements with butylscopolamine.

DISCUSSION

This study showed that delayed fluorescence measurements of ALA-induced PpIX in the GI tract during upper GI endoscopy are technically feasible and that the measured signal is oxygen-dependent. We determined an optimal dose of 5mg/kg ALA and duodenal bulb and descending duodenum as suitable measurement locations. Administration of butylscopolamine during upper GI endoscopy did not influence the measured GI delayed fluorescence signal (reciprocal lifetimes).

ALA-induced enhancement of mitochondrial PpIX provided the first method to measure mitochondrial PO_2 in living cells(1). In a time window of some hours after administration of ALA the PpIX is confined in the mitochondria as shown in animal studies in rat liver(18) and rat heart(19). Since PpIX diffuses slowly out of the mitochondria, it will not solely remain in the mitochondria, making the localization of the signal less specific over time. The COMET system provides the clinical parameter "mitoPO_2", in order to distinguish the measurement from e.g. hemoglobin-based "tissue oxygen" measurements, since such parameters provide other information from different tissue compartments(4). However, the reader should keep in mind that the origin of the PpIX delayed fluorescence signal

is not only mitochondrial and depends on tissue type, and the amount of time after ALA administration.

Administration of ALA is needed for reliable endoscopic delayed fluorescence lifetime measurements since the amount of endogenously present PpIX is not sufficient for measurements using the current setup. The optimal dose of ALA is a compromise between sufficient signal quality and no or few side effects. The signal quality was high for a dose of 20mg/kg ALA, however phototoxicity was reported in 60%. Measured reciprocal lifetime values were disproportionally high at a dose of 1mg/kg ALA compared to the values measured with 5 or 20mg/kg ALA. This finding suggests the occurrence of disproportional high reciprocal lifetime values at low SNRs due to insufficient ALA dose. An explanation may be the occurrence of PpIX photobleaching, caused by the white xenon light source of the endoscope plus the potential photobleaching effect of the green laser light. The total amount of light exposure depends on the endoscopic observation time. But despite the endoscopic light source the measurements could be performed with sufficient signal quality. With technical and medical considerations in mind we advise an ALA dose of 5mg/kg for endoscopic oxygen-dependent delayed fluorescence measurements, since we showed reliable delayed fluorescence measurements without any side effects after administration of this dose.

The COMET device determines mitoPO_2 by the delayed fluorescence lifetime of PpIX after excitation with a laser pulse. The measurement has been calibrated for skin and in that case reciprocal lifetime is linear proportional to oxygen tension in mmHg(1). The calibration constants in the human gastro-duodenal tract are unknown, as a consequence all data is represented in reciprocal lifetimes $1/\tau$ (μs^{-1}). The measured lifetimes in the gastric antrum were short, with a median value of 10.8 µs, that would have corresponded with non-physiological high PO_2 values if the current available calibration constants were used(1). The reason why the gastric antrum has short delayed fluorescent lifetimes has not been studied. We consider the histological composition and function of the mucosa could interfere with the excitation light of the delayed fluorescent signal itself. It could be that the ability of these cells to accumulate PpIX is lower, e.g. due to a relatively slow cellular turnover, resulting in low SNRs and unreliable short lifetimes.

We determined the influence of administration of butylscopolamine on the endoscopic delayed fluorescence signal since butylscopolamine is commonly administered intravenously in clinical practice if intestinal contractions hamper the endoscopy. Delayed fluorescence lifetimes before and after administration of butylscopolamine did not differ significantly in the duodenal bulb, however in the descending duodenum the reciprocal lifetimes before administration of butylscopolamine were significantly lower than after administration. These lower values were due to unintended application of pressure during measurements, caused by peristaltic movements of the bowels. During the endoscopic GI delayed fluorescence measurements the green light emitted by the laser is visible when the endoscopic light is switched off. When peristaltic movements of the bowels were present we frequently observed fading or even disappearance of the green light when the GI mucosa pressed against the fiber. At the same time, lower reciprocal lifetime values were noted. Since the endoscopic light has to be switched off during GI delayed fluorescence measurements, correcting the position of the probe in order to avoid contact with the mucosa is difficult in contractile bowels. After excluding the low values caused by unintended application of pressure, no significant differences in reciprocal lifetime before and after butylscopolamine remained. Therefore we conclude that butylscopolamine does not influence the endoscopic GI tissue reciprocal lifetime values, however when intestinal contractions are present measurements can be affected by unintended application of pressure. We advise to administer butylscopolamine during duodenal delayed fluorescence measurements when intestinal contractions are present, to increase the reliability of the measurements. Furthermore, future design of the probe with development of pressure sensors on the probe tip to avoid measurements during unintended application of pressure with the probe tip on the GI mucosa could be a solution for this problem.

This study has some limitations. First, the measured GI tract delayed fluorescence measurements in this study are presented as reciprocal lifetime since the calibration constants for the mucosa of the GI tract are unknown yet. Second, during the GI tissue measurements the light of the endoscope has to be switched off to minimize background noise. Furthermore, the probe tip currently consists of sharp edges, which can possibly damage the GI mucosa. Finally, the amount of endogenous PpIX is far from sufficient to measure GI delayed fluorescence using COMET. Necessity to administrate ALA causes a delay between oral intake and the first measurement opportunity, aside from potential phototoxic effects. Fortunately we did not register any adverse events with 5mg/kg

ALA. The use of a commercial device limited our choice to an excitation wavelength of 515nm, since this is the excitation wavelength of the COMET device, which is designed for cutaneous delayed fluorescence measurements after topical application of ALA(4). This wavelength is a tradeoff between melatonin and hemoglobin absorption, topical applied ALA penetration depth, and measurement volume depth. The penetration depth of green light in the gut is very limited(21), and in our application the use of 515 nm excitation light likely limits the measurement depth to the mucosa. However, since ALA is systemically administered in this application, other excitation wavelengths could provide more efficient photo excitation and improve SNR, or alter the penetration depth and increase measurement volume.

For the interpretation of the signal in terms of quantitative oxygen measurements additional research into the localization of PpIX and the photo-physical properties of the delayed fluorescence would be very helpful. For example, Vinklárek et al. described a Singlet Oxygen Feedback-Induced mechanism (SOFDF) that influences the delayed fluorescence of PpIX under certain non-physiologic circumstances(22). It is currently unknown to what extent other mechanisms than T-type delayed fluorescence, like this SOFDF mechanism, contribute to the *in vivo* delayed fluorescence signal. Although we are determined to improve our measurement and eventually hope to be able to convert the measured lifetimes to PO_2 levels this in itself is not necessary for successful clinical application. The only relevant question here is whether the measured lifetimes in healthy subjects differ from patients with e.g. CMI. Sensitivity and specificity of the technique could equally well be studied and calculated on reciprocal lifetimes instead of oxygen tensions.

In conclusion, measurement of oxygen-dependent delayed fluorescence of ALA-induced PpIX during upper GI endoscopy is feasible and safe. Further research is needed for the clinical applicability of this technique in the diagnostic work-up of CMI, starting with endoscopic GI delayed fluorescence measurements in patients suspected of CMI to determine its discriminative ability and to determine cut-off values for the inverse lifetime measurements for mucosal ischemia. Further research has to determine whether a more accurate diagnosis of CMI can be established when the presence of mucosal ischemia detected by endoscopic delayed fluorescence measurements is combined with the symptoms and imaging of the mesenteric arteries, and ultimately whether its use results in less patients treated for suspected CMI (with the associated

risks and costs of revascularization therapy) who will not experience relief of symptoms since they are false positively diagnosed by current standards.

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PART III

Therapy

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Covered stents versus bare-metal stents in chronic atherosclerotic gastrointestinal ischemia (CoBaGI): study protocol for a randomized controlled trial

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CHAPTER
8

Covered stents versus bare-metal stents in chronic atherosclerotic gastrointestinal ischemia (CoBaGI): study protocol for a randomized controlled trial

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ABSTRACT

Background

Chronic mesenteric ischemia (CMI) is the result of insufficient blood supply to the gastrointestinal tract and is caused by atherosclerotic stenosis of one or more mesenteric arteries in >90% of cases. Revascularization therapy is indicated in patients with a diagnosis of atherosclerotic CMI to relieve symptoms and to prevent acute-on-chronic mesenteric ischemia, which is associated with high morbidity and mortality. Endovascular therapy has rapidly evolved and has replaced surgery as first choice of treatment in CMI. Bare-metal stents (BMS) are standard care currently, although retrospective studies suggested significantly higher patency rates for covered stents (CS). The CoBaGI trial is designed to prospectively assess the patency of CS versus BMS in patients with atherosclerotic CMI.

Methods

The CoBaGI trial is a randomized controlled, parallel group, patient and investigator blinded, superiority, multicenter trial conducted in 6 centers of the Dutch Mesenteric Ischemia Study group (DMIS). Eighty-four patients with a consensus diagnosis of atherosclerotic CMI are 1:1 randomized to either a balloon-expandable BMS (Palmaz Blue with rapid exchange delivery system, Cordis Corporation, Bridgewater, NJ, USA) or balloon-expandable CS (Advanta V12 over-the-wire, Atrium Maquet Getinge Group, Hudson, NH, USA). Primary endpoint is primary stent patency rate at 24 months assessed with CT-angiography. Secondary endpoints are primary stent patency at 6 and 12 months and secondary patency rates, freedom from restenosis, freedom from symptom recurrence, freedom from re-intervention, quality of life according the EQ-5D-5L and SF-36 and cost-effectiveness at 6, 12 and 24 months.

Discussion

The CoBaGI trial is designed to assess the patency rates of CS versus BMS in patients treated for CMI caused by atherosclerotic mesenteric stenosis. Furthermore, the CoBaGI trial will provide insights in the quality of life of these patients before and after stenting and its cost-effectiveness. The CoBaGI trial is the first randomized controlled trial performed in CMI caused by atherosclerotic mesenteric artery stenosis.

BACKGROUND

Chronic mesenteric ischemia (CMI) is the result of insufficient blood supply to the gastrointestinal (GI) tract and is caused by atherosclerotic stenosis of one or more mesenteric arteries in >90% of cases(1, 2). The mesenteric arteries are the celiac artery (CA), superior mesenteric artery (SMA) and inferior mesenteric artery (IMA). Classic symptoms of CMI are postprandial abdominal pain and weight loss due to fear of eating. However, CMI may present atypically with constant abdominal discomfort, nausea, vomiting, diarrhea or even constipation(1). The "classic triad" of CMI consisting of postprandial abdominal pain, weight loss and abdominal bruit is present in only 16-22% of patients(3, 4).

The diagnosis of CMI is established by consensus in a multidisciplinary meeting joined by vascular surgeons, gastroenterologists and interventional radiologists(1). Consensus is an accepted method of diagnosing if a gold standard test is absent(5). Symptoms alone do not predict the diagnosis of CMI accurately(4, 6, 7). Therefore consensus diagnosis is based on the combination of clinical symptoms, radiological evaluation of the mesenteric vasculature and if available, assessment of mucosal ischemia with a functional test such as gastric-jejunal tonometry(3, 8, 9) or visible light spectroscopy (VLS)(10, 11). A definitive diagnosis of CMI is established if successful therapy of patients with CMI consensus diagnosis results in a durable relief of presenting symptoms.

Revascularization therapy is indicated in patients with a diagnosis of atherosclerotic CMI to relieve symptoms and to prevent acute-on-chronic mesenteric ischemia, which is associated with high morbidity and mortality. Endovascular revascularization has largely replaced open surgical revascularization (1, 12, 13). Endovascular revascularization of mesenteric arteries is achieved by means of stent placement. The SMA and CA are target vessels for therapy because of their larger diameter compared to the IMA. Furthermore, a protective collateral network ensures blood supply when the IMA is occluded as shown in patients with an aortic stent occluding the IMA. Literature on revascularization of the IMA is scarce. A study reported successful stenting of the IMA in 4 patients who were not candidates for CA or SMA revascularization(14). The classic percutaneous approach for mesenteric endovascular procedure is trans-brachial and trans-femoral, but a trans-radial approach is currently gaining popularity(15).

Endovascular revascularization is associated with a significant decreased risk of in-hospital complications compared to open mesenteric surgical revascularization(16). Despite the advantages of endovascular revascularization short term, re-stenosis is a common event occurring in 28-55% of patients within 2 years after endovascular mesenteric stenting(13, 17) whereas 0-25% of surgically treated patients develop re-stenosis(2, 18). The primary patency rate of open surgical revascularization is significantly higher than that of endovascular revascularization (cumulative OR 3.57, 95% CI 1.82-6.87, p=0.0002)(19).

Currently, balloon-expendable bare-metal stents (BMS) are standard care for mesenteric endovascular revascularization(1, 20). Retrospective data however, showed significantly higher primary patency rates of balloon-expendable covered stents (CS) at 3 years for mesenteric artery stenosis(21). Furthermore, patients treated with CS had less restenosis, symptom recurrence and re-intervention than patients treated with BMS(21). The Covered versus Balloon Expandable Stent Trial (COBEST) showed significantly higher patency rates of CS than BMS for aortoiliac arterial disease 18, 24, 48 and 60 months after stent placement(22, 23). Possibly, the membrane that covers the vascular atherosclerotic lesion functions as a physical barrier for intimal hyperplasia and is therefore associated with less restenosis in contrast with BMS. The performance of CS for mesenteric artery stenosis is promising, but prospective confirmation is lacking. The CoBaGI trial is a multicenter randomized controlled patient and investigator blinded clinical trial designed to compare patency rates of the CS versus standard care therapy with BMS in patients with CMI based on atherosclerosis.

Study hypothesis

CS have a significantly higher patency rate than BMS in patients with CMI due to atherosclerotic origin stenosis of the CA and/or SMA.

METHODS/DESIGN

This study protocol is written according to the SPIRIT 2013 statement for study protocols of clinical trials(24). The SPIRIT diagram is shown as Table 1.

Table 1. Schedule of enrollment, interventions and assessments for the CoBaGI trial acoording to SPIRIT(24).

	Study period						
	Enrolment	Allocation	Post-allocation				Close-out
Time point	$-t_1$	0	t_1	t_2	t_3	t_4	t_x
Enrollment:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
Interventions:							
Intervention CS			X				
Intervention BMS			X				
Assessments:							
CTA	X			X	X	X	
EQ-5D-5L	X			X	X	X	
SF-36	X			X	X	X	
Cost-effectiveness	X			X	X	X	
SAE				X	X	X	X
Mortality				X	X	X	X

$-t_1$ = screening and enrollment; t_1 = endovascular stent placement; t_2 = 6 months; t_3 = 12 months; t_4 = 24 months after intervention; t_x = end of follow-up 24 months. BMS = bare-metal stent; CS = covered stent; CTA = computed tomography angiography; SAE = serious adverse event.

Study design

The CoBaGI trial is a randomized controlled, parallel group, patient and investigator blinded, superiority, multicenter trial conducted in 6 centers of the Dutch Mesenteric Ischemia Study group (DMIS). Patients with atherosclerotic CMI will be randomly allocated for standard care therapy using a BMS (Palmaz Blue with rapid exchange

delivery system, Cordis Corporation, Bridgewater, NJ, USA) or a CS (Advanta V12 over-the-wire, Atrium Maquet Getinge Group, Hudson, NH, USA).

Study setting

The CoBaGI trial is conducted within the framework of the DMIS. Six Dutch centers participate in the CoBaGI trial. Initiating center is the Erasmus MC University Medical Center, an academic hospital in Rotterdam together with Medisch Spectrum Twente in Enschede which serves as a CMI specialized referral center. Furthermore, 4 other Dutch tertiary referral centers participate in the study: Maasstad Hospital in Rotterdam; St. Antonius Hospital in Nieuwegein; Bernhoven Hospital in Uden, and Jeroen Bosch Hospital in 's-Hertogenbosch.

Eligibility criteria

Patients with a consensus diagnosis of atherosclerotic CMI eligible for endovascular stent placement will be included in this trial.

Inclusion criteria are:

- Consensus diagnosis of CMI based on atherosclerotic mesenteric artery stenosis of the origin of the CA and/or SMA established in a multidisciplinary meeting attended by a gastroenterologist, interventional radiologist and vascular surgeon. This consensus diagnosis is based on:
  - Typical symptoms (presence of postprandial pain, unexplained weight loss)
  - Significant stenosis of >50% of at least one of the mesenteric arteries on previous computed tomography angiography (CTA)*
  - Functional assessment of mucosal ischemia with VLS or tonometry
- ≥18 years old
- Signed informed consent
- Total length of mesenteric stenosis <25 mm.

* Requirements for CTA are: CTA not older than one year, maximum slice thickness 1 mm, enhancement in aorta 300HU).

Exclusion criteria are:

- Absence of informed consent
- <18 years old
- No stenosis detected during angiography
- Renal insufficiency (glomerular filtration rate (GFR) below 30 ml/min or GFR below 60 ml/min in presence of comorbidities relevant to renal function)
- Previous stent placement in the target vessel
- Pregnancy
- Stenosis based on median arcuate ligament syndrome (MALS)
- Stenosis based on vasculitis
- Other criteria which the physician considers not compatible with inclusion in this trial.

Recruitment and consent

Patients with CMI based on atherosclerotic mesenteric artery stenosis are eligible for the CoBaGI trial. A gastroenterologist, surgeon or research physician will screen the patient according to the inclusion and exclusion criteria. When the patient is eligible for study inclusion, the treating physician will inform the patient about the possibility to participate in the CoBaGI trial and will hand-out the patient information form. Furthermore, the treating physician will inform the patient that study participation is voluntary and that participation may be withdrawn at any time without the need of having to provide a reason. At the return visit, the patient is given the opportunity to ask questions. If the patient consents to participate in the CoBaGI trial, written informed consent is obtained.

Randomization

Patients are 1:1 randomized for a BMS or CS with a web-based randomization module (9 Knots Business Solutions Ltd, Mansfield, UK) in random blocks of four or six stratified by center.

Interventions

At the start of the endovascular procedure patients are randomized for either a BMS or CS. The approach of the intervention is at the discretion of the attending

interventionalist (femoral, brachial, radial or retrograde). During the angiography the stenoses are assessed and if a suspected stenosis is not significant, this vessel will not be treated. If the stenosis is detected significant during angiography and the stenosis length is <25 mm the stenosis will be treated with the allocated stent. In case multiple stenosis are present and eligible for inclusion (*i.c.* CA and SMA), the same allocated stent type is used. After completion of the intervention various procedural details such as duration, approach, stent length, treated vessels and complications are entered in web-based case record forms by the interventionalist. The antiplatelet regimen in the CoBaGI trial consists of aspirin and clopidogrel combined for 12 months followed by aspirin lifelong and applies for both treatment arms. Table 1 presents the schedule of enrollment, interventions and assessments for the CoBaGI trial and Figure 1 presents the study flowchart according to CONSORT(25).

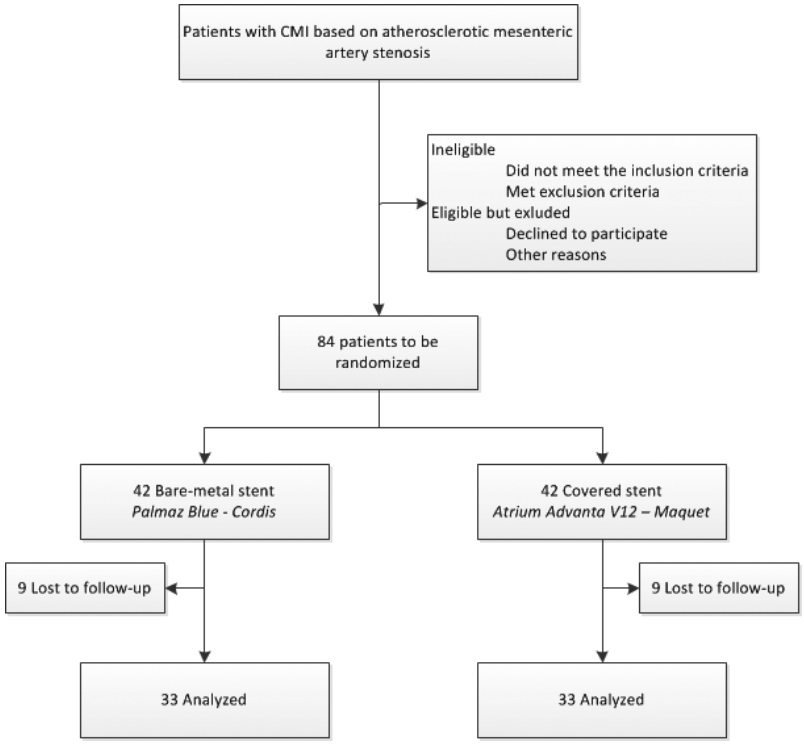

Figure 1. Flow of participants in the CoBaGI trial according to CONSORT(25).

Follow-up

After the endovascular procedure, the patients are followed-up at 6, 12 and 24 months with CTA to assess stent patency and with a visit to the outpatient clinic to assess symptoms and bodyweight. The patients also receive questionnaires to assess quality of life and cost-effectiveness before stent placement and 6, 12 and 24 months after stent placement.

Outcome

The primary endpoint is the primary patency rate 24 months after stent placement based on intention-to-treat analyses.

The secondary endpoints are (definitions are shown in Table 2):

- Primary patency rates at 6 and 12 months
- Secondary patency rates at 6, 12 and 24 months
- Freedom from restenosis at 6, 12 and 24 months
- Freedom from symptom recurrence at 6, 12 and 24 months
- Freedom from re-intervention at 6, 12 and 24 months
- Quality of Life at 6, 12 and 24 months
- Cost-effectiveness at 6, 12 and 24 months

Table 2. Definitions.

	Definition
Restenosis	>50% intra-stent stenosis regardless whether the patient had clinical symptoms
Symptom recurrence	Occurrence of presenting symptoms regardless of stent patency
Re-intervention	Intervention due to symptom occurrence in the presence of >50% intra-stent stenosis, either a reimplantation of stent or a surgical procedure

Blinding

The patient, investigator and the treating physician at the outpatient clinic are blinded for the treatment allocation (BMS or CS). For the duration of the trial the allocated stent will not be disclosed unless there is a medical need (i.e. restenosis, stent fracture).

Sample size

The sample size calculation for this randomized controlled superiority trial is based on the retrospective data of Oderich et al(21). Assuming that CS improves the patency rate of BMS after 24 months from 63% to 95%, and accounting for a 20% dropout rate, 42 participants are required per arm to achieve 80% power with a two-sided alpha of 0.05. The sample size calculation is performed using the Comparison of Independent proportions test (SAS Power and Sample size, SAS Institute Inc, Cary, NC, USA).

Data collection methods

Clinical data are collected using web-based case record forms (9 Knots Business Solutions Ltd, Mansfield, UK). Quality of life is assessed by the validated EQ-5D-5L(26, 27) and SF36(28, 29) questionnaires. The cost-effectiveness questionnaire deals with work omission, hospital visits and use of healthcare. All trial documents are kept for 15 years after study completion.

Data management

Data entry is performed by local study personnel or personnel of the initiating study center. Data-entry is anonymized replacing all patient names with a code. Only these codes are used as reference in reports and publications about this investigation. The web-based case record forms contain range checks for data values. The handling of personal data is compliant with the Dutch Personal Data Protection Act, the Code of Good Behavior and the General Data Protection Regulation effective since May 2018.

Data monitoring

Institution of a data monitoring committee (DMC) was waived by the ethical committee because the added risk of the interventional study arm is considered to be negligible. An interim analysis will not be performed. The initiating center Erasmus MC University Medical Center is responsible for the data monitoring activities to ensure data quality.

Statistical methods

Descriptive analyses will be provided regarding patient characteristics before randomization. Because this is a randomized controlled trial, statistical tests to detect differences in these baseline characteristics between both intervention arms will not be performed. The following patient characteristics before randomization will be

provided: age, gender, body mass index (BMI), smoking, comorbidity as hypertension, dyslipidemia, diabetes, and cardiovascular disease. Furthermore presenting symptoms will be described as abdominal pain, postprandial pain, exercise related pain, nausea, diarrhea, weight loss and symptom duration. Patient characteristics will be described as numbers and percentages for dichotomous variables, or as means and standard deviations for continuous variables with normal distribution or medians and interquartile ranges (IQR) for continuous variables if not normally distributed.

The primary analysis will be performed according the intention-to-treat principle. A per-protocol analysis will also be performed for the primary outcome of stent patency for those patients who were treated according to the treatment protocol.

The primary endpoint of stent patency will be analyzed with a 'two-sample z-test' for comparison of two proportions. Furthermore, a predictive model for time-to-event will be obtained by proportional hazards regression and Kaplan-Meier analysis to compare patency rates of CS versus BMS. All other continuous outcome measures will be reported as difference in mean improvement between CS versus BMS group. Change in quality of life assessed by the validated questionnaires EQ-5D-5L(26, 27) and SF-36(28, 29) will be compared between the CS and BMS group. Furthermore, the costs of both groups will be compared. All costs will be estimated based on actual input in terms of resource use, personnel and indirect costs from loss of productivity assessed by the cost-effectiveness questionnaire.

Harms

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the implantation of a BMS or CS. A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when,

based upon appropriate medical judgement, the event may jeopardize the subjector and may require an intervention to prevent one of the outcomes listed above.

All physicians who are involved in the trial are asked to report all adverse events to the coordinating investigator. The coordinating investigator will report the SAEs through the web portal ToetsingOnline (https://www.toetsingonline.nl) of the Dutch Central Committee on Research involving human subjects to the accredited Institutional Review Board that approved the protocol, within 15 days after the coordinating investigator has first knowledge of the serious adverse reactions. SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

Auditing

Representatives of the initiating center Erasmus MC University Medical Center audit the participating centers during the course of the study. All protocol modifications are communicated to the relevant parties.

Research ethics approval

The CoBaGI trial is performed in accordance with declaration of Helsinki and the Dutch law regarding research involving human subjects (Wet Medisch wetenschappelijk Onderzoek met mensen (WMO)). The Institutional Review Board of the Erasmus MC University Medical Center, Rotterdam, the Netherlands approved the study protocol on 15th of October, 2013. The boards of the other 5 Dutch participating centers gave permission for conducting the trial in their center. The CoBaGI trail is registered on 29th of April, 2015 in ClinicalTrials.gov with identification number NCT02428582.

Protocol amendments

Five protocol amendments were approved after initial approval of the CoBaGI protocol by the Institutional Review Board. The subjects of these amendments were the addition of new inclusion centers, addition of one inclusion criterion and adjustment of the patient information form. The contents of these amendments are incorporated in this protocol.

Confidentially

The investigators and the study staff will keep all information about the study patients during and after the trial in strict confidence. All study data is saved in the web-based case record forms. This study database is anonymized, the names of the enrolled study patients are replaced with a patient study number.

Ancillary and post-trial care

Compensation for post-trial care, for those patients who suffered harm from trial participation, is covered by trial health insurance.

Dissemination policy

Study protocol and study results will be presented at scientific conferences and in peer-reviewed publications. Authorship eligibility follows the common standards of author responsibility, conflict of interest, transparency and the recommendations of the International Committee of Medical Journal Editors (http://www.icmje.org). There are no limitations or restrictions for publication.

DISCUSSION

The CoBaGI trial is designed to compare the patency rate of BMS (standard care) with CS in patients with CMI based on an atherosclerotic mesenteric stenosis. Besides, the study will provide insights into the change in quality of life of patients induced by both stents and their cost-effectiveness. The CoBaGI trial is the first randomized controlled trial to compare BMS with CS in patients with CMI based on an atherosclerotic mesenteric stenosis.

The recently published clinical practice guidelines of the European Society of Vascular Surgery (ESVS) recommend with a low level of evidence (C: expert opinion and/or small studies, retrospective studies) to consider CS over BMS for patients requiring mesenteric artery stenting based a single retrospective study of Oderich et al.(21). A stronger, level A recommendation can only be issued based on the results of randomized controlled trials. The optimal design would be a double-blinded controlled trial. Since the physician who performs the endovascular procedure cannot be blinded, the CoBaGI trial is designed as a patient and investigator blinded randomized controlled trial.

The primary endpoint of the CoBaGI trial is primary stent patency assessed with CTA. The primary endpoint is a hard endpoint which can be assessed objectively. The secondary endpoint of symptom recurrence is dependent on reports of patient and investigator. In order to ensure unbiased collection and an objective assessment of the endpoints, blinding of the patient and investigator is important.

To perform a fair comparison between the two stent designs all participating centers will use the same brand/type of BMS as standard of care in the CoBaGI trial. The initiating center Erasmus MC University Medical Center had already ample experience with the BMS Palmaz Blue from Cordis for mesenteric stenting and therefore this stent was chosen to be used in all participating centers. BMS from different manufacturers are considered comparable in use and outcome although studies comparing BMS from different manufacturers are lacking.

Of note is the inclusion criterion that the length of the stenosis cannot exceed 24 mm because all stenoses needing stent extension had to be excluded in the CoBaGI trial since a CS will obstruct blood flow when a side-branche is over-stented in contrast to a BMS. The longest available Palmaz Blue BMS during the inclusion of the CoBaGI trial had a length of 24 mm and the longest CS had a length of 59 mm.

A pivotal inclusion criterion for the CoBaGI trial is a consensus diagnosis of CMI based on atherosclerotic mesenteric artery stenosis which is established in a multidisciplinary meeting joined by gastroenterologists, interventional radiologists and vascular surgeons. Medisch Spectrum Twente and Erasmus MC University Medical Center are specialized CMI referral centers. All patients eligible for the CoBaGI trial therefore, will be discussed during a CMI multidisciplinary meeting in one of these two centers. If functional assessment of mucosal ischemia is required to reach a consensus diagnosis, especially in case of single-vessel disease, the patient is referred to the Erasmus MC University Medical Center (VLS)(10, 11) or Medisch Spectrum Twente (24-hours tonometry)(3, 8, 9).

After endovascular revascularization for CMI, antiplatelet therapy is recommended and dual antiplatelet therapy might be considered for 3-12 months(1). Exact dose and duration schedules are lacking for mesenteric revascularization. All stented patients in the CoBaGI trial regardless of allocation will receive aspirin and clopidogrel for 12 months after stenting followed by aspirin lifelong.

The true incidence of atherosclerotic CMI is unknown. It is expected that in the upcoming years the incidence of atherosclerotic CMI will increase, mainly because of the aging population and the increasing prevalence of cardiovascular disease. The predicted increase in the prevalence of atherosclerotic CMI, the significant patient burden in terms of pain and loss of quality of life, and in particular risk of an acute ischemic events with an exceedingly high mortality risk, underscore the importance of the CoBaGI trial. The CoBaGI trial aimed to improve the patient outcome in terms of pain relief, improvement of quality of life and prevention of acute ischemic events. The fact that the CoBaGI trial is carried out within the framework of the DMIS with patients being recruited from multiple academic and community hospitals should facilitate the generalizability of the study outcomes.

In conclusion, the CoBaGI trial is a multicenter randomized controlled patient and investigator blinded superiority trial comparing BMS (standard of care) with CS in patients with CMI caused by an atherosclerotic mesenteric artery origin stenosis.

Trial registration

ClinicalTrials.gov Identifier, NCT02428582, registered on 29 April 2015. https://clinicaltrials.gov/ct2/show/NCT02428582

Trial status

The CoBaGI trial has started inclusion in May 2015. In September 2018 71 patients of the 84 (85%) patients were included. Inclusion is expected to be completed at the end of 2018. Follow-up duration is two years. Latest protocol version is version 5, date 28th June 2017.

DECLARATIONS

Ethics approval and consent to participate

The CoBaGI trial is performed in accordance with declaration of Helsinki and the Dutch law regarding research involving human subjects (Wet Medisch wetenschappelijk Onderzoek met mensen (WMO)). The Institutional Review Board of the Erasmus MC University Medical Center, Rotterdam, the Netherlands approved the study protocol with identification number MEC-2013-476 on 15th of October, 2013. The boards of the other 5 Dutch participating centers gave permission for conducting the trial

in their center: Maasstad Hospital in Rotterdam on 12th November 2015, Medisch Spectrum Twente in Enschede on 9th June 2016, Antonius Hospital in Nieuwegein on 14th September 2016, Bernhoven Hospital in Uden on 28th Nov 2016 and Jeroen Bosch Hospital in 's-Hertogenbosch on 23th November 2017. Informed consent will be obtained from all study participants.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

An unrestricted grant was received from Atrium Maquet Getinge Group. The CoBaGI trial is investigator-initiated trial. The sponsor had no influence on the design of the study, data collection, results or publications.

Access to data

All investigators will have access to the final trial dataset.

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CHAPTER

9

Persistent symptom relief after revascularization in patients with single artery chronic mesenteric ischemia

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ABSTRACT

Objective

An isolated stenosis of the celiac artery (CA) or the superior mesenteric artery (SMA) is frequently detected in patients with abdominal complaints. The dilemma is whether these patients suffer from chronic mesenteric ischemia (CMI) and whether they benefit from revascularization. We evaluated the long-term clinical success rates for single CA or SMA revascularization in patients with gastrointestinal symptoms and confirmed mucosal ischemia.

Methods

Retrospective cohort analysis of 59 consecutive patients with gastrointestinal symptoms and a single atherosclerotic mesenteric artery stenosis who were referred to our tertiary care institution between 2006 and 2010 for standardized diagnostic work-up of CMI, including measurement of mucosal ischemia with visible light spectroscopy or gastric-jejunal tonometry. Patients with multidisciplinary consensus diagnosis of CMI underwent surgical or endovascular revascularization. The primary outcome was clinical response to revascularization, defined as relief of presenting symptoms as experienced by the patient.

Results

Consensus diagnosis of CMI was obtained in 37/59 patients. Isolated CA stenosis was present in 30/37 patients (81%) and isolated SMA stenosis in 7 patients. After a mean follow-up of 5.0±3.0 years, 27/37 patients (73%) experienced sustained symptom relief after revascularization. Response was not related to lesion localization (CA 73% versus SMA 71%, p=0.919).

Conclusion

Revascularization of the CA or SMA provides persistent symptom relief in 73% of patients diagnosed with CMI due to single atherosclerotic mesenteric artery stenosis.

INTRODUCTION

The medical evaluation of patients with abdominal pain is frequently a process of elimination. When common causes of pain such as gastritis, gastric ulcer disease, gallstones, inflammatory bowel disease or pancreatitis are ruled out with the proposed diagnostic algorithms(1-3), a majority of patients is diagnosed with a functional gastrointestinal syndrome, including functional dyspepsia or irritable bowel syndrome (IBS). Failure to respond to empirical treatment or the presence of alarm features such as unintentional weight loss often trigger further imaging studies to identify chronic mesenteric ischemia (CMI) as a potential underlying cause.

Isolated stenosis of the celiac artery (CA) or the superior mesenteric artery (SMA) is frequently detected during the work-up of patients with abdominal symptoms. Imaging studies have demonstrated prevalence rates for isolated CA stenosis up to 15% and for isolated SMA stenosis of approximately 1% in the asymptomatic general population(4-7, and even higher rates in patients with peripheral or coronary artery disease(8). Isolated CA stenosis due to external compression by the median arcuate ligament (median arcuate ligament syndrome, MALS) occurs in about 7% of the population(5, 9, 10). However, single mesenteric artery stenosis rarely gives rise to symptoms due to the abundant collateral circulation of the splanchnic vascular bed. Symptoms of CMI, including postprandial pain, are nonspecific and no single symptom can predict who will respond to revascularization(11). Furthermore, the correlation between severity of abdominal symptoms, degree of stenosis, and number of affected mesenteric arteries is poor(12-15).

The challenge is to identify the subset of patients with abdominal complaints due to mesenteric ischemia who might benefit from revascularization of a solitary mesenteric artery stenosis. Assessment of mucosal ischemia with a functional test, either gastric-jejunal tonometry or visible light spectroscopy (VLS), enhances the diagnostic accuracy for mesenteric ischemia(12, 13, 16, 17). In the present study, we evaluated the long-term clinical success rates for single mesenteric artery revascularization of either CA or SMA in patients with chronic gastrointestinal symptoms and confirmed mucosal ischemia.

METHODS

Study design and setting

Retrospective cohort analysis was conducted for all consecutive patients with gastrointestinal symptoms and an isolated atherosclerotic stenosis of either CA or SMA who were referred to our tertiary referral center between January 2006 and October 2010 for a standardized diagnostic work-up of CMI. This center is one of the two Dutch centers that perform functional tests to detect mucosal ischemia. During the inclusion period, a consensus diagnosis of CMI was established in approximately 50% of the 450 patients who underwent evaluation for suspected CMI.

Patients with a significant stenosis of the inferior mesenteric artery were excluded from this study, as were patients with MALS. The diagnosis of MALS was established if CTA demonstrated focal narrowing of the proximal CA ≥50% with post-stenotic dilatation and indentation on the superior aspect of the CA, creating characteristic kinking in the absence of calcifications(18). In unclear cases additional catheter angiography of the CA in inspiration and expiration was performed.

Follow-up data was retrieved from the medical records in the context of routine clinical care. The medical research ethics committee of Erasmus University Medical Centre approved that the Medical Research Involving Human Subjects Act does not apply to this study and that no informed consent was required according to the local directives for retrospective studies (MEC-2012-336). The study complies with the Helsinki declaration on research ethics. To enhance transparency this article is written according to the STROBE checklist for cohort studies(19).

Participants

All referred patients underwent a standardized diagnostic work-up at baseline in our specialized CMI center, including medical history and physical examination, imaging of the mesenteric arteries with either computed tomography angiography (CTA) or magnetic resonance angiography (MRA) and/or conventional catheter angiography, and a functional test for mucosal ischemia detection with either 24-hour gastric-jejunal tonometry or VLS(11, 16, 20-22). All patients also underwent upper endoscopy with standard biopsies of the duodenum, gastric corpus, and antrum to rule out Helicobacter

pylori colonization and celiac disease. Psychiatric evaluation is not included in the routine diagnostic work-up.

All referred cases were discussed in a multidisciplinary meeting attended by vascular surgeons, interventional radiologists, and gastroenterologists, all specialized in CMI, leading to an expert based consensus diagnosis. The diagnosis of CMI was established if the following three criteria were met: 1) at least one of the following symptoms: (postprandial) abdominal pain, weight loss, or diarrhea; 2) significant stenosis (≥ 50% diameter reduction (23-26)) on CTA or MRA and/or conventional catheter angiography of either the CA or SMA while the other two mesenteric arteries were patent; and 3) mucosal ischemia as determined by 24-hour gastric-jejunal tonometry or VLS. The 24-hour gastric-jejunal tonometry was considered to be positive for ischemia when three or more (standard) meals were followed by a pathologic response or when one or two pathologic responses after (standard) meals were combined with a median PCO_2 >8.0 kPa between meals. A pathologic response was defined as PCO_2 >12.1 kPa for breakfast, >11.4 kPa for dinner, >11.3 kPa for compound solution meals in the stomach and PCO_2 >12.0 kPa for breakfast, >13.6 kPa for dinner and >10.6 kPa for compound solution meals in the jejunum(21). VLS measurements were considered to be positive for ischemia when the mucosal oxygen saturation measurements in the antrum were <63%, and/or in the duodenal bulb were <62%, and/or in the descending duodenum were <58%(16).

Patients with a consensus diagnosis of CMI were treated with either surgical or endovascular revascularization. Patients with atherosclerotic single mesenteric artery stenosis were primarily treated with an endovascular intervention: percutaneous transluminal angioplasty (PTA) combined with bare metal stent placement (Palmaz Blue, Cordis Cooperation), as part of standard care. The post-stenting medical regimen consisted of lifelong acetylsalicylic acid combined with clopidogrel for the first 12 months post-procedure. In-stent restenosis was initially treated with PTA and/or stent placement. Medical management of atherosclerotic risk factors consisted of antiplatelet drugs, statin treatment, and treatment of diabetes and hypertension if indicated; smokers were advised to quit smoking. Patients who were not eligible for endovascular intervention, including those with recurrent in-stent restenosis, were treated with mesenteric bypass surgery. Patients not meeting the criteria for the consensus diagnosis of CMI were discharged without further follow-up.

Variables

Baseline characteristics included age, gender, past medical history, presenting symptoms such as abdominal pain and weight loss (kg), body mass index (BMI) at presentation, abdominal bruit, cardiovascular risk factors, ulcer observed at upper endoscopy, and routine blood tests. Exercise induced abdominal pain was defined as abdominal pain during any form of exercise, including walking and stair climbing. Hypertension was defined as a blood pressure ≥140/90 mmHg or use of antihypertensive medication. Dyslipidemia was defined as LDL-C >4.2 mmol/L or HDL-C <0.9 mmol/L or use of lipid lowering medication. Smoking status was defined as current, former or non-smoker. Obesity was defined as a BMI ≥30 kg/m^2.

The primary outcome was the clinical response to revascularization, defined as patient-reported relief of the presenting symptoms, which was classified into two groups: symptom relief or no symptom relief. The presence or absence of symptom relief was initially evaluated at 3-month intervals following treatment with decreasing frequency over time. Stent patency was routinely evaluated with duplex ultrasound 3 to 6 months after the primary revascularization procedure. In case of recurrent symptoms after technical and clinical successful revascularization therapy, the date of recurrence was registered and patients were further evaluated with CTA. Recurrent symptoms were similar to presenting symptoms. Secondary outcomes were intervention-related morbidity and mortality.

Data sources

Patients attended the outpatient clinic in our center and/or were contacted by phone for clinical follow-up. Standard protocol visits were 1, 3, 6, 12, and 24 months after revascularization. These visits were mostly in-clinic follow-up. After two years, follow-up was annually and mostly done by phone, unless the patient's clinical condition changed. Standard protocol contains questions about recurrent symptoms (i.e. similar to presenting symptoms before revascularization therapy) and actual weight. No standard questionnaire was used. Survival status was obtained from the civil registry database. All other data was retrieved from the hospital records in the context of usual care.

Statistical methods

Baseline characteristics and secondary outcomes were described either as numbers and percentages for dichotomous variables, or as means and standard deviations or medians and interquartile ranges (IQR) for continuous variables. Differences in baseline characteristics and clinical response to treatment were determined by the χ^2 test or student's T-test. Statistical significance was defined as $p < 0.05$.

RESULTS

Patient characteristics

During the study, 59 consecutive patients with abdominal complaints and/or unexplained weight loss and a single atherosclerotic mesenteric artery stenosis were referred to our center and underwent a standardized diagnostic work-up for CMI (Figure 1). Baseline characteristics are shown in Table 1. CTA was the diagnostic vascular imaging modality in the majority of patients (55/59 patients, 93%). MRA was performed in 9/59 patients (15%) and correlated with CTA, DSA and/or duplex ultrasound in 7/9 patients. A minority of 2 patients underwent only MRA for vascular imaging.

In 37 patients (63%) a consensus diagnosis of CMI was established. Single vessel CMI was caused by CA stenosis in 30 patients (81%) and by SMA stenosis in 7 patients (19%). Patients with CMI more often presented with exercise related abdominal pain, normal blood pressure, and a lower BMI then those without CMI. Alternative diagnoses were established in 12/22 patients (55%) without a consensus diagnosis of CMI: 3 obstipation, 2 Helicobacter Pylori infection, 2 decreased cardiac function, 1 IBS, 1 abdominal pain due to adhesions, 1 Cronkhite Canada syndrome, 1 dyspepsia, and 1 obstructive sleep apnea.

Table 1. Baseline characteristics.

	All patients (n=59)	CMI (n=37)	No-CMI (n=22)
Patient characteristics			
Age (y)	66.2 ± 10.1	65.3 ± 10.9	67.9 ± 8.6
Female	59.3%	54.1%	68.2%
Caucasian	98.3%	97.3%	100%
Hypertension	44.1%	29.7%	68.2%*
Smoking	56.9%	63.9%	45.5%
Dyslipidemia	35.2%	27.8%	50.0%
Diabetes	8.5%	8.1%	9.1%
BMI at presentation (kg/m^2)	22.4 ± 5.6	20.7 ± 5.0	25.4 ± 5.4*
History of CVD	54.2%	48.6%	63.6%
Presenting symptoms			
Abdominal pain	91.5%	94.6%	86.4%
Postprandial	66.1%	70.3%	59.1%
Exercise related	35.6%	48.6%	13.6%*
Nausea	47.5%	45.9%	50.0%
Diarrhea	18.6%	18.9%	18.2%
Constipation	10.2%	8.1%	13.6%
Weight loss	67.8%	73.0%	59.1%
Abdominal bruit	20.3%	18.9%	22.7%
Classic triad of CMI	15.3%	16.2%	13.6%
Gastric ulcer	5.2%	5.6%	4.5%
Duration of symptoms (months)	32.1 ± 58.2	35.3 ± 67.8	26.6 ± 37.8
Vascular lesions			
CA stenosis	84.7%	81.1%	90.9%
SMA stenosis	15.3%	18.9%	9.1%
Functional test			
Tonometry positive	78.8%	100%	25.0%*
VLS positive	63.6%	100%	20.0%*

Data are presented as percentages or as mean ± SD.

* $p < 0.05$ CMI versus no-CMI

CVD = cardiovascular disease; Classic triad of CMI is postprandial abdominal pain, bruit and weight loss.

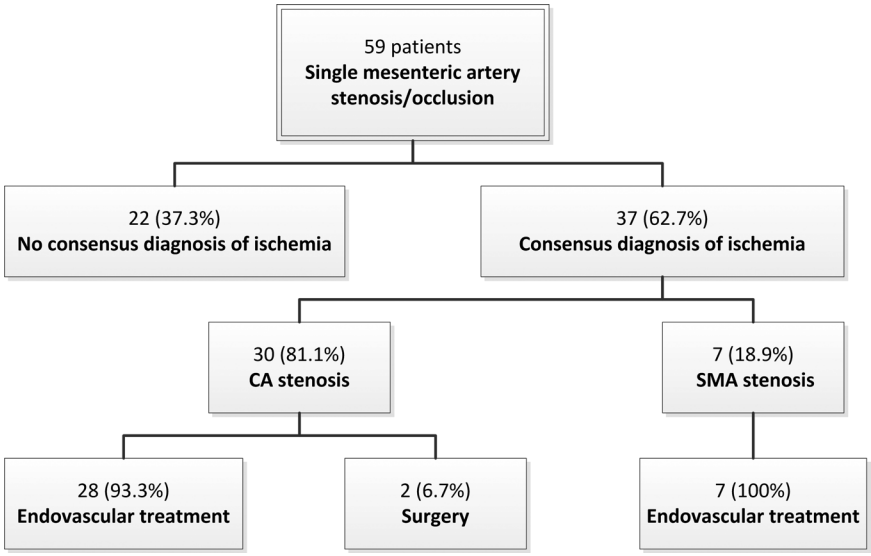

Figure 1. Flowchart consensus diagnosis.

Treatment

All 37 patients diagnosed with CMI were treated with solitary mesenteric artery revascularization. The 7 patients with SMA stenosis were all treated with endovascular stent placement. The 30 patients with CA stenosis underwent endovascular revascularization (n=26 bare metal stent placement and n=2 PTA only) or bypass surgery (n=2).

Endovascular treatment was technically successful in 33/35 patients (94%). The endovascular approach was in 25/35 primary endovascular procedures (71%) via the brachial artery and in 10/35 endovascular procedures (29%) via the femoral artery. Stenting was discontinued in one patient who developed a stroke during the procedure. Stent placement was technically unfeasible in the other patient. The two surgical procedures were technically successful.

Overall, 16% of patients developed symptomatic restenosis during follow-up. Following primary endovascular treatment, 5/35 patients (14%) underwent a secondary procedure for symptomatic restenosis: endovascular revascularization in 3 patients (9%) and surgical revascularization in 2 patients (6%). Following primary surgical treatment,

1/2 patients (50%) underwent a secondary endovascular procedure for restenosis. All secondary procedures resulted in recurrent relief of symptoms.

Clinical response to revascularization

Symptom relief categorized by vascular lesion is shown in Table 2. After a mean follow-up of 5.0±3.0 years of the initial intervention (median 5.9, IQR 1.6-7.6 years, 10.8% lost to follow-up in 2016), 27/37 patients (73%) experienced sustained symptom relief.

Table 2. Clinical response to treatment.

	Symptom relief	No symptom relief
All patients	27/37 (73%)	10/37 (27%)
CA stenosis	22/30 (73%)	8/30 (27%)
SMA stenosis	5/7 (71%)	2/7 (29%)

Response to revascularization was not related to lesion localization (symptom relief in 73% of CA stenosis versus 71% of SMA stenosis, p=0.919). No baseline characteristics differed significantly between responders and non-responders. Particularly, there was no significant difference in symptom duration, use of pain medication or narcotics, and previous abdominal trauma or abdominal surgery between responders and non-responders to revascularization.

Of the 10 patients who did not experience long-term benefit after technically successful revascularization, five patients l50%) did not experience any symptom relief after treatment, whereas five patients (50%) had initial symptom relief after treatment but had recurrent symptoms during follow-up despite three patent mesenteric arteries. Persistent or recurrent symptoms were similar to presenting symptoms in these patients. Alternative diagnoses were established in 5/10 non-responders (50%: 1 chronic pancreatitis, 3 IBS and 1 abdominal pain due to adhesions).

Complications

The overall complication rate for all 43 revascularization procedures was 26%. In 8/35 primary endovascular procedures an access site complication occurred with a major access site complication rate of 11% (2 pseudoaneurysms and 2 thromboses, all

requiring intervention) and a minor access site complication rate of 11% (3 hematomas and 1 arteriovenous fistula not requiring intervention). In 1/35 primary endovascular procedures a patient developed a stroke. In 1/2 primary surgical procedures a patient developed pneumonia. No complications occurred after secondary surgical therapy, whereas 1/4 secondary endovascular therapy procedures was complicated by pseudoaneurysm. Overall, 13/37 patients died during follow-up (35.1%, mean age 73.2±7.5years). Causes of death were heart failure (n=1), sepsis due to urinary tract infection and pneumonia (n=1), metastasized lung cancer (n=3), euthanasia (n=1), end-stage COPD (n=2). The cause of death was irretrievable in 5 patients.

DISCUSSION

The present study shows that 73% of patients with longstanding abdominal complaints and single, atherosclerotic CA or SMA stenosis experience sustained long-term symptom relief after revascularization.

To our knowledge, the current study is the first report on the long-term clinical outcome with a median follow-up of 5.9 years for revascularization of either CA or SMA in patients with abdominal symptoms attributed to CMI. Apart from a previous report from our research group of a 64% short-term (median follow-up 13 months) clinical success rate for revascularization in patients with single artery CMI(22), the outcomes of treatment for single vessel CMI are not specified in the majority of prior studies(13, 17, 27-29). The long-term clinical benefit was not related to lesion localization, i.e. CA or SMA, in spite of the differences in blood flow distribution between these two arteries. The prevalence of single SMA stenosis was substantially lower than CA stenosis in our cohort, which is in line with population-wide studies(4, 6).

The diagnosis of single vessel CMI and the selection of patients for revascularization are challenging. The existence of single artery mesenteric ischemia is a topic of continuous clinical debate. Sceptics argue that stenosis of one of the mesenteric arteries is a common finding in the general -asymptomatic- population and is often incidentally discovered on imaging studies. Furthermore, given the extensive collateral network, they dispute that stenosis of one mesenteric artery leads to CMI and, hence, gives rise to abdominal symptoms. Revascularization of a single mesenteric artery stenosis without confirming mucosal ischemia first would lead to overtreatment. We found no differentiating characteristics in demographics, comorbidities, presenting symptoms,

physical findings, or vascular lesions between patients with and those without a consensus diagnosis of CMI, except for a higher frequency of exercise-related abdominal pain, normal blood pressure, and a lower BMI in patients with CMI. Furthermore, neither baseline characteristics nor the localization of the mesenteric artery lesions were associated with a clinical response to treatment. In this cohort study, patients were selected for revascularization therapy if mucosal ischemia was confirmed with a functional test in addition to the presence of a significant stenosis of the CA or SMA and a history of symptoms suggestive of CMI. Objective confirmation of mucosal ischemia in the diagnostic work-up for patients suspected of CMI is important(11, 17, 20, 30). Tests for mucosal ischemia include gastric exercise tonometry(17), 24-hour tonometry(21) and VLS(16) with sensitivities of 78%, 76%, and 90% and specificities of 92%, 94%, and 60%, respectively. Our findings stress the importance of 1) extensive diagnostic gastro-intestinal work-up to rule out common causes of chronic abdominal pain, and 2) assessment of mucosal ischemia using a functional test to select patients for revascularization. The topic of chronic mesenteric ischemia is an evolving field in vascular surgery and gastroenterology. The European Society of Vascular Surgery (ESVS) recently published guidelines about 'Management of the Diseases of Mesenteric Arteries and Veins'(31).

The overall technical success rates in the current study were 94% for endovascular and 100% for surgical procedures with an overall complication rate of 26%. Overall, 16% of patients developed symptomatic restenosis during follow-up, which is in line with previous reports(32-34). All patients with symptomatic restenosis were revascularized, resulting in recurrent relief of symptoms in all. In the absence of randomized controlled trials and given the limited number of patients in the available cohort studies, there are no evidence-based recommendations for a preferred revascularization strategy for mesenteric ischemia. Endovascular revascularization in this cohort consisted of stent implantation in the majority of patients. Only bare metal stents were used, in line with the common practice at the time of inclusion. Current evidence suggests a lower restenosis rate for covered stents for treatment of mesenteric artery stenosis(32). Yet, these findings still await randomized controlled confirmation. The minimally invasive character and the effectiveness of novel technologies to prevent restenosis, including covered stents, drug-eluting stents, and drug-coated balloons, are promising for a primary endovascular approach to the splanchnic vascular bed in the majority of patients.

This study carries the limitations inherent to its retrospective cohort design. Moreover, the results obtained in our tertiary referral center may not be representative for the general gastroenterology practice. Although we attempted to define whether any clinical characteristics factors are predictive of treatment response, the limited sample size is susceptible to false negative findings. Furthermore, the optimal follow-up would include functional testing before and after revascularization and again in case of recurrent symptoms. Although a post-interventional mucosal ischemia test could have supported our data, functional testing was not performed after revascularization and for recurrent symptoms for reasons of costs and patient burden. Since the presence or absence of symptom relief following revascularization was considered the most important and relevant patient reported outcome, "sustained symptom relief'' was used as the primary outcome measure. Although it might be argued that a patient reported outcome in this non-randomized, non-blinded study may be subject to a placebo effect, the sustained clinical benefit rate of revascularization of 73% is significantly higher than the reported effects of either surgical sham interventions (18-32%)(35, 36) or placebo medical treatments (30-38%)(37-39) for functional gastrointestinal disorders in randomized controlled trials. Although every attempt was made to contact the patients for follow-up, 10.8% of the patients were lost to follow-up in 2016; recurrence of symptoms in these patients may have been missed.

In conclusion, it is generally accepted that an asymptomatic or incidentally discovered stenotic or occluded mesenteric artery does not warrant intervention. However, in case of gastrointestinal symptoms and mucosal ischemia, revascularization of a solitary atherosclerotic mesenteric artery stenosis provides persistent symptom relief in 73% of patients with otherwise unexplained, refractory abdominal pain.

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CHAPTER
10.1

Single-center retrospective comparative analysis of trans-radial, trans-brachial and trans-femoral approach for mesenteric arterial procedures

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ABSTRACT

Purpose

To assess the feasibility and safety of trans-radial access (TRA) compared to trans-femoral access (TFA) and trans-brachial access (TBA) for mesenteric arterial endovascular procedures.

Material and Methods

A retrospective cohort analysis was performed including all consecutive patients who underwent a mesenteric arterial procedure in a tertiary referral center between May 2012 and February 2018. Exclusion criteria were absence of data and lost to follow-up within 24 hours after the procedure. During the study period, 103 patients underwent a total of 148 mesenteric arterial procedures (TBA n=52, TFA n=39 and TRA n=57). The mean patient age was 64.3±13.3 years and 91 patients (62%) were female. The primary outcomes were vascular access specified technical success rate and access site complication rate, as reported in the hospital records.

Results

The technical success rate specified for the vascular access technique differed not between the three approaches (TBA 96%, TFA 87%, TRA 91%, TRA-TBA p=0.295, TBA-TFA p=0.112, TRA-TFA p=0.524) and the overall access site complication rate was not different between the three approaches (TBA 42%, TFA 23%, TRA 35%, TRA-TBA p=0.439, TBA-TFA p=0.055, TRA-TFA p=0.208). However, more major access site complications were reported for TBA than for TRA or TFA (TBA 17%, TFA 3%, TRA 2%, TRA-TBA p=0.005, TBA-TFA p=0.026, TRA-TFA p=0.785).

Conclusion

TRA is a safe and feasible approach for mesenteric arterial procedures comparable to TFA, but with a significant lower major access site complication rate than TBA.

INTRODUCTION

Trans-brachial access (TBA) and trans-femoral access (TFA) are distinct approaches for endovascular mesenteric arterial procedures according the recently published 'Quality Improvement Guidelines for Mesenteric Angioplasty and Stent Placement for the Treatment of Chronic Mesenteric Ischemia' of the Society of Interventional Radiology (SIR)(1). For coronary artery interventions, trans-radial access (TRA) has been shown to be associated with less major access-site complications than TBA and TFA with similar procedural and clinical outcomes(2). No recommendations are issued in the SIR guideline on the use of TRA for mesenteric arterial procedures since the efficacy and feasibility of this approach has not been established yet for this specific indication(1).

Potential advantages of TRA are the patient friendly compression device for TRA enabling fast mobilization after the procedure leading to shorter hospital stay, reduced costs, and fewer bleeding and vascular complications in coronary interventions(2-6). In addition, when performing mesenteric endovascular procedures, the vessels generally arise at a steep acute angle from the aorta making retrograde TFA potentially technically more difficult compared to an antegrade approach. Posham et al.(7) described 1,512 non-coronary endovascular procedures, including mesenteric arterial procedures, using TRA, showing that TRA is feasible for non-coronary procedures, with a technical success rate of 98%, and a low major complication rate of only 0.1% and a minor complication rate of 2.4%. Thakor et al.(8) described 749 non-coronary TRA procedures and reported that 98% of the patients who had a previous TFA procedure would choose TRA over TFA. However, there is a deficiency of studies comparing TRA, TFA and TBA for non-coronary endovascular procedures and, more specifically, there is a lack of studies comparing these three approaches for mesenteric arterial procedures.

The aim of this study was to assess the feasibility and safety of TRA compared to TFA and TBA for mesenteric arterial endovascular procedures.

MATERIAL AND METHODS

Study design and setting

A retrospective cohort analysis was conducted for all consecutive patients who underwent an-endovascular procedure of the mesenteric vessels in a tertiary referral center between May 2012 and February 2018. Inclusion criteria were: endovascular procedure of the celiac artery (CA), superior mesenteric artery (SMA) and/or inferior mesenteric artery (IMA)) and all types of endovascular procedures were eligible: diagnostic angiography, percutaneous transluminal angioplasty (PTA), stenting procedures, and thrombolysis. Exclusion criteria were absence of data and lost to follow-up within 24 hours after the procedure. The local medical research ethics committee concluded that the Medical Research Involving Human Subjects Act does not apply to this study (MEC-2017-461). The study complies with the Helsinki declaration on research ethics. To enhance transparency, this article is written according to the STROBE checklist for cohort studies(9).

In total, 148 mesenteric arterial procedures (TBA n=52, TFA n=39 and TRA n=57) performed in 103 patients were reviewed (Figure 1). Twenty-eight patients underwent two or more procedures of the mesenteric vessels due to development of re-stenosis or new mesenteric stenosis during follow-up. Four patients needed a repeated procedure on the same vessel(s) on a later date due to technical failure of a previous procedure. One patient underwent 6 mesenteric procedures during the inclusion period, and two other patients each 5 procedures. Eight interventionalists of in total 10 interventionalists who performed the included procedures, performed TRA procedures. All interventionalists had minimally two years of experience and performed his/her first TRA procedure within this study, none of the interventionalists were experienced in TRA procedures before start of this study. See Table 1 for the specifications of each interventionalist.

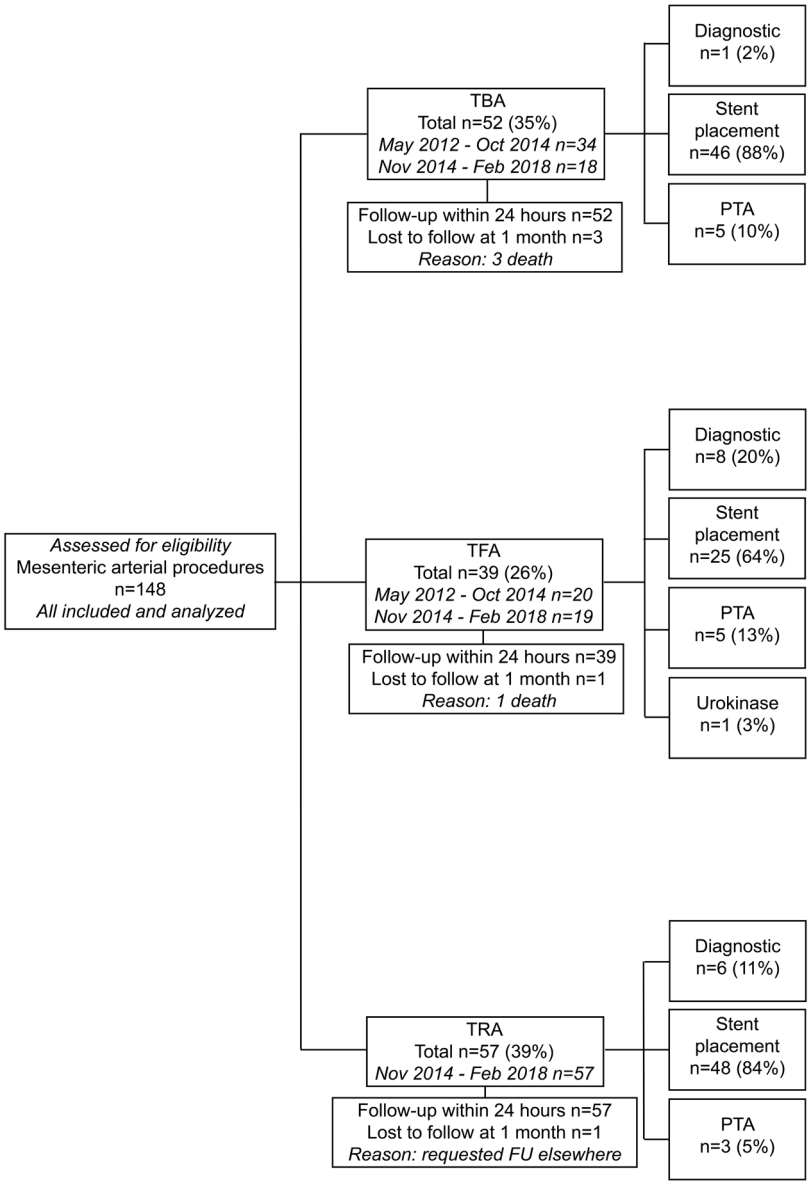

Figure 1. Flowchart.
PTA = percutaneous angioplasty; TBA = trans-brachial access; TFA = trans-femoral access; TRA = trans-radial access.

Table 1. Characteristics of first interventionalists.

Interventionalist	Years of IR experience	TBA	TFA	TRA	Period of procedures performed	Period of TRA procedures performed
1	5	15	14	22	May 2012 – Dec 2017	Nov 2014 – Aug 2017
2	1	14	8	14	Oct 2012 – Dec 2017	Jan 2015 – Mar 2017
3	3	10	5	6	Aug 2012 – Feb 2016	Jan 2015 – Feb 2016
4	3	8	6	4	Jul 2012 – Aug 2016	Mar 2015 – Aug 2016
5	3	3	1	5	Dec 2012 – Dec 2017	Jul 2016 – Dec 2017
6	1	2	1	3	Mar 2016 – Feb 2018	Oct 2016 – Sept 2017
7	2	0	2	2	Jun 2015 – Mar 2017	Dec 2016 – Mar 2017
8	2	0	0	1	Jul 2017 – Jul 2017	Jul 2017 – Jul 2017
9	4	0	1	0	Feb 2018 – Feb 2018	NA
10	>10	0	1	0	Jun 2012 – Jun 2012	NA
Total		**52**	**39**	**57**	**2.7 [0.0 – 6.6] years**	**1.2 [0.0-2.7] years**

Time periods are presented as median [minimum-maximum].
IR = interventional radiology; NA = not applicable; TBA = trans-brachial access; TFA = trans-femoral access; TRA = trans-radial access.

Data sources

Cases were included by searching the radiology reports on the terms “radial”, “brachial” and “femoral” and all found reports were manually checked for eligibility. In addition, all mesenteric multidisciplinary meeting reports were screened for patients that were planned to undergo a diagnostic or therapeutic endovascular procedure. Data were retrieved from the hospital records in the context of standard clinical care. Since November 2014 TRA procedures were performed in the study center and the TBA and TFA procedures were included backwards until a comparable number of TFA and TBA procedures were included. Follow-up of patients was by outpatient clinic contact and by phone. A standard protocol visit was scheduled within 24 hours after the mesenteric arterial procedure at the ward and one month after the procedure at the outpatient clinic during which symptoms and complications were assessed.

Participants

Since November 2014 endovascular procedures of the mesenteric vasculature in the study center are performed by means of TRA, when either a normal modified Allen test or Barbeau test result of A, B or C and sufficient radial artery diameter is present: RA diameter > 2.0 mm for 4-F sheath, > 2.2 mm for 5-F sheath, and > 2.4 mm for 6-F sheath(10). If TRA is not possible, the procedure is performed per TBA or TFA according to the vessel anatomy of the patient: TBA is first approach but TFA is used when the angle of the culprit mesenteric artery with the aorta is obtuse (towards 90 degrees, decided by the interventionalist). Before November 2014, mesenteric arterial procedures were performed per TBA or TFA according to the vessel anatomy of the patient (mesenteric anatomy-driven).

All access techniques used local anesthesia with 2% lidocaine and all punctures were ultrasound guided. TRA procedure was performed as follows: the RA was punctured and a dedicated RA sheath (Prelude; Merit Medical Systems, Inc, South Jordan, Utah) was introduced. A solution containing 200 µg nitroglycerin, 2.5 mg verapamil, and 5,000 IU heparin was slowly injected intra-arterially. Thereafter a 110-cm Flexor sheath (Cook, Inc, Bloomington, Indiana) with dilator or a 6.5-F 100-cm Eaucath sheathless guide with dilator (Asahi Intecc, Aichi, Japan) was exchanged using a Glidewire Advantage (Terumo Corp, Tokyo, Japan). Access to the mesenteric vessel was acquired with a 125 cm 4-F angiographic catheter. Rapid-exchange delivery systems were at 4-F or 5-F for balloons

and bare metal stents and 6-F for covered stent. After the procedure the radial puncture site was compressed with a compression device (Air-Band; Merit Medical Systems, Inc).

TBA procedure was performed as follows: the brachial artery was punctured with a 7 cm 18 G needle and a 11 cm vascular sheath of 6-F (Brite Tip, Cardinal Health, Dublin, Ireland) was inserted. A 90-cm 6-F multipurpose guiding catheter (Cardinal Health) loaded with a 125 cm 4-F angiographic catheter was advanced to the mesenteric vessel. For covered stent placement, the short sheath and guiding catheter were exchanged for a long sheath or sheathless guiding catheter. The brachial puncture site was compressed manually followed by compression bandage after the procedure for 6 hours.

TFA procedure was performed as follows: the common femoral artery was punctured with a 7 cm 18 G needle and a 11 cm vascular sheath of 6-F (Brite Tip, Cardinal Health, Dublin, Ireland) was inserted. A 55-cm 6-F renal double curve guiding (RDC-guiding, Cardinal Health) loaded with an 80 cm 4-F angiographic catheter was advanced to the mesenteric vessel. For covered stenting, the short sheath and guiding were exchanged for a 55-cm 6-F sheath (Flexor, Cook Medical). The femoral puncture site was closed with a closure device (Angio-Seal; Terumo Corp).

Type of balloons used were rapid exchange systems 20 mm balloon of 4 to 7 mm diameter (Submarine Rapido, Invatec, Roncadelle Italy). Type of stents used were bare-metal balloon-expandable stents (Palmaz-Blue, Cardinal Health) and covered stents (Advanta V12; Atrium Medical Corp, Hudson, New Hampshire).

After the mesenteric endovascular procedure was completed, patients were transferred to a clinical ward for observation. During follow-up, routinely ultrasound investigation of the access site was not performed, only on indication (e.g. symptoms of occlusion). Magnetic resonance imaging of the brain was not routinely performed after TBA or TRA, only on indication (e.g. symptoms of cerebral stroke).

Life-long acetylsalicylic acid and clopidogrel for 12 months were prescribed after stent-placement. If only PTA was performed acetylsalicylic acid life-long was prescribed if atherosclerosis was present.

Variables

Patient and procedure characteristics included age, gender, use of anti-coagulation, type of endovascular intervention, specific mesenteric artery (CA, SMA and/or IMA), sheath size, puncture side, anti-coagulation during the procedure, platelet count and international normalized ratio (INR) before procedure, and the hemostasis method used.

Characteristics of the mesenteric arterial endovascular procedures are shown in Table 2. The majority of procedures was performed in female patients (TBA 64%, TFA 51%, TRA 67%). TFA patients were younger than TRA patients (59.9±18.1 years versus 66.6±9.2 years, p=0.037). The majority of procedures were primary procedures (TBA 73%, TFA 59% and TRA 72%). Used sheath sizes varied from 4-F to 7-F. A sheath size of 6-F was more used in TRA and TBA than in TFA procedures (TBA 86%, TFA 49%, TRA 77%, TRA-TFA p=0.005, TBA-TFA p<0.001), whereas a sheath size of 7-F was more used in TFA procedures than in TBA and TRA procedures (TBA 4%, TFA 34%, TRA 6%, TRA-TFA p<0.001, TBA-TFA p<0.001). A puncture side on the left side of the patient was preferably used for TBA and TRA, but the right side was more used for TFA (left side TBA 83%, TFA 21%, TRA 69%, TRA-TFA p<0.001, TBA-TFA p<0.001). In the majority of procedures stent placement was performed, however less stent placements were performed in TFA procedures compared to TBA and TRA procedures (TBA 88%, TFA 64%, TRA 84%, TRA-TFA p=0.023 and TRA-TFA p=0.005). Diagnostic angiography was less frequently performed in TBA procedures than in TFA procedures (TBA 2%, TFA 20%, TBA-TFA p=0.003). The INR was lower in TRA procedure than in TBA and TFA procedures (TBA 1.2±0.3, TFA 1.2±0.2, TRA 1.1±0.14, TBA-TRA p=0.002 and TFA-TRA p=0.003), whereas platelet count was not different between the three approaches. In 38% of all 133 interventional procedures the vessel of intervention was the SMA, in 38% the CA, in 1% the IMA and in 23% both CA as SMA. Hemostasis was achieved with manual compression and pressure bandage in 92% of all TBA procedures, with Angioseal (Terumo Medical Corporation, Tokyo, Japan) in 89% of all TFA procedures and with an Airband (Merit Medical Sytems Inc., South Jordan, UT, USA) in all TRA procedures. Table 3 shows the use of anti-coagulation at baseline and the continuation of anti-coagulation during the procedure. At baseline, only 16% of all patients (TBA 17%, TFA 15%, TRA 16%) were not on anti-coagulation therapy. In 30% of all 148 procedures (TBA 38%, TFA 26%, TRA 25%) no anti-coagulation was used during the procedure besides heparin.

Table 2. Characteristics of the mesenteric arterial procedures.

	TBA (n=52)	TFA (n=39)	TRA (n=57)	p-value TRA-TBA	p-value TRA-TFA	p-value TBA-TFA
Female	33 (64%)	20 (51%)	38 (67%)	0.726	0.130	0.244
Age (y)	65.0±12.4	59.9±18.1	66.6±9.2	0.451	0.037*	0.109
Primary procedure	38 (73%)	23 (59%)	41 (72%)	0.893	0.186	0.157
Vessel of intervention (PTA/stenting/thrombolysis)						
CA	19 (37%)	12 (31%)	19 (33%)	0.726	0.792	0.566
SMA	16 (31%)	13 (33%)	21 (37%)	0.504	0.724	0.795
IMA	2 (4%)	0 (0%)	0 (0%)	0.135	NA	0.216
CA+SMA	14 (27%)	6 (15%)	11 (19%)	0.344	0.622	0.188
Diagnostic procedure	1 (2%)	8 (21%)	6 (11%)	0.067	0.173	0.003*
Type of procedure						
Stent placement	46 (88%)	25 (64%)	48 (84%)	0.520	0.023*	0.005*
PTA	5 (10%)	5 (13%)	3 (5%)	0.384	0.188	0.629
Thrombolysis	0 (0%)	1 (3%)	0 (0%)	NA	0.224	0.246
Diagnostic procedure	1 (2%)	8 (20%)	6 (11%)	0.067	0.173	0.003*
Sheath size						
4-F	1 (2%)	1 (3%)	2 (4%)	0.617	0.817	0.820
5-F	4 (8%)	5 (14%)	7 (13%)	0.432	0.885	0.389
6-F	41 (86%)	17 (49%)	41 (77%)	0.301	0.005*	<0.001*
7-F	2 (4%)	12 (34%)	3 (6%)	0.730	<0.001*	<0.001*
Puncture side = left	43 (83%)	8 (21%)	37 (69%)	0.066	<0.001*	<0.001*

Table 2. Continued

	TBA (n=52)	TFA (n=39)	TRA (n=57)	p-value TRA-TBA	p-value TRA-TFA	p-value TBA-TFA
Laboratory values						
Platelets (10^9/L)	274±107	287±125	296±102	0.343	0.737	0.130
INR	1.2±0.3	1.2±0.2	1.1±0.14	0.002*	0.003*	0.712
Hemostasis						
Airband	0 (0%)	0 (0%)	57 (100%)	<0.001*	<0.001*	NA
Manual compression and pressure bandage	48 (92%)	4 (11%)	0 (0%)	<0.001*	0.011*	<0.001*
Angioseal	3 (6%)	33 (89%)	0 (0%)	0.066	<0.001*	<0.001*
Surgical	1 (2%)	0 (0%)	0 (0%)	0.293	NA	0.396

Data are presented as N (percentages) or as mean ± SD.
* p-value <0.05 tested with χ^2-test or student's T-test.
INR = international normalized ratio; PTA = percutaneous angioplasty; TBA = trans-brachial access; TFA = trans-femoral access; TRA = trans-radial access.

Table 3. Anti-coagulation at baseline and during the mesenteric arterial procedures.

	TBA (n=52)	**TFA** (n=39)	**TRA** (n=57)
Anti-coagulation at baseline			
Aspirin	17 (33%)	7 (18%)	21 (37%)
Aspirin + clopidogrel	9 (17%)	9 (23%)	12 (21%)
Clopidogrel	2 (4%)	6 (15%)	5 (9%)
Aspirin + heparin	4 (8%)	2 (5%)	3 (5%)
Vit K antagonist	5 (9%)	1 (3%)	2 (3%)
Aspirin + dipyradimole	3 (6%)	1 (3%)	0 (0%)
Vit K antagonist + aspirin	1 (2%)	3 (8%)	0 (0%)
Vit K antagonist + clopidogrel	0 (0%)	3 (8%)	1 (2%)
Aspirin + ticagrelor	0 (0%)	1 (3%)	1 (2%)
Heparin	0 (0%)	0 (0%)	2 (3%)
DOAC	1 (2%)	0 (0%)	1 (2%)
Dipyradimole	1 (2%)	0 (0%)	0 (0%)
None	9 (17%)	6 (15%)	9 (16%)
Anti-coagulation continuation during procedure			
Aspirin	25 (48%)	19 (49%)	28 (49%)
Aspirin + clopidogrel	2 (4%)	2 (5%)	6 (10%)
Clopidogrel	2 (4%)	3 (8%)	6 (10%)
Vit K antagonist	2 (4%)	0 (0%)	0 (0%)
Aspirin + dipyradimole	1 (2%)	1 (2%)	0 (0%)
Vit K antagonist + aspirin	0 (0%)	1 (2%)	0 (0%)
Aspirin + ticagrelor	0 (0%)	0 (0%)	1 (2%)
Heparin	0 (0%)	2 (5%)	2 (4%)
Heparin + clopidogrel	0 (0%)	1 (3%)	0 (0%)
None	20 (38%)	10 (26%)	14 (25%)

DOAC = direct oral antiocoagulants; TBA = trans-brachial access; TFA = trans-femoral access; TRA = trans-radial access.

The primary outcomes were technical success rate vascular access specified (technical success related to the vascular access) and access site complication rates. Secondary outcomes were overall technical success rates, non-access site complication rates, conversion rate and mortality. Technical success is defined as achievement of the aimed goal of the procedure. Technical success of mesenteric revascularization was specified

according the Quality Improvement Guidelines for Mesenteric Angioplasty and Stent Placement for the Treatment of CMI(1). The complication rates were specified according the SIR Quality Improvement Guidelines for Diagnostic Arteriography (11).

Statistical methods

Baseline procedure characteristics were described either as numbers and percentages for dichotomous variables, or as means and standard deviations or medians and interquartile ranges (IQR) for continuous variables. Differences in baseline procedure characteristics, technical success rates and complication rates between the different approaches were determined by the χ^2-test or student's T-test. Assumption of normality was based on the sample size (>30)(12, 13). Univariable logistic regression analysis was performed to assess predictors for access site complications. Statistical significance was defined as $p < 0.05$. Since the inclusion period of the TRA procedures in this study started simultaneously with the moment of introduction of TRA in the study center, a comparison of the success rate and complication rate of the first 25% of the TRA procedures versus the latter 75% of the TRA procedures was performed.

RESULTS

Feasibility

Table 4 shows the technical success and conversion rates specified per approach. The technical success rate specified for the vascular access technique differed not between the three access techniques (TBA 96%, TFA 87%, TRA 91%, TRA-TBA p=0.295, TBA-TFA p=0.112, TRA-TFA p=0.524). The overall procedural technical success rate differed also not between the three access methods (TBA 75%, TFA 80%, TRA 83%, TRA-TBA p=0.341, TBA-TFA p=0.615, TRA-TFA p=0.714). Both the technical success rate vascular access specified (93% for the first 25% of TRA procedures versus 90% of following 75% of TRA procedures, p=0.737) and the complication rate (27% for the first 25% of TRA procedures versus 43% of following 75% of TRA procedures, p=0.269) were not different. The conversion rate differed also not between the access methods (TBA 2%, TFA 8%, TRA 4%, TRA-TBA p=0.613, TBA-TFA p=0.184, TRA-TFA p=0.365). One TBA procedure was converted to TFA, however both approaches did not result in successful catheterization of the CA. In total 3 TFA procedures were converted: 1 procedure to TBA, which resulted in a successful procedure. Two TFA procedures were converted to the contralateral common femoral artery, which was unsuccessful in both cases, however

the procedure per TBA the following day was successful for both. Two TRA procedures were converted to TBA successfully, one patient suffered from radial spasm and in a second patient, puncture of the radial artery failed despite sufficient radial diameter. Of the 52 TRA procedures, 8 patients underwent a second TRA procedure with ipsilateral radial puncture (mean interval time between radial ipsilateral punctures: 12.0±9.0 months). Of the 52 TBA procedures, 5 patients underwent a second TBA procedure with ipsilateral puncture and 1 patient underwent three procedures with ipsilateral brachial puncture (mean interval time between brachial ipsilateral punctures: 14.7±22.5 months). Of the 39 TFA procedures, 3 patients underwent a second TFA procedure with ipsilateral puncture and 1 patient underwent 4 procedures with ipsilateral femoral puncture (mean interval time between femoral ipsilateral punctures: 11.9±3.9 months).

Complications

Table 5 shows the complication rates specified per approach. The overall access site complication rate was not different between the three approaches (TBA 42%, TFA 23%, TRA 35%, TRA-TBA p=0.439, TBA-TFA p=0.055, TRA-TFA p=0.208), however more major access site complications were reported for TBA than for TRA or TFA (TBA 17%, TFA 3%, TRA 2%, TRA-TBA p=0.005, TBA-TFA p=0.026, TRA-TFA p=0.785). The minor access site complications were not different between the three approaches (TBA 25%, TFA 20%, TRA 33%, TRA-TBA p=0.351, TBA-TFA p=0.615, TRA-TFA p=0.170). The non-access site complication rate for TFA was higher than for TRA (TBA 8%, TFA 15%, TRA 4%, TRA-TBA p=0.339 TBA-TFA p=0.246, TRA-TFA p=0.039). Neurological complications did not occur in the three groups, despite right sided performance of 31% of all TRA procedures and 17% of all TBA procedures. Predictors for access site complications were assessed with univariable logistic regression analysis. Baseline characteristics significantly different between the three approaches were assessed (age, INR, type of procedure, sheath size, puncture side) combined with age, platelets and use of anticoagulation during the procedure. None of the assessed characteristics was a significant predictor for access site complications (Table 6).

Table 4. Technical success and conversion rates of the mesenteric arterial procedures.

	TBA (n=52)	TFA (n=39)	TRA (n=57)	p-value TRA-TBA	p-value TRA-TFA	p-value TBA-TFA
Technical success rate vascular access specified	50 (96%)	34 (87%)	52 (91%)	0.295	0.524	0.112
Overall technical success rate	39 (75%)	31 (80%)	47 (83%)	0.341	0.714	0.615
Conversion rate	1 (2%)	3 (8%)	2 (4%)	0.613	0.365	0.184

Data are presented as N (percentages).
* p-value < 0.05 and tested with χ^2-test.
TBA = trans-brachial access; TFA = trans-femoral access; TRA = trans-radial access.

Table 5. Characteristics of the complications of the mesenteric arterial procedures.

	TBA (n=52)	TFA (n=39)	TRA (n=57)	p-value TRA-TBA	p-value TRA-TFA	p-value TBA-TFA
Access site complications	**22 (42%)**	**9 (23%)**	**20 (35%)**	**0.439**	**0.208**	**0.055**
Minor	*13 (25%)*	*8 (20%)*	*19 (33%)*	*0.351*	*0.170*	*0.615*
Local hematoma	11 (85%)	4 (50%)	12 (63%)			
Minor bleeding	0 (0%)	2 (25%)	2 (11%)			
Pseudo-aneurysm	0 (0%)	1 (13%)	1 (5%)			
Pain access site	0 (0%)	0 (0%)	2 (11%)			
Transient swellingand tingling	2 (15%)	0 (0%)	0 (0%)			
Cellulitis	0 (0%)	0 (0%)	1 (5%)			
Transient sensibility loss	0 (0%)	0 (0%)	1 (5%)			
Occlusion access site	0 (0%)	1 (13%)	0 (0%)			
Major	*9 (17%)*	*1 (3%)*	*1 (2%)*	*0.005**	*0.785*	*0.026**
Pseudo-aneurysm	3 (33%)	0 (0%)	0 (0%)			
Local hematoma	2 (22%)	0 (0%)	0 (0%)			
Occlusion access site	0 (0%)	1 (100%)	1 (100%)			
Major bleeding	1 (11%)	0 (0%)	0 (0%)			
Access site thrombosis	1 (11%)	0 (0%)	0 (0%)			
Dissection	1 (11%)	0 (0%)	0 (0%)			
PTA balloon disconnection#	1 (11%)	0 (0%)	0 (0%)			
Non-access site complications	**4 (8%)**	**6 (15%)**	**2 (4%)**	**0.339**	**0.039***	**0.246**

Table 5. Continued

	TBA (n=52)	TFA (n=39)	TRA (n=57)	p-value TRA-TBA	p-value TRA-TFA	p-value TBA-TFA
Minor	*0 (0%)*	*1 (3%)*	*0 (0%)*	*NA*	*0.224*	*0.246*
Angina pectoris	0 (0%)	1 (100%)	0 (0%)			
Major	*4 (8%)*	*5 (13%)*	*2 (4%)*	*0.339*	*0.085*	*0.417*
Sepsis	3 (75%)	1 (20%)	0 (0%)			
Major bleeding	0 (0%)	1 (20%)	1 (50%)			
Mesenteric artery dissection	1 (25%)	0 (0%)	0 (0%)			
Myocardial infarction	0 (0%)	0 (0%)	1 (50%)			
Reperfusion pain	0 (0%)	1 (20%)	0 (0%)			
Angina pectoris	0 (0%)	1 (20%)	0 (0%)			
Diarrhea	0 (0%)	1 (20%)	0 (0%)			
Neurological event	0 (0%)	0 (0%)	0 (0%)			
All complications	**26 (50%)**	**15 (39%)**	**22 (39%)**	**0.231**	**0.989**	**0.274**
Minor complications	13 (25%)	9 (23%)	19 (33%)	0.340	0.278	0.832
Major complications	13 (25%)	6 (15%)	3 (5%)	0.004*	0.095	0.264

Data are presented as N (percentages).
* p-value <0.05 tested with χ^2-test.
# disconnected from the shaft - could not be retrieved through the sheath, requiring surgery.
TBA = trans-brachial access; TFA = trans-femoral access; TRA = trans-radial access.

Table 6. Univariable logistic regression analysis for access site complications.

Characteristics	OR (95% CI)	p-value
Female	0.624 (0.305-1.277)	0.197
Age	0.979 (0.952-1.007)	0.148
Platelets	0.999 (0.995-1.002)	0.435
INR	0.981 (0.204-4.711)	0.981
Sheath size	1.054 (0.585-1.899)	0.861
Type of procedure	0.922 (0.725-1.714)	0.922
Anticoagulation during procedure	1.018 (0.908-1.142)	0.758
Puncture side = left	1.893 (0.916-3.914)	0.085

CI = confidence interval; INR = international normalized ratio; OR = odds ratio.

Follow-up and survival

During follow up (mean follow-up time of all 148 procedures: 23.0±18.0 months), 17 of all 103 patients (17%) died. Causes of death were mesenteric ischemia (n=6), cancer (n=4), sepsis (n=3), unknown (n=2), ruptured aortic aneurysm (n=1) and death related to surgical aortic repair (n=1). None of these deaths were directly related to the procedure. Four patients died within 1 month after the procedure (TBA n=3, TFA n=1, all 4 stenting procedures), all of them because of mesenteric ischemia. Three out of four patients who died of mesenteric ischemia underwent a technically successful stent procedure as confirmed by angiography at the end of the interventional procedure. However the mesenteric ischemia was too extensive to prevent death after revascularization. The SMA of the fourth patient was successfully treated, but a synchronous total occlusion of the CA could not be crossed and this patient died from ongoing mesenteric ischemia. Two other patients died of mesenteric ischemia 2 months and 5 months after the procedure. The first patient underwent bypass surgery of the SMA, complicated by cardiac arrest and ongoing mesenteric ischemia. The second patient had end-stage kidney disease requiring dialysis resulting in a low-flow blood state causing ongoing mesenteric ischemia.

DISCUSSION

This study presents single-center data of 148 mesenteric arterial procedures performed by either a TBA, TFA or TRA approach. The data shows that TRA is a feasible approach for mesenteric arterial procedures with a technical success rate of 91%, not significantly different from the vascular access specified technical success rates of TFA and TBA. In addition, this study shows that TRA is safe for mesenteric arterial procedures as shown by a minor access site complication rate similar to TFA and TBA and a major access site complication rate of TRA similar to TFA but significantly lower than TBA.

This study consists of a unique series of mesenteric arterial endovascular procedures comparing TFA, TBA and TRA. Reported technical success rates of non-coronary artery procedures per TRA in literature vary from 91-99%(7, 8, 14-17). This study aimed at mesenteric arterial procedures shows a technical success rate of 91% for TRA, the lower limit of the reported technical success rates for non-coronary procedures. Posham et al. reported a significant higher crossover risk for renal/visceral interventions (OR 4.91 (2.07-11.7), p=0.0003) compared to oncologic liver interventions(7). A tentative explanation for this higher crossover rate could be due to the complexity of renal/visceral interventions, which include mesenteric arterial procedures. Furthermore, this study is performed in a tertiary referral center which possibly leads to selection of procedures with even higher difficulty which is substantiated by the similar technical success rates of TFA and TBA (technical success rate TBA 96% and TFA 87%).

The TRA procedures described in this study were included directly at the start of implementation of the TRA approach in this center. The described data indicates no learning curve for the TRA approach in the hands of experienced interventionalists, since the complication rate and technical success rate were not significantly different for the first 25% of the TRA procedures versus the latter 75% of TRA procedures.

The complication rates for non-coronary procedures per TRA reported vary from 1.8%-8.0% (7, 14-17). These rates are difficult to compare since the reporting standards differ between studies and data specified for mesenteric arterial procedures are lacking. Madden et al. reported an overall access site complication rate of TBA for non-coronary procedures of 11%(18). Complication rates specifically reported for mesenteric arterial procedures are scarce. Oderich et al report a complication rate for mesenteric procedures per TBA of 32% and per TFA of 28% (19). Rajaratnam et

al. reports a complication rate of 20% for mesenteric procedures in a combined TBA and TFA cohort(20). These numbers suggest a lower complication rate for mesenteric procedures per TRA compared to TBA and TFA, as previously proven for major access site complications for coronary procedures(2).

A potential limitation of this study is that it is an analysis based on a retrospective cohort, which could have led to reporting bias. The chosen vascular approach was not randomized but based on the angle between the mesenteric vessel and the aorta at the discretion of the performing interventionalist before November 2014 and if TRA was not possible from November 2014 onwards, potentially leading to selection bias and time-period bias. However, this study is a first step to assess the feasibility and safety of TRA for mesenteric arterial procedures. Ideally, a randomized controlled trial has to confirm the results of this study, such as conducted by Kiemeneij et al. published for coronary artery interventions(2). Procedure time, radiation exposure and the amount of contrast administered were not documented for the included patients. These characteristics could be interesting when comparing the different approaches in future studies. Finally, standard procedures did not include post procedural ultrasound of the access artery to assess occlusion or other access site complications after the procedure. Post procedural ultrasound was only performed if clinically indicated.

In conclusion, TRA is a safe and feasible technique for mesenteric arterial procedures and is comparable with TFA. TBA should be considered with caution, because of its significantly higher major complications rate. Prospective studies need to confirm the results of this study.

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10.1


CHAPTER
10.2

Rupture of the radial artery after brachiocephalic stent placement per trans-radial access

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Since November 2014, in our hospital, all non-coronary endovascular interventions initially selected for trans-brachial access with normal modified Allen test or Barbeau test result and sufficient radial artery (RA) diameter are performed per radial approach. We describe one rare but severe complication that occurred in 150 trans-radial procedures. Institutional review board approval was not required to publish this letter. Written informed consent was obtained from the patient.

A 36-year-old woman with a 1-year history of transient vertigo, bilateral blurred vision and nausea was evaluated for potential vertebrobasilar transient ischemic attacks. She also reported pain in the left arm. Her medical history was extensive with antiphospholipid syndrome, Budd-Chiari syndrome with hepatosplenomegaly, portal hypertension, esophageal varices, and right hemiparesis after stroke. Computed tomography angiography (CTA) showed a high-grade stenosis of >90% at the origin of the left subclavian artery (LSA) (Figure 1). Duplex ultrasonography showed no reversed blood flow in the left vertebral artery. The transient ischemic attacks were explained by microemboli to and/or hypoperfusion of the posterior circulation. The pain in the left arm was explained by hypoperfusion and endovascular revascularization of the LSA was planned.

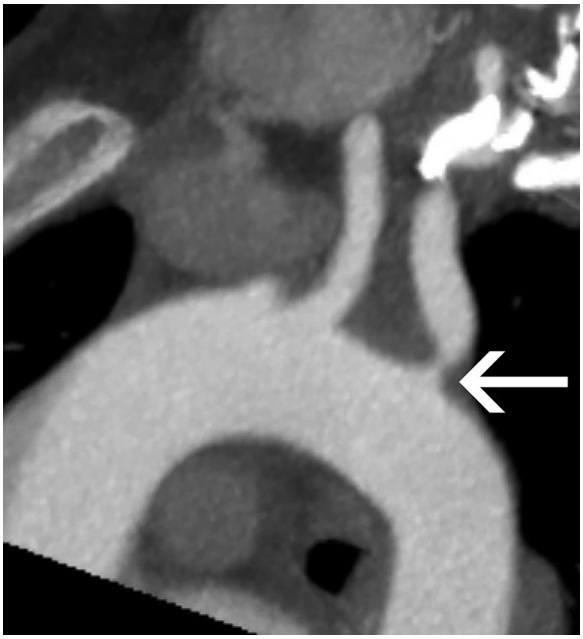

Figure 1. CTA image showing a high-grade stenosis of > 90% at the origin of the LSA (arrow).

The modified Allen test was normal. The RA diameter was 2 mm assessed by ultrasound and no anatomical variation of the RA was detected. After local anesthesia with 2% lidocaine, the left RA was punctured using ultrasound. An 11-cm 6-F dedicated RA sheath (Prelude; Merit Medical Systems, Inc, South Jordan, Utah, USA) was introduced. A solution containing 200 µg nitroglycerin, 2.5 mg verapamil and 5,000IE heparin was slowly injected intra-arterially. An 110-cm length 6-F Flexor sheath (Cook, Inc, Bloomington, Indiana, USA) with dilator was exchanged without resistance using a 0.035-inch Glidewire Advantage (Terumo Corp, Tokyo, Japan). The LSA stenosis was passed easily, and a 6 x 16 mm covered stent (Advanta V12; Atrium Medical Corp, Hudson, New Hampshire, USA) compatible with a 6-F sheath was placed. Additional inflation using a 7-mm balloon was attempted which resulted in stent dislocation towards the descending aorta. A 7-F sheath was placed in the left common femoral artery. The covered stent was parked into the external iliac artery and dilated to 8 mm. An 8 x 29 mm balloon expandable stent (Isthmus, CID SpA, Saluggia, Italy) was placed in the LSA via a femoral approach. Angiography images showed good position and stent patency. The femoral puncture side was closed with a closure device (Angio-Seal; Terumo Corp).

At the end of the procedure, the trans-radial Flexor sheath resisted removal. Manipulation was very painful for the patient. The patient was sedated with propofol to relax the RA and the sheath could slowly be retracted without resistance. Small injury of the RA with extravasation of contrast agent was visible (Figure 2, 3), but the RA was shown to be patent angiographically. After complete removal of the sheath, a pressure bandage was placed around the forearm, and the puncture side was closed with a compression device (Air-Band; Merit Medical Systems, Inc). The circulation of the hand was assessed frequently. The patient's left fingers were pale with normal sensibility and mobility. The same night, the fingertips of the left hand discolored blue and became painful. Surgical exploration of the left forearm was performed demonstrating a total rupture of the RA. A venous brachial artery–RA jump graft was made to restore vascularization. Fasciotomy was performed to release compartments of the left forearm.

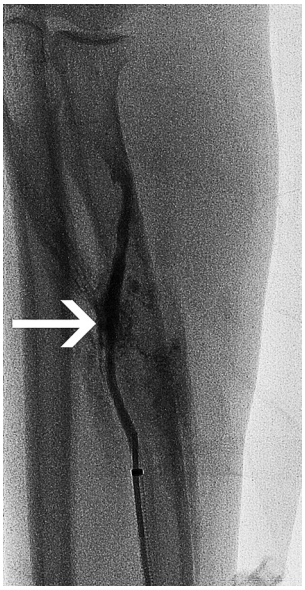

Figure 2. The sheath was removed under propofol sedation. While the sheath was halfway out, injection of contrast agent demonstrated partial rupture of the RA and contrast extravasation (arrow) in the soft tissue surrounding the rupture.

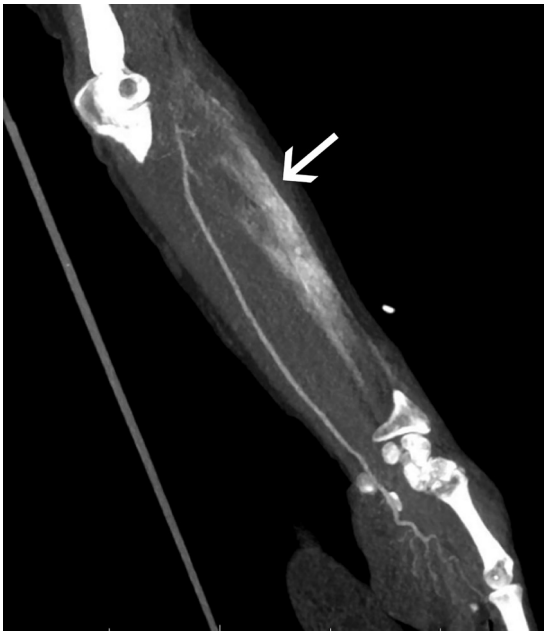

Figure 3. Minimum intensity reconstruction of CTA performed after the procedure demonstrates absence of contrast in the RA because of total occlusion and contrast in the soft tissue around the RA (arrow). Contrast in the soft tissues resulted from the invasive procedure and was not considered active contrast extravasation during CTA acquisition.

The following days, the fingers remained painful, discolored, and cold and morphine was started. The patient was discharged 2 weeks after the procedure. She had monthly follow-up at the outpatient clinic. During follow-up, dry gangrene developed on the thumb, index finger and middle finger (Figure 4). After 1 year, the fingertips of the index and middle finger were lost; the thumb was still intact with dry gangrene. The patient was free of pain and stopped all pain medication.

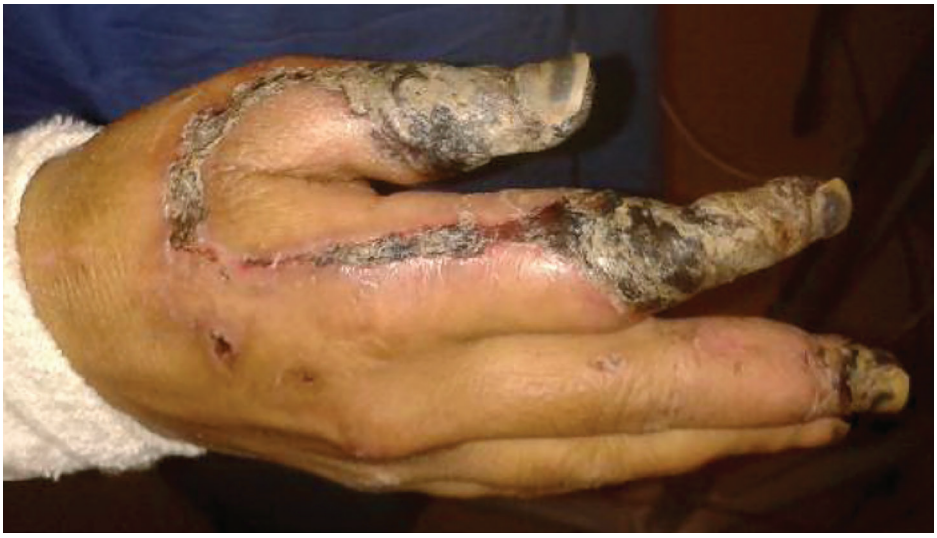

Figure 4. The patient's left hand 6 weeks after the procedure. Dry gangrene developed on the fingertips of the thumb, index finger and middle finger.

A severe complication of the radial access technique is described here. A relatively large sheath diameter(1) likely caused the severe vasospasm resisting removal of the RA sheath in combination with the prolonged procedure duration of 1 hour. The distal 25 cm of the Flexor sheath is hydrophilic coated. The remaining 85 cm of the sheath is not hydrophilic coated which may have contributed to this complication. Moreover, vasospasms may have been augmented owing to patient stress stimulating the adrenergic system. Because the modified Allen test indicated a sufficient palmar arch, insufficient radial blood flow owing to occlusion at the puncture side could not explain the ischemic sequelae. Small injury of the RA with extravasation of contrast agent was present at the end of the procedure. The RA itself was patent. Therefore, it is more likely that embolization of the thrombus near the target site dislodged distally after the procedure.

In a case in which RA sheaths resists removal, vasodilatation should be sought by: (1) intra-arterial injection of vasodilatators, (2) local infiltration of the tissue around the RA (eg, 1 mg nitroglycerin diluted in 10 ml saline), or (3) some form of sedation. Cases of RA injury treated with covered stent placement have been described in literature(2). However, follow-up in these cases was short and long-term stent patency rates are unknown. Another report described treatment with long-term sheath insertion to cover the rupture(3). This was not considered in our case, as the sheath itself caused the RA injury. The clarification of distal embolization of target site thrombi was not considered initially but might have changed the treatment strategy. Possibly, in retrospect, complete RA occlusion (eg, by using coils) might have been a better option than external compression.

This complication should be evaluated extensively. RA diameter assessment using ultrasound before trans-radial procedures is now always performed in our hospital. Minimum outer sheath diameter equals the RA diameter plus an additional 0.2 mm owing to vasodilation(4): RA diameter > 2.0 mm for 4-F sheath, > 2.2 mm for 5-F sheath, and > 2.4 mm for 6-F sheath.

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CHAPTER
11

Endovascular pressure measurements to assess the functional severity of mesenteric arterial stenoses

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ABSTRACT

Purpose

To assess the ability of pressure measurements to discriminate clinically significant celiac artery (CA) or superior mesenteric artery (SMA) stenosis in patients suspected chronic mesenteric ischemia (CMI).

Material and Methods

Single-center, retrospective cohort study of 41 intra-arterial pressure measurements during mesenteric angiography with intended revascularization, performed in 37 patients (mean age 67.7±10.8 years, 62% female) between April 2015 and May 2017. Simultaneous pre-stenotic and post-stenotic pressure measurements had been obtained before and after intra-arterial administration of nitroglycerin. Revascularization was performed in 38 out of 41 procedures. Definitive diagnosis of CMI was defined as patient-reported symptom relief or improvement after successful revascularization.

Results

Pressure gradients obtained after vasodilator administration were significantly higher in CAs and SMAs with ≥50% stenosis. Pressure ratios (Pd (pressure distal)/Pa (pressure aorta)) obtained after vasodilator administration were significantly higher in CA's with ≥50% stenosis. Subgroup analysis of 22 patients with a ≥50% stenosis of either CA or SMA showed significantly higher pressure gradients and Pd/Pa ratios after vasodilator administration in CMI patients (median pressure gradient: CMI (IQR) 36 (21-40) mmHg versus no-CMI 20 (9-21) mmHg, p=0.041; Pd/Pa: CMI 0.703 (0.598-0.769) versus no-CMI 0.827 (0.818-0.906), p=0.009)). A ≤0.8 Pd/Pa cut-off value after administration of a vasodilator best identified a clinically relevant stenosis, with 86% sensitivity and 83% specificity. Complications related to the pressure measurements were not observed.

Conclusion

Intra-arterial pressure measurements are feasible and safe. Low Pd/Pa ratios were associated with clinically relevant CA or SMA stenosis.

INTRODUCTION

Determination of the clinical significance of a mesenteric arterial stenosis is challenging, since an asymptomatic mesenteric arterial stenosis is found in 11-29% of the general population(1). The abundant mesenteric collateral network prevents development of symptoms in these individuals. However, when this collateral network is insufficient and/or the mesenteric arterial stenosis is too extensive, symptoms of chronic mesenteric ischemia (CMI), such as postprandial abdominal pain, food fear, and weight loss, may develop. Revascularization may then be beneficial. Patients with significant multi-vessel mesenteric arterial stenosis and corresponding symptoms are likely to have CMI and revascularization is therefore recommended(2). Establishing a diagnosis of CMI is more complex in patients with stenosis of a single mesenteric artery, in which case a diagnostic test assessing functional severity of the stenosis is indispensable.

Intra-arterial pressure measurements performed during angiography enable direct measurement of blood pressure proximal and distal to a stenosis. The myocardial fractional flow reserve (FFR) is a validated method to assess the hemodynamic significance of a coronary artery stenosis during coronary angiography(3, 4). A FFR <0.8 implicates that a coronary artery lesion is hemodynamically significant and should be treated(4). Guidelines on peripheral arterial disease issued by the European Society of Cardiology (ESC) and European Society of Vascular Surgery (ESVS) define a significant renal artery stenosis as a >20 mmHg translesional systolic pressure gradient or a <0.90 resting pressure ratio (5).

Validated cut-off values defining a significant mesenteric arterial stenosis are lacking. Guidelines for mesenteric endovascular interventions issued by the Society of Interventional Radiology (SIR) define a significant stenosis as narrowing of the mesenteric arterial lumen by ≥70% or >20 mmHg systolic pressure gradient across the lesion(6). This definition has been derived from an article by AbuRahma et al.(7). The ESVS guidelines on arterial and venous mesenteric diseases define a severe SMA stenosis as a ≥10 mmHg mean arterial pressure gradient across the lesion, referring to two studies which each used completely different cut-off values (>10% peak systolic blood pressure gradient; ≥20 mmHg mean pressure gradient)(2, 8, 9).

In conclusion, consensus on the value of pressure measurements during mesenteric procedures is currently lacking; cut-off values applicable to the mesenteric arteries have

not been defined. The aim of this study is to define a clinically significant CA or SMA stenosis by correlating mesenteric pressure measurements with a definitive diagnosis of CMI.

MATERIAL AND METHODS

Study design

All patients undergoing a digital subtraction angiography (DSA) of the mesenteric arteries with intended revascularization and intra-arterial pressure measurements in a specialized center between April 2015 and May 2017 were included in this retrospective cohort study. A total of 73 mesenteric angiograms with intended revascularization had been performed during the study period. Pressure measurements had been obtained during 41 procedures in 37 patients, these procedures were included in the study. Revascularization had been performed in 38 of the 41 procedures and these 38 procedures were included for the clinical success analysis. Revascularization had not been performed in three cases because the stenoses were judged to be not significant. The local medical research ethics committee concluded that the Medical Research Involving Human Subjects Act does not apply to this study. The investigators complied with the Helsinki declaration on research ethics. The STROBE checklist for cohort studies was used to write this manuscript(10).

Standard diagnostic work-up

Patients suspected of CMI referred to the specialized center underwent a standardized diagnostic work-up consisting of assessment of symptoms, imaging of the mesenteric arteries (computed tomography angiography (CTA)) and visible light spectroscopy. The latter is a functional test assessing mucosal ischemia during upper gastro-intestinal endoscopy(11). Results of the diagnostic work-up were discussed in a multidisciplinary meeting attended by interventional radiologists, vascular surgeons, and gastroenterologists, all specialized in CMI. When CMI was judged to be a likely explanation for the presenting symptoms and alternative diagnoses were adequately excluded, a presumptive diagnosis of CMI was established. Patients with a presumptive diagnosis of CMI based on vascular disease were scheduled for DSA with intended mesenteric revascularization. Patients suspected of median arcuate ligament syndrome (MALS) were not scheduled for DSA since treatment for MALS consists of surgical release. The ultimate decision to perform revascularization was made if during the

DSA procedure a significant stenosis was found, defined as ≥50% luminal reduction. If the interventional radiologist had doubts about the significance of the stenosis, a mean pressure gradient of >10 mmHg was an indication for revascularization. A definitive diagnosis of CMI was established when a patient reported relief or improvement of presenting symptoms after a technically successful revascularization procedure.

Data sources

Baseline and follow-up data was retrieved from the hospital records. A standardized follow-up protocol had been used throughout the study period, consisting of history and physical examination 24 hours after the procedure and at 1, 3, 6, 12, and 24 months. Most of the follow-up had been obtained in outpatient clinic visits or by phone.

For the purpose of this study the DSA derived during the procedure was re-examined by two interventional radiologists with 8 and 5 years of experience. Time between DSA and re-examination ranged from 12 to 36 months. The interventional radiologists were blinded to symptom improvement after treatment and independently graded the severity of CA and SMA stenoses on a scale from 0 (no stenosis) to 100 (occlusion). The grading was based on the luminal diameter of the stenosis and adherent normal vessel in two directions. In case of a ≥10% difference in severity of the stenosis established by the two radiologists, the DSA images were reassessed and discussed until consensus was reached. Information on the presence of an IMA stenosis was obtained from the multidisciplinary meeting reports.

Procedure and pressure measurements

Pressures were measured using a 4-F catheter — positioned just distal to the stenosis — and a 5-F or 6-F sheath — with the tip positioned in the aorta just proximal to the stenosis. Both catheter and sheath were externally connected to pressure measurement devices (Meritrans DTXPlus, Merit Medical, South Jordan, USA) connected to a monitoring system (Infinity C500, Dräger, Lübeck, Germany). In some cases, both a catheter and a 0.014” pressure wire (Aeris Agile, St Jude Medical, Minnesota, USA) were used. The catheter was pulled into the sheath before pressure wire measurements were obtained. Pressure measurements obtained with the pressure wire were compared with measurements obtained with the pressure catheter, since the diameter of the pressure catheter (1.33mm) is larger than the diameter of the pressure wire (0.36mm). Positioning a catheter through a severe stenosis reduces the luminal diameter even

further, thereby obstructing blood flow, possibly resulting in lower pressures distal to the stenosis, with subsequent larger pressure gradients.

The pressure devices were calibrated against atmospheric pressure at the level of the left atrium. Translesional pressure measurements were performed simultaneously, before and after intra-arterial injection of nitroglycerine 300 microgram(12). This vasodilator was injected distal to the stenosis, through the 4-F catheter, and measurements were obtained within seconds thereafter. These measurements were performed before and after endovascular intervention of the CA and/or SMA.

At the discretion of the interventionalist, the access approach was trans-radial, trans-brachial or trans-femoral. Patients undergoing mesenteric artery stenting were treated with life-long acetylsalicylic acid and clopidogrel for a duration of 12 months. When revascularization was performed by percutaneous transluminal angioplasty (PTA) alone, life-long acetylsalicylic acid was prescribed. In patients undergoing DSA without revascularization, anticoagulation was not indicated.

Variables

Table 1 shows the patient characteristics, the presenting symptoms, and the CTA results. Mean age of the 37 patients was 67.7±10.8 years and most were female (62.2%). A definitive diagnosis of CMI had been made in 28 out of 37 patients (75.7%). Current smoking or a history of smoking was significantly more frequent in patients with a definitive diagnosis of CMI (CMI patients 96.3% versus no-CMI patients 66.7%; p=0.014). All patients without a definitive diagnosis of CMI presented with nausea, versus 57.9% of CMI patients p=0.039). Pre-procedural CTA imaging showed ≥1 mesenteric artery stenosis in all patients and procedures.

Table 1. Baseline characteristics in presence or absence of a definitive diagnosis of CMI.

	All patients (n=37)	CMI patients (n=28)	No-CMI patients (n=9)	P-value
Patient characteristics				
Age (y)	67.7 ± 10.8	68.5 ± 10.7	65.0 ± 11.1	0.37
Female	62.2% (23)	60.7% (17)	66.7% (6)	0.75
Caucasian	100.0% (37)	100.0% (28)	100.0% (9)	1.00
Weight at angiography (kg)	65.4 ± 19.8	66.0 ± 19.9	63.6 ± 20.5	0.85
BMI at angiography (kg/m^2)	23.4 ± 5.6	23.3 ± 5.3	23.9 ± 6.8	0.88
Current/former smoker	88.9% (32)	96.3% (26)	66.7% (6)	0.01*
Hypertension^	52.8% (19)	55.6% (15)	44.4% (4)	0.56
Dyslipidemia@	47.2% (17)	51.9% (14)	33.3% (3)	0.34
Diabetes#	13.9% (5)	18.5% (5)	0.0% (0)	0.16
History of CVD	70.3% (26)	71.4% (20)	66.7% (6)	0.79
Presenting symptoms				
Abdominal pain	94.6% (35)	92.9% (26)	100.0% (9)	0.41
Postprandial abdominal pain	73.0% (27)	67.9% (19)	88.9% (8)	0.22
Exercise related abdominal pain	30.0% (9)	25.0% (6)	50.0% (3)	0.23
Nausea	69.2% (18)	57.9% (11)	100.0% (7)	0.04*
Diarrhea	44.4% (16)	44.4% (12)	44.4% (4)	1.00
Obstipation	30.6% (11)	33.3% (9)	22.2%(2)	0.53
Weight loss	63.9% (23)	59.3% (16)	77.8% (7)	0.32
Abdominal bruit	32.1% (9)	33.3% (7)	28.6% (2)	0.82
Classic triad of CMI	21.1% (7)	20.0% (5)	25.0% (2)	0.76
Gastric and/or duodenal ulcer	6.1% (2)	8.3% (2)	0.0% (0)	0.37
Duration of symptoms (months)	12.5 ± 11.1	11.3 ± 8.3	16.2 ± 17.5	1.00
Stenotic mesenteric arteries on CTA per procedure				
CA	9.8% (4)	14.3% (4)	0% (0)	0.56
SMA	14.6% (6)	10.6% (3)	23.0% (3)	0.29
IMA	2.4% (1)	0% (0)	7.8% (1)	0.55
CA+IMA	17.1% (7)	14.3% (4)	23.0% (3)	1.00
SMA+IMA	17.1% (7)	17.9% (5)	15.4% (2)	0.84
CA+SMA	17.1% (7)	14.3% (4)	23.0% (3)	1.00
CA+SMA+IMA	21.9% (9)	28.6% (8)	7.8% (1)	0.54

Data are presented as percentages (numbers) or as mean ± SD.
^ blood pressure ≥140/90 mmHg or use of antihypertensive medication
@ LDL-C >4.2 mmol/L or HDL-C <0.9 mmol/L or use of lipid lowering medication
#all Diabetes type II
* p<0.05
BMI = body mass index; CA = celiac artery; CMI = chronic mesenteric ischemia; CVD = cardiovascular disease; IMA = inferior mesenteric artery; PTA = percutaneous transluminal angioplasty; SMA = superior mesenteric artery.

Table 2 contains the procedural characteristics. In most of the procedures (28/41; 68.3%) a transradial approach was used. DSA showed an atherosclerotic stenosis in 40 procedures (97.5%); one procedure concerned revascularization of a stenosis in a patient with known vasculitis (Takayasu arteritis) (2.5%). A combination of a significant atherosclerotic stenosis of the SMA and a non-significant CA stenosis due to external compression was observed in one procedure. None of the patients was diagnosed with MALS. Mesenteric artery stenting was the most frequent intervention (28 primary stent placements (68.3%) and 7 stent-in-stent placements (18.4%)). Technical success of revascularization was defined as a <30% residual stenosis after stenting or PTA. Procedural reports did not specify the precise severity of the residual stenosis. Technical success was achieved in 89.5% of 38 revascularizations. Stent specifications could not be assessed, since 19 of the 38 (50.%) revascularization procedures were included in an ongoing double blinded randomized controlled trial, comparing the patency of bare metal stents (Palmaz blue, Cordis, Baar, Switzerland) with the patency of covered stents (V12, Atrium Medical Corporation, Merrimack, United States of America)(13).

Table 2. Procedure characteristics.

	All procedures n=41
Cause stenosis atherosclerosis	97.5% (40)
Cause stenosis vasculitis	2.5% (1)
Radial access	68.3% (28)
Brachial access	17.1% (7)
Femoral access	14.6% (6)
Sheath size 4-F	2.6% (1)
Sheath size 5-F	13.1% (5)
Sheath size 6-F	71.1% (27)
Sheath size 7-F	10.6% (4)
Sheath size 8-F	2.6% (1)
Diagnostic angiography	7.3% (3)
Technical success rate revascularizations	89.5% (34)
Clinical success rate revascularizations	73.7% (28)

Table 2. Continued

	All procedures n=41
Primary interventions (N=29)	
Stent placement CA	23.7% (9)
Stent placement SMA	29.0% (11)
Stent placement CA + SMA	21.1% (8)
PTA CA	2.6% (1)
Re-interventions (N=9)	
Stent-in-stent placement CA	7.9% (3)
Stent-in-stent placement SMA	10.5% (4)
In-stent PTA CA	2.6% (1)
In-stent PTA CA + SMA	2.6% (1)

Data are presented as percentages (number).
CA = celiac artery; PTA = percutaneous transluminal angioplasty; SMA = superior mesenteric artery.

Pressure gradients across the lesion (= pressure distal to the stenosis (Pd)–pressure aorta (Pa)) and Pd/Pa ratios were calculated to assess the primary outcome and the secondary outcomes. The primary outcome was the ability of pressure measurements to define a clinically significant stenosis by discriminating patients with a definitive diagnosis of CMI — patient-reported relief or improvement of presenting symptoms after a technically successful revascularization procedure — from patients without a definitive diagnosis of CMI. Secondary outcomes were the ability of pressure measurements to discriminate a <50% stenosis from a ≥50% stenosis; differences between BMI at baseline and at 12 months after the intervention; differences in pressure readings obtained with wire and obtained with catheter; complication rate; and mortality rate. The complication rates were specified according to the SIR Quality Improvement Guidelines for Diagnostic Arteriography(14).

Statistical methods

Patient characteristics are described as either number and percentage for dichotomous variables, or as mean and standard deviation or median and interquartile range (IQR) for continuous variables. Differences in patient characteristics between CMI patients and no-CMI patients were determined by the χ^2 test, independent T-test or Mann-Whitney U test. Pressure measurement values are presented as median with IQR, since

the data was not normally distributed. Pressure measurements (stenosis versus no stenosis and patients with and without a definitive diagnosis of CMI) were compared with the Mann Whitney-U test. The Wilcoxon Signed Rank test served to compare BMI before and 12 months after intervention and to compare measurements obtained by catheter with measurements obtained by pressure wire. Statistical significance was defined as $p<0.05$. Receiver-operating characteristics (ROC) curves were computed to define pressure cut-off values for clinically significant stenosis. The area under the curve (AUC) or C-statistic defined the discriminative ability of the pressure measurements for clinical success. A C-statistic of 0.5 suggests no discrimination; C-statistic of 0.7-0.8 is considered acceptable discrimination, C-statistic of 0.8-0.9 as excellent discrimination; and a C-statistic ≥0.9 as outstanding discrimination(15). AUCs were compared with the DeLong test.

RESULTS

Severity of stenosis and intra-arterial pressure measurements

Re-examination of DSA images obtained before revascularization, showed a significant stenosis of 24 out of 41 (58.5%) imaged SMAs and 23 out of 32 (71.9%) imaged CAs (Table 3). Grading of stenosis severity differed ≥10% in 8 out of 75 graded stenoses (6 CA and 2 SMA), consensus on the grading had been reached after reassessment by both interventional radiologists.

Table 3. Grading of severity of stenosis of CA and SMA based on DSA.

Vessel	Severity stenosis	All patients	CMI patients	No-CMI patients
CA	**<50%**	28.1% (9)	20.8% (5)	50.0% (4)
	≥50% - <70%	37.5% (12)	45.8% (11)	12.5% (1)
	≥70% - <100%	25.0% (8)	25.0% (6)	25.0% (2)
	100% (Occlusion)	9.4% (3)	8.4% (2)	12.5% (1)
SMA	**<50%**	36.8% (14)	39.3% (11)	37.5% (3)
	≥50% - <70%	44.8% (17)	39.3% (11)	75.0% (6)
	≥70% - <100%	10.5% (4)	10.7% (3)	12.5% (1)
	100% (Occlusion)	7.9% (3)	10.7% (3)	0.0% (0)

Data are presented as percentages (number).
CA = celiac artery; CMI = chronic mesenteric ischemia; DSA = digital subtraction angiography; SMA = superior mesenteric artery.

Table 4 shows the results of the mean pressure gradients and Pd/Pa ratios in arteries with and without a significant stenosis, as classified by re-examination of the DSA images. Pressure gradients obtained after administration of a vasodilator were significantly higher in vessels with a significant stenosis (pressure gradient after vasodilator injection CA median (IQR): stenosis 38.5 (17.0-50.0) versus no stenosis 12.5 (8.5-19.0), p=0.035 and SMA: stenosis 36.5 (21.0-56.0) versus no stenosis 17.0 (13.0-31.5), p=0.047). Calculated Pd/Pa ratios obtained after injection of a vasodilator in the CA were significantly lower when a significant stenosis was present (Pd/Pa after vasodilator injection in the CA median (IQR): stenosis 0.63 (0.47-0.85) versus no stenosis 0.86 (0.83-0.91), p=0.042).

Table 4. Pressure measurements before intervention in mmHg for the CA and SMA.

	Stenosis	No stenosis	N	p-value
CA				
Pressure gradient without vasodilator	23.0 (14.5-43.0)	7.5 (3.0-13.5)	28	0.016*
Pressure gradient after vasodilator	38.5 (17.0-50.0)	12.5 (8.5-19.0)	23	0.035*
Pd/Pa without vasodilator	0.74 (0.55-0.87)	0.93 (0.89-0.97)	28	0.013*
Pd/Pa after vasodilator	0.63 (0.47-0.85)	0.86 (0.83-0.91)	23	0.042*
SMA				
Pressure gradient without vasodilator	17.0 (7.5-41.5)	8.0 (5.0-13.0)	29	0.056
Pressure gradient after vasodilator	36.5 (21.0-56.0)	17.0 (13.0-31.5)	26	0.047*
Pd/Pa without vasodilator	0.84 (0.53-0.93)	0.92 (0.88-0.95)	29	0.085
Pd/Pa after vasodilator	0.68 (0.35-0.77)	0.78 (0.66-0.85)	26	0.080

Data are presented as median (IQR).
* p<0.05
CA = celiac artery; Pa = pressure aorta; Pd = pressure distal; SMA = superior mesenteric artery.

Pressure measurements had been obtained with both a catheter and a pressure wire in 8 vessels (4 CA and 4 SMA). Measurements obtained with a catheter were significantly lower than measurements obtained with a pressure wire (mean pressure measurements by a catheter, median (IQR) 83.0 (68.0-95.0) versus pressure wire 85.0 (76.0-105.5), p=0.03). When comparing measurements, the catheter-derived measurements obtained distal to the stenosis were significantly lower (mean pressure measurements by a catheter, median (IQR) 75.5 (56.5-83.0) versus pressure wire 79.0 (74.3-105.5), p=0.006). Measured aortal pressures did not differ significantly (Table 5).

Table 5. Mean pressures derived by catheter versus pressure wire in 4 CAs and 4 SMAs in mmHg before intervention.

	Catheter derived		Pressure wire		
	N	**Pressure**	**N**	**Pressure**	**P-value**
Pressure aorta	15	88.0 (82.0-116.0)	9	100.0 (82.5-130.0)	0.811
Pressure distal to stenosis	16	75.5 (56.5-83.0)	16	79.0 (74.3-89.8)	0.006*
All measurements	31	83.0 (68.0-95.0)	25	85.0 (76.0-105.5)	0.029*

Data are presented as median (IQR).
* $p<0.05$
CA = celiac artery; SMA = superior mesenteric artery.

Clinical outcomes and complications

Clinical success — resulting in a definitive diagnosis of CMI — was achieved in 28 out of 38 (73.7%) revascularizations, with a median follow-up of 17 months (range 2-37 months, mean follow-up 17±10 months). Clinical success was achieved in all 4 (100%) patients with a stenosis of the CA; in 3 out of 4 (75.0%) patients with a stenosis of the SMA; in 4 out of 7 (57.1%) patients with a stenosis of CA and IMA; in 5 out of 7 (71.4%) with a stenosis of SMA and IMA; in 4 out of 7 (57.1%) with a stenosis of CA and SMA; and in 8 out of 9 (88.9%) with a stenosis of all three mesenteric arteries. Symptoms had recurred in 2 patients with a definitive diagnosis of CMI (1 in-stent stenosis, 1 stent fracture). A re-intervention had improved symptoms in both patients. At 12 months after revascularization, BMI had increased significantly in patients with a definitive diagnosis of CMI (BMI at revascularization 23.3±5.3 versus BMI 12 months after revascularization 23.9±5.6, p=0.024). BMI showed a decreasing trend after revascularization in patients without a definitive diagnosis (BMI at revascularization 23.5±5.6 versus BMI 12 months after revascularization 19.9±4.3, p=0.171).

Major complications requiring intervention and/or extension of hospital admission had occurred in 3 of the 41 procedures (7.3%) and minor complications in 8 procedures (19.5%). Major complications consisted of a hematoma, a pseudoaneurysm of the brachial artery and a gastro-intestinal bleeding four days after the procedure. Minor complications were 5 hematomas, a CA dissection during recanalization of an occluded CA performed after successful pressure measurements in the SMA, a swollen arm after radial approach and a painful leg after femoral approach. Complications were not related to the pressure measurements. Three out of 37 patients (8.1%) died during

the study period. Causes of death were liver failure, urosepsis and cardiac arrest; none were related to the procedure.

Pressure measurements in stenosis of either CA or SMA

Subgroup analysis was performed to compare pre-interventional pressure measurements in patients with a significant stenosis of either CA or SMA on the re-examined DSA images and a technically successful revascularization. Pressure gradients obtained after administration of a vasodilator were significantly higher in patients with a definitive diagnosis of CMI (pressure gradient after injection of vasodilator in 16 CMI patients 36.0 (21.0-40.0) versus 6 patients without CMI 20.0 (9.0-21.0), p=0.041) (Table 6). Calculated Pd/Pa ratios obtained after administration of a vasodilator were significantly lower in patients with CMI compared to patients without CMI (Pd/Pa after injection of vasodilator in 16 CMI patients 0.70 (0.60-0.77) versus 6 patients without CMI 0.83 (0.82-0.91), p=0.009) (Table 6). Figure 1 shows ROC curves reflecting the discriminative ability of pressure measurements in the described subgroup. A ≤0.8 Pd/Pa ratio obtained after administration of a vasodilator provided the optimal sensitivity (86%) and specificity (83%); the C-statistic was 0.869 (confidence interval (CI) 0.71-1.00), indicating excellent discrimination. The C-statistic representing the discriminative ability of severity of stenosis measured on DSA was lower, though not significantly lower (AUC 0.772, CI 0.55-0.99, p=0.17).

Table 6. Pressure measurements in mmHg before intervention in patients with single-vessel disease or stenosis of the IMA and stenosis of either SMA or CA for patients with and without a definitive diagnosis of CMI.

	CMI patients	No-CMI patients	N	p-value
Pressure gradient without vasodilator	17.5 (11.0-29.0)	8.00 (4.0-15.0)	24	0.047*
Pressure gradient after vasodilator	36.0 (21.0-40.0)	20.00 (9.0-21.0)	22	0.041*
Pd/Pa without vasodilator	0.86 (0.74-0.90)	0.92 (0.90-0.96)	24	0.040*
Pd/Pa after vasodilator	0.70 (0.60-0.77)	0.83 (0.82-0.91)	22	0.009*

Data are presented as median (IQR).
* p<0.05
CA = celiac artery; CMI = chronic mesenteric ischemia; IMA = inferior mesenteric artery; Pa = pressure aorta; Pd = pressure distal; SMA = superior mesenteric artery.

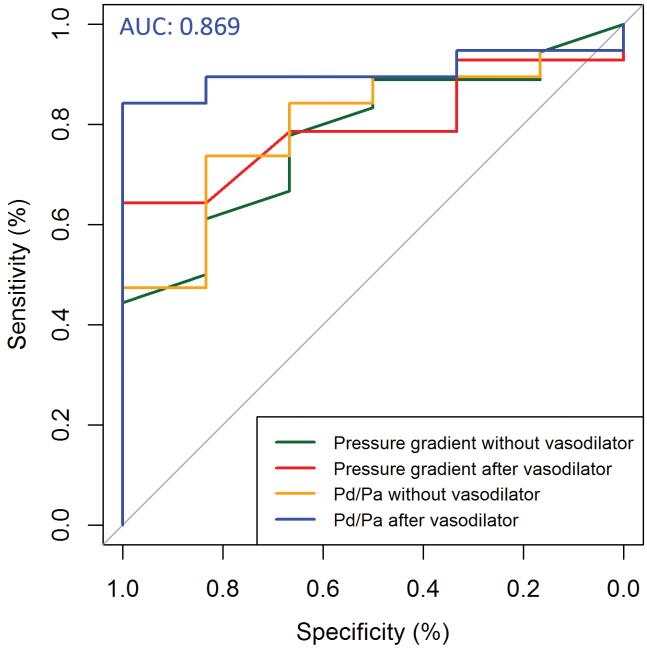

Figure 1. ROC curves of the ability to identify clinically relevant mesenteric artery stenosis by pressure measurements in a subgroup of patients with single-vessel disease or stenosis of the IMA and either CA or SMA.
AUC = area under the curve.

DISCUSSION

The results of this study suggest that pressure measurements of the mesenteric arteries, in particular after injection of a vasodilator, guide the decision to perform revascularization of CA or SMA stenosis in patients with presumptive CMI. Pressure measurements may be valuable in patients with a single-vessel stenosis, since the clinical significance of a single-vessel stenosis is often disputed. Furthermore, this study showed that pressure measurements were feasible and safe.

CMI is a challenging diagnosis because the symptoms are non-specific, mimicking symptoms of more prevalent diagnoses, and mesenteric artery stenoses are common though often not hemodynamically significant. Development of a validated test quantifying the hemodynamic significance of stenoses is complicated by two factors.

The first factor is the extensive collateral circulation, often compensating for the reduced post-stenotic blood flow. Van Petersen et al. showed that an extensive collateral circulation in MALS patients was associated with a lower clinical success rate after CA release(16). Translesional pressure gradients are measured only when the collateral circulation is unable to compensate for the reduced blood flow caused by the stenosis. The second factor is the dynamic process of ischemia, since ischemia is often temporary and elicited only after a meal(1, 2). Pre-prandial measurements could be false negative, since the pre-prandial blood flow is not maximal. Pressure measurements after administration of a vasodilator simulates the postprandial physiology of the mesenteric vasculature and challenges both factors needed to cause CMI, i.e. an insufficient collateral circulation and a stenosis severe enough to limit maximal blood flow. This study supports the hypothesis that ischemia in CMI is a dynamic process, since clinically significant stenoses were best identified after the injection of a vasodilating agent, as is illustrated by the ROC curves in Figure 1.

Consensus on the use of pressure measurements for mesenteric procedures is currently not established and validated cut-off values are lacking. This study suggests that a clinically relevant CA or SMA stenosis — caused by vascular disease — is identified by a ≤0.8 Pd/Pa ratio obtained after administering a vasodilator. This ratio is in line with ratios established in other vascular beds(4, 5). The increase in BMI of patients with clinical success and the decrease in BMI of patients without CMI is the most objective outcome supporting that patient-reported relief of presenting symptoms after a technically successful intervention indicates a definitive diagnosis of CMI and underlines the potential clinical value of pressure measurements.

Pressure had been measured with both a catheter and a pressure wire in 8 vessels. Mean pressures distal to the stenosis were slightly but significantly lower when measured with a catheter. Imbesi and colleagues reported similar findings when comparing translesional pressure measurements in an atherosclerotic human carotid bulb replica using catheters of different diameters(17). Pressures were lower when a larger diameter catheter was used. Similar differences have been reported in a clinical study by Garcia et al.(18), comparing both pressure wire and catheter derived measurements. The results of the present study suggest that cut-off values established with catheters differ from cut-off values established with pressure wires, which should be considered when designing a future study to determine cut-off values in mesenteric arteries.

Several limitations of the study need to be addressed. First, the limitations inherent to the retrospective design of the study. For example, not obtaining pressure measurements in 32 of 73 procedures, which could potentially introduce selection bias, though clear selection criteria for the performance of pressure measurements could not be identified. Second, the large heterogeneity in number and type of affected mesenteric arteries. Third, clinical success had been defined as patient-reported symptom relief after revascularization, since a standardized or validated assessment is absent. Fourth, patients without significant stenosis during DSA did not undergo revascularization, clinical success could therefore not be assessed. Fifth, the limited number of patients made it impossible to suggest cut-off values per vessel, while one could argue that the clinical relevance and the cut-offs of CA and SMA stenoses may differ. Sixth, patients undergoing mesenteric artery revascularization were carefully selected; results of this study may therefore not be applicable to populations with a less thorough diagnostic work-up.

Despite these limitations, the results of this study provide a valuable first step in the assessment of the clinical applicability of treatment guidance by mesenteric pressure measurements. Larger prospective studies are needed to verify these findings and validate the suggested cut-off, a ≤0.8 PdP/a ratio obtained after administering a vasodilator. Furthermore, application of pressure measurements for the detection of MALS and assessment of technical success of stenting could be investigated.

In conclusion, the intra-arterial pressure measurements in the studied population are proven feasible and safe and may discriminate between clinically relevant CA or SMA stenosis and adequately compensated CA or SMA stenosis in patients with a presumptive diagnosis of CMI. When confirmed and validated the use of intra-arterial pressure measurements could improve clinical success after mesenteric artery revascularization and prevent over-treatment with its associated risks and costs.

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PART IV

Summary, discussion and conclusion

Chapter 12.1
Summary

Chapter 12.2
General discussion

Chapter 12.3
Future perspectives

Chapter 12.4
Conclusion


CHAPTER
12.1

Summary

This thesis aims to provide insights in different aspects of the diagnosis and therapy of chronic mesenteric ischemia (CMI) to optimize the diagnostic work-up and therapy for this specific patient group. The disease CMI is introduced in **Part I** with an overview of the definition, epidemiology, etiology, clinical presentation, diagnostic work-up, therapy and clinical outcome of CMI and the anatomy of the mesenteric vasculature in **Chapter 1.1** followed by the aims and outline of the thesis in **Chapter 1.2**.

DIAGNOSIS

Part II discusses different aspects of the current diagnostic work-up for CMI and strategies and insights to optimize the diagnostic work-up. An overview of the current imaging modalities for the mesenteric vasculature such as duplex ultrasound (DUS), computed tomography angiography (CTA), magnetic resonance angiography (MRA) and digital subtraction angiography (DSA) is given in **Chapter 2. Chapter 3** describes the external validation of a prediction model, previously published by our study group, to predict the risk of CMI based on 5 simple predictors (female gender, presence of weight loss, presence of cardiovascular disease (CVD), degree of celiac artery (CA) stenosis, and degree of superior mesenteric artery (SMA) stenosis). The performance of the prediction model in the new multicenter cohort was good. However, experts in the field discussed the absence of the etiology of the CA stenosis (median arcuate ligament syndrome (MALS), atherosclerosis) as a predictor in the prediction model. Therefore, we updated the model based on the performance of the model in the combined original and validation cohort, in a total of 666 patients suspected of CMI, with inclusion of the cause of CA stenosis. This updated model includes the predictors: presence of weight loss, presence of CVD, degree of CA stenosis combined with the cause of CA stenosis, and degree of SMA stenosis. The updated score chart shows excellent discriminative ability with an absolute low-risk of CMI of 19%, an intermediate risk of 45% and a high risk of CMI of 92%. The updated score chart is a useful tool to guide clinical decision making for the diagnostic work-up. We suggest a wait-and-see policy for patients stratified as low-risk of CMI, additional functional testing for patients stratified as intermediate risk of CMI and immediate vascular intervention for patients stratified as high risk of CMI. This strategy should lead to a more efficient diagnostic approach, reducing diagnostic delays due to superfluous diagnostic procedures, thereby resulting in a decrease in patient-burden and reduced health costs.

Visible light spectroscopy (VLS) performed during upper endoscopy is used in clinical practice as a component of the diagnostic work-up of CMI. Interobserver and intraobserver validation of endoscopic VLS is not described in literature; therefore we performed an observer reliability study. We show in **Chapter 4** that the observer reliability of VLS is fair to good with intraobserver reliability being better than interobserver reliability. VLS measurements during upper gastro-intestinal (GI) endoscopy are reproducible and our findings support the use of VLS in the diagnostic work-up of CMI.

In **Chapter 5** we determined whether postprandial VLS measurements increase the discriminative ability of VLS measurements, since CMI patients are often symptomatic after a meal due to increased oxygen demand. Our prospective cohort study shows that postprandial VLS measurements have no added benefit for the diagnosis of CMI.

Chapter 6 describes the validation of the VLS technique in a porcine model based on 3 experiments. First, we compared VLS values and calibrated microvascular oxygen tension (μPO_2) measurement values at different levels of FiO_2. We show that the VLS values decrease with increasing FiO_2 in contrast to the μPO_2 values that increase with increasing FiO_2. VLS levels show a large spread at all FiO_2 levels resulting in a poor linear correlation. Second, we assessed the effect of the presence of bile on the VLS values. We show a significant influence of bile on the measured VLS values. Finally, we compared VLS measurements and μPO_2 measurements during asystole. We show that the VLS values, in contrast to the μPO_2 values, did not decrease towards a value of 0 in the first 25 minutes of asystole. Our findings support the idea that VLS measures the mixed venous hemoglobin oxygen saturation and not the mucosal capillary hemoglobin oxygen saturation. Given the effect of bile on the measured VLS values, we advise to remove any fluid on the measuring area of the GI mucosa before performing VLS measurements.

In **Chapter 7** we performed a feasibility study of a novel promising technique to measure mitochondrial oxygen levels during upper GI endoscopy: delayed fluorescence measurements of 5-aminolevulinic acid (ALA)-induced protoporphyrin IX (PpIX). This study in healthy volunteers shows that measurement of oxygen-dependent delayed fluorescence during upper GI endoscopy is feasible and we detected an oxygen-dependent signal. We determined a dose of 5mg/kg ALA as optimal and the duodenal

bulb and descending duodenum as suitable measurement locations. Administration of butylscopolamine during the procedure did not influence the measured values.

THERAPY

Part III discusses various therapeutic elements of CMI with focus on endovascular revascularization. **Chapter 8** describes a study protocol for a multicenter randomized controlled trial on covered stents versus bare-metal stents for CMI to prospectively confirm the superior patency of covered stents over bare-metals stents for atherosclerotic CMI, as suggested by a retrospective cohort study.

In **Chapter 9** we evaluated the long-term clinical success rates of revascularization of single vessel disease based on vascular disease of the CA or SMA in a retrospective cohort analysis. We show persistent symptom relief in 73% of patients diagnosed with CMI based on single vessel disease with GI symptoms and VLS or tonometry confirmed mucosal ischemia.

Non-coronary endovascular interventions are performed with trans-brachial access (TBA) or trans-femoral access (TFA). However, coronary literature shows lower major access-site complication rates for trans-radial access (TRA) than for TBA and for TFA with similar procedural and clinical outcomes. In **Chapter 10.1** we assessed the feasibility and safety of TRA compared to TFA and TBA for mesenteric arterial procedures. We show that TRA is a safe and feasible approach for mesenteric arterial procedures comparable to TFA, whereas TBA shows a significantly higher major complication rate. In **Chapter 10.2.** however, we describe a severe complication of a TRA procedure. Brachiocephalic stent placement was performed in a young female patient per TRA complicated by total rupture of the radial artery.

Intra-arterial pressure measurements during coronary artery procedures are performed to define the clinical significance of a coronary artery stenosis. We performed in **Chapter 11** a cohort study to assess the feasibility of intra-arterial pressure measurements for definition of a clinical significant mesenteric arterial stenosis. We show that clinical significance of a mesenteric arterial stenosis can be predicted using pressure measurements.

In **Part IV** we summarize the main findings of this thesis in **Chapter 12.1** and provide an overall discussion in **Chapter 12.2**. Furthermore, directions for future research are provided in **Chapter 12.3** and the last part of the thesis ends with the overall conclusion (**Chapter 12.4)**.


CHAPTER
12.2

General discussion

This thesis aims to provide insights in different aspects of the diagnosis and therapy of CMI to optimize the diagnostic work-up and therapy for this specific patient group. A general limitation of this thesis is that the studies are single-center and performed in a CMI specialized center, which could potentially limit the generalizability of the results. One study (**Chapter 3)** is a multicenter study performed in collaboration with another Dutch CMI specialized center, Medical Spectrum Twente.

DIAGNOSIS OF CMI

Symptoms and characteristics of CMI patients

The typical characteristics of CMI patients as described in current literature are female preponderance with a high prevalence of atherosclerotic risk factors as hypercholesterolemia, smoking history and CVD history(1, 2). Table 1 shows the characteristics of the CMI patients included in this thesis (Chapter 3, Chapter 5, Chapter 9 and Chapter 11) which confirm current literature data. In **Chapter 3** we show that independent characteristics predictive of CMI are the presence of weight loss, presence of CVD, degree of CA stenosis and degree of SMA stenosis. In this series female gender was not an independent predictor of CMI.

Symptoms such as postprandial abdominal pain or exercise induced abdominal pain are also not independent predictors in a population of patients suspected of having CMI, since the prevalence of postprandial abdominal pain is also high in patients without CMI. The only symptom with discriminative ability for the diagnosis of CMI is the presence of weight loss. This finding confirms the European Society of Vascular Surgery (ESVS) guideline, in which is stated that if substantial weight loss is absent in a patient suspected of CMI, further investigations for an alternative diagnosis should be performed(3).

Literature shows that patients with atherosclerotic CMI most likely have atherosclerosis on other sites as well, e.g. coronary artery disease, peripheral artery disease(2, 4). The prevalence of CVD in patients with CMI in our clinical studies was high varying from 49% - 73% (Table 1) and the presence of CVD was a predictor for the score chart of CMI as described in **Chapter 3.**

Table 1. Characteristics of CMI patients described in this thesis.

	CMI patients *Cohort Chapter 3* n=93	**CMI patients** *Cohort Chapter 5* n=23	**CMI patients** *Cohort Chapter 9* n=37	**CMI patients** *Cohort Chapter 11* n=28
Patient characteristics				
Age (y)	65.8±14.4	60.7±15.6	65.3±10.9	68.5±10.7
Female	62.4%	47.8%	54.1%	60.7%
Hypertension*	66.7%	65.2%	29.7%	55.6%
Ever smoked	85.9%	78.3%	63.9%	96.3%
Dyslipidemia#	67.4%	59.1%	27.8%	51.9%
Diabetes	26.9%	26.1%	8.1%	18.5%
BMI at presentation (kg/m^2)	23.5±5.1	24.0±4.6	20.7±5.0	23.3±5.3
History of CVD	73.1%	60.9%	48.6%	71.4%
Presenting symptoms				
Symptom duration (months)	18.0±31.4	21.3±36.8	35.3±67.8	11.3±8.3
Abdominal pain	94.6%	91.3%	94.6%	92.9%
Postprandial pain	70.7%	91.3%	70.3%	67.9%
Exercise related pain	28.7%	36.4%	48.6%	25.0%
Nausea	60.0%	39.1%	45.9%	57.9%
Diarrhea	36.8%	17.4%	18.9%	44.4%
Weight loss	81.7%	56.5%	73.0%	59.3%

Data are presented as N (percentages) or as mean ± SD. *Hypertension was defined as a blood pressure of ≥140/90 mmHg or use of antihypertensive medication. #Dyslipidemia was defined as LDL-C >4.2 mmol/L or HDL-C <0.9 mmol/L or use of lipid lowering medication.
CMI = chronic mesenteric ischemia; BMI = body mass index; CVD = cardiovascular disease.

VLS

In 2004 Benaron et al. published the first study on endoscopic VLS measurements in 10 patients undergoing upper GI endoscopy(5). They demonstrated the feasibility of VLS measurements to measure oxygen saturation during endoscopy and they demonstrated that VLS was a sensitive technique to show hypoxia(5). In 2007 Friedland et al. published a preliminary study on the use of VLS to detect GI ischemia(6). They performed VLS measurements in 30 healthy volunteers and 3 patients with CMI. The reported normal oxygen saturation in the duodenum and jejunum was 60-73% and the saturation of ischemic areas was 16-30% increasing to 51-60% after revascularization. In 2011 van

Noord et al. published a prospective cohort study of 121 patients suspected of CMI and determined the diagnostic accuracy of VLS during upper GI endoscopy for the detection of GI ischemia(7). Cut-off values for GI ischemia were determined: antrum of the stomach <63%, duodenal bulb <62% and descending duodenum <58%. The sensitivity of these cut-off values for CMI is 90% and the specificity is 60%. Since the publication of van Noord et al., VLS is used in clinical practice for the diagnostic work-up of CMI.

The study by Friedland et al. demonstrated that the VLS-measurements are easy to perform without a steep learning curve and with a good interobserver reliability with an average absolute difference of 2% between an experienced VLS endoscopist (>200 cases) versus a limited experienced VLS endoscopist (<10 cases)(6). However, both interobserver and intraobserver reliability had not been determined at that time. We show in **Chapter 4** a fair to good observer reliability of VLS during upper GI endoscopy with, as expected, a better intraobserver reliability than interobserver reliability.

Further validation of endoscopic VLS measurements was performed in **Chapter 6** in a porcine model study**.** We compared VLS measurements with calibrated μPO_2 measurements and show an inverse relationship of the mucosal oxygen saturation measurements by VLS with FiO_2. Furthermore, we show that VLS still measured a reasonable oxygen saturation 25 minutes after asystole. These findings confirm the idea that VLS measures mixed venous oxygen saturation instead of the mucosal capillary hemoglobin oxygen saturation. It is not known whether the mixed venous oxygen saturation is reliable to assess ischemia of the GI tract.

Spectros, the manufacturer of the T-Stat 303 Microvascular Oximeter, states that the measurement surface must be cleaned of any bile remnants since these will influence the measured VLS values. The exact influence of bile on the VLS values was not investigated yet. We show in **Chapter 6** a significant influence of different bile mixtures on the measured VLS values. The exact influence, an increase of the measured VLS values or a decrease of the measured VLS values, was dependent of the sort of bile mixture present (porcine bile mixture from the stomach or from the small bowel). Our results assume that the exact content of the bile and also the amount of bile present and the thickness of the bile layer influence the light absorption by the bile and subsequently effect the measured VLS value. Our results confirm the advice to remove any fluid on the measurement surface before performing the VLS measurements.

In **Chapter 5** we assessed the hypothesis that VLS measurements after a meal would have a higher discriminative ability for the diagnosis of CMI than VLS measurements in fasting state, since CMI patients are usually symptomatic after a meal due to increased oxygen demand. Surprisingly, we found that postprandial VLS measurement do not provide additional discriminative ability for the diagnosis of CMI. Possibly, this result is also an effect of the finding in Chapter 6 that VLS measures mixed venous oxygen saturation instead of the mucosal capillary hemoglobin oxygen saturation. Most likely, postprandial hyperemia has less influence on the oxygen level of the venous compartment than on the oxygen level of the microvascular arterial compartment.

Table 2 shows an overview of the reported normal values of VLS measurements in the literature and Table 3 shows the reported VLS values in patients with CMI in literature. The two studies of van Dijk et al. are part of this thesis (**Chapter 4** and **Chapter 5**). The overall trend shown in Table 2 and Table 3 is that VLS values are lower in the distal part of the upper GI tract. However, the normal values provided in the early publications of Benaron et al.(5) and Friendland et al.(6) are higher than those found by our group(8, 9) (Table 2). A hypothesis could be that normal values for GI mucosal saturation are age related and possibly comorbidity related. In **Chapter 5** we performed VLS measurements in healthy controls (mean age 35.2 ± 8.1 years, smoking 43.8%, dyslipidemia 0.0%, diabetes 0.0%, no presenting symptoms, hypertension 6.3% and 0.0% history of CVD) and no-CMI patients (mean age 59.1±13.2 years, smoking 81.1%, dyslipidemia 40.5%, diabetes 13.5%, presenting symptoms as abdominal pain 86.5% and weight loss 64.9%, hypertension 43.2% and 35.1% history of CVD). The preprandial mucosal oxygen saturation levels between the healthy controls and no-CMI patients were not significantly different in any of the three measurements locations, which did not confirm the hypothesis that normal values for GI mucosal saturation are age related and possibly comorbidity related.

Table 2. Overview of described normal values of endoscopic VLS in literature.

	Antrum	Duodenal bulb	Descending duodenum
Benaron et al. 2004(5) Control patients	70 (4) n=5	-	71 (3) n=10
Friedland et al. 2007(6) Healthy controls and no-CMI patients	72 (4) n=30	-	66 (5) n=25
Van Noord et al. 2011(7) No-CMI patients	66 (4) n=30	62 (5) n=29	59 (5) n=31
Van Dijk et al. 2018(8) Control patients	61 (4) n=24	56 (4) n=24	53 (4) n=24
Van Dijk et al. 2019(9) Healthy controls	62 (60-65) n=16	58 (54-63) n=16	54 (49-56) n=16
Van Dijk et al. 2019(9) no-CMI patients	61 (60-63) n=37	58 (55-60) n=37	55 (51-57) n=37

VLS measurements in percentages described as mean (SD) or median (interquartile range).

Table 3. Overview of described ischemic values of endoscopic VLS in literature.

	Antrum	Duodenal bulb	Descending duodenum
Van Noord et al. 2011(7)	63.4 (4.8) n=85	59.3 (4.9) n=80	53.9 (6.2) n=89
Van Dijk et al. 2019(9)	59 (55-62) n=23	54 (51-58) n=23	51 (48-53) n=23

VLS measurements in percentages described as mean (SD) or median (interquartile range)

In conclusion, we determined several limitations of endoscopic VLS measurements for the diagnosis of CMI: 1. VLS seems to measure the mixed venous oxygen saturation rather than the mucosal capillary hemoglobin oxygen saturation, 2. the measurement location for VLS should be free of any bile fluids since bile influences the measurement values, 3. peristaltic movements influence the VLS measurements and 4. the discriminatory value of VLS is not improved in a postprandial state. Given these limitations and a sensitivity of 90% and a specificity of 60% for CMI, there is a need for a new easy-to-use and reliable functional test to detect GI ischemia.

Functional test to assess GI ischemia: what's on the horizon?

In **Chapter 7** we show that measurements of oxygen-dependent delayed fluorescence of ALA-induced PpIX during upper GI endoscopy are feasible and safe. We demonstrated measurements of an oxygen dependent signal during upper GI endoscopy in healthy volunteers. The next step would be to perform these endoscopic measurements in patients suspected of CMI to assess the discriminative ability of oxygen-dependent delayed fluorescence of ALA-induced PpIX measurements for the diagnosis of CMI. Furthermore, measurements during enteroscopy could be performed to assess mucosal ischemia of the small bowel vascularized by the SMA. Since upper GI endoscopy is usually performed in the diagnostic work-up for CMI to exclude other diagnosis as peptic ulcer, a functional test performed during upper endoscopy is not invasive for the patient. In contrast, pressure measurements performed during DSA as described in **Chapter 11** are not eligible to include in the standard diagnostic work-up for patients suspected of CMI, since DSA is an invasive investigation, currently reserved for the patients with a consensus diagnosis of CMI. Pressure measurements may have additional value to guide clinical decision-making during a DSA procedure, especially in case of single vessel disease or a mesenteric stenosis of 50-70%.

If endoscopic oxygen-dependent delayed fluorescence of ALA-induced PpIX measurements have shown to be discriminative for the diagnosis of CMI, the technique can be further refined. Endoscopic oxygen-dependent delayed fluorescence of ALA-induced PpIX measurements have the potential to become the new functional test for detection of mucosal ischemia.

THERAPY FOR CMI

Covered stents versus bare-metal stents

In **Chapter 8** we present a study protocol for a multicenter randomized controlled trial in patients with atherosclerotic CMI to compare covered stents versus standard care bare-metal stents. Oderich et al.(10) show better patency rates for covered stents than bare-metal stents in their retrospective cohort study. However, prospective confirmation is needed to issue any recommendations for the use of covered stents as standard care in atherosclerotic CMI patients. For long mesenteric arterial stenosis the covered stent is not applicable since the covered stent will obstruct blood flow when mesenteric side-branches are over-stented. However, mesenteric arterial stenoses are often ostial

stenoses(11, 12). Furthermore, this trial will generate data on the quality of life of CMI patients at baseline and after revascularization. Quality of life studies are currently lacking in literature for patients with CMI.

Single vessel

Revascularization in mesenteric multi-vessel disease is generally accepted, however controversy exists on single vessel disease. The presence of a large mesenteric collateral network should prevent symptomatic disease from single vessel stenosis. However, we show in **Chapter 9** that symptomatic single vessel disease does exist. The challenge is to select those patients with single vessel disease who will benefit from revascularization. We show that 73% of revascularized patients with single vessel atherosclerotic disease of the CA or SMA with GI symptoms and confirmed mucosal ischemia experienced long-term symptom relief. Given the increase in abdominal imaging and as a consequence an increase in incidentally discovered single vessel mesenteric disease this is a relevant finding for clinical practice. When a single vessel mesenteric arterial stenosis based on atherosclerosis is incidentally discovered and a patient reports GI symptoms, mucosal ischemia has to be confirmed before revascularization. This should lead to less overtreatment in this patient group.

Approach of endovascular mesenteric intervention

Current guidelines state that TBA and TFA are the approaches for mesenteric arterial interventions. Given the positive experience of TRA in coronary artery interventions we described in **Chapter 10.1** a retrospective cohort study comparing TRA with TBA and TFA for mesenteric arterial interventions. We show that TRA is a feasible and safe approach, comparable with TFA. TBA shows significantly more major complications. Given the retrospective design of the study, prospective confirmation is needed, preferably through a randomized controlled trial. Posham et al.(13) published in 2016 a large retrospective cohort study of 1,512 non-coronary endovascular procedures per TRA, including mesenteric arterial procedures. Their study shows that TRA is safe and well-tolerated for non-coronary interventions, however they did not specify their results for mesenteric arterial interventions. They performed TRA according the description of Fischman et al.(14). The occurrence of a severe complication during a TRA procedure as described in **Chapter 10.2** resulted in the fact that now in every patient planned for TRA a radial artery (RA) diameter assessment using ultrasound is performed. Since diameter assessment of the RA using ultrasound was not described in the publication

of Fischman et al.(14), it should be added to the standard procedure to prevent severe complications such as a total rupture of the RA.

Pressure measurements

Intra-arterial pressure measurements are used during coronary artery interventions to define the clinical significance of a coronary artery stenosis. In **Chapter 11** we assessed the feasibility of intra-arterial pressure measurements to define a clinical significant mesenteric arterial stenosis. We show that mesenteric intra-arterial pressure measurements are able to predict the clinical significance of a stenosis. Since consensus on the use of pressure measurements for mesenteric stenosis is lacking, this study is the first step in defining cut-off values of pressure measure measurements to guide clinical decision making. We propose a cut-off value based on our cohort analysis, however this needs to be confirmed prospectively.

As mentioned before, pressure measurements will not be added to the standard diagnostic work-up of CMI suspected patients, given the invasive character of the measurements. Pressure measurements are reserved for those patients with a consensus diagnosis of CMI who are planned for angiography to guide the decision of performing revascularization of a mesenteric vessel or not.


CHAPTER
12.3

Future perspectives

The level of evidence for recommendations on the clinical management of CMI is low, since literature specific on CMI is scarce and prospective cohort studies and randomized controlled trials with sufficient patient numbers are lacking. Recently, three guidelines for CMI management have been published: a clinical practice guideline of the ESVS(3), criteria on radiological management by the American College of Radiology (ACR)(15) and quality improvement guidelines for endovascular revascularization by the Society of Interventional Radiology (SIR)(16). Multidisciplinary guidelines on CMI are awaited in 2020 from United European Gastroenterology (UEG), in collaboration with European Association for Gastroenterology, Endoscopy and Nutrition (EAGEN), European Society of Gastrointestinal and Abdominal Radiology (ESGAR), Cardiovascular and Interventional Radiological Society of Europe (CIRSE), Netherlands Association of Hepatogastroenterologists (NVMDL), Hellenic Society of Gastroenterology (HSG) and Dutch Mesenteric Ischemia Study group (DMIS). Specific topics for future research on CMI are summarized in this chapter.

DIAGNOSIS

The most important limitation of clinical studies on CMI is the absence of a gold standard test to diagnose CMI. A definitive diagnosis of CMI is currently established when symptom relief is reported after technically successful therapy for CMI. However, symptom relief is a subjective outcome and only patients with a consensus diagnosis of CMI are eligible for therapy. Furthermore, the current diagnostic work-up is cumbersome and time-consuming. Several diagnostic investigations have to be performed for every patient suspected of CMI. Therefore, the quest for a gold standard test to diagnose CMI is the most important topic for research on CMI. When a potential functional test has been discovered, the discriminative ability of this potential test has to be validated in patients suspected of CMI. Also the test must be performed before and after successful therapy to demonstrate the ability of the test to detect improvement after therapy.

In **Chapter 4, Chapter 5** and **Chapter 6** we validated the currently used functional test VLS. We concluded that VLS measures the mixed venous compartments and further research is needed to establish whether GI ischemia is optimally assessed by mucosal hemoglobin saturation of the mixed venous compartment.

In **Chapter 7** we performed a pilot study of a novel promising technique to measure oxygen levels in the cells of the GI tract during upper GI endoscopy. We show that

the ALA-induced PpIX measurements performed during upper endoscopy are feasible, oxygen dependent and safe. Further research needs to be conducted to assess if the ALA-induced PpIX measurements have discriminative ability for CMI patients and to define site specified cut-off values for GI mucosal ischemia. Furthermore, calibrations constants in the human GI tract are unknown and therefore we presented our measurements as reciprocal lifetimes 1/τ (μs-1). The assessment of calibrations constants for the human gastro-duodenal tract will result in presentation of the measurements in a more general and better comparable and understandable unit as mmHg. Our pilot-study shows very short delayed fluorescent lifetimes in the gastric antrum, possibly due to the histological composition and function of the gastric antrum mucosa which interferes with the excitation light of the delayed fluorescent signal. The ability of these cells to accumulate PpIX might be lower due to a relatively slow cellular turnover compared to the duodenal mucosal cells which results in unreliable short lifetimes. This hypothesis should be studied in the future. Furthermore, the design of the endoscopic probe could be improved by developing a pressure sensor on the probe tip, to avoid unintended application of pressure on the GI mucosa while measuring. Finally, the optimal excitation wavelength for measurements in the GI tract could be determined. We used 515 nm wavelength since this wavelength is used by the COMET device.

Mesenteric blood flow measurements performed by magnetic resonance (MR) imaging could be a useful functional test for CMI. Several studies performed mesenteric blood flow measurements with MRI both in fasting state and post-prandial state in healthy volunteers and CMI patients(17-21). Physiologically, the flow in the mesenteric vessels increases after a meal referred to as hyperemia. However, this increase in post-prandial flow compared to pre-prandial appears to be less pronounced in CMI patients compared to the healthy volunteers. In some CMI patients, even a decrease of the post-prandial blood flow compared to the pre-prandial blood flow was observed. MR blood flow measurements after food stimulation might be able to distinguish patients with CMI from patients without CMI. A clinical study, including patients suspected of CMI, is currently performed by our group using this MR blood flow measurement technique in fasting state and after the intake of nutritional drink.

A simple blood test to determine a CMI specific biomarker would be the ultimate goal for the diagnosis of CMI. A sensitive and specific biomarker in blood however is currently not yet identified.

Currently, validated questionnaires specific for CMI do not exist. Future research on CMI would also be more accurate and reliable if CMI reporting standards would be developed and validated, along with specific CMI patient reported outcome measures (PROMs).

In **Chapter 3** an updated version of the prediction model for CMI is presented. Further research on this topic would consists of prospective validation of this updated version of the prediction model in a new multicenter cohort and assessment of the cost-effectiveness of the model used with the proposed risk stratified strategy.

Finally, literature on chronic NOMI is scarce. Studies in these patients are needed to better understand this entity and to improve diagnostic and therapeutic strategies.

THERAPY

The protocol for a multi-center randomized controlled trial of covered versus bare-metal stents is described in **Chapter 8.** The CoBaGI trial is performed by our group and inclusion has currently been completed. The two-years follow-up period after stent-placement has to be awaited before the final results can be published. We hypothesized that covered stents will have better patency rates than bare metal stents. If our hypothesis is confirmed, covered stents will become standard of care in the future. The CoBaGI trial will also provide data on the quality of life of CMI patients and cost-effectiveness. Further research topics on endovascular therapy of CMI will be the assessment of the best strategy for in-stent stenosis: covered stent placement or PTA alone, follow-up strategy after revascularization to detect in-stent stenosis (routine radiologic assessment or symptom driven radiologic assessment) and assessment of anti-platelet strategy for mesenteric interventions, since consensus on anti-platelet strategy is lacking for this specific patient group.

We show in **Chapter 10** that radial approach of mesenteric endovascular interventions is feasible and safe. Since we performed a retrospective cohort study, prospective confirmation of our results is needed. A randomized controlled trial comparing brachial,

femoral and radial approach would be the most ideal design. Besides technical success rate and complication rate, other outcome measures to include in such a study are procedure time, radiation exposure and the amount of contrast agents used.

Interventional cardiologists use intravascular pressure measurements to guide treatment decisions. We show in **Chapter 11** that pressure measurements during mesenteric endovascular interventions are feasible to perform and predictive of clinical response. We suggest cut-off values but these need to be validated.

In **Chapter 9** we show that a single vessel mesenteric stenosis may cause symptomatic disease and that if the patients are selected carefully, 73% of the treated patients will experience symptom relief after successful revascularization. Since this was a retrospective cohort study, prospective confirmation, preferably by others, is needed. Furthermore, our cohort study consisted of patients with single vessel stenosis based on atherosclerosis. Future studies with inclusion of patients with single vessel disease based on MALS would of interest, since the existence of MALS is a debate in literature.

DUTCH MESENTERIC ISCHEMIA STUDY GROUP (DMIS)

Multicenter, multidisciplinary collaboration is needed to perform high quality studies on CMI. The Dutch Mesenteric Ischemia Study group (DMIS) is a Dutch multicenter and multidisciplinary study group with focus on mesenteric ischemia. The DMIS is founded in 2015. The aim of the DMIS is to improve diagnostics, therapy and medical care for patients with acute and chronic mesenteric ischemia through scientific research, consultation and centralization. The most important features of the DMIS are: multidisciplinary collaboration, multicenter studies, joint discussion about study protocols and joint publication with inclusion of all participating hospitals. Twice a year, a study group meeting is organized in Utrecht. On the map (Figure 1) the centers on the DMIS mailing list are shown and the centers with a red bullet are actively participating in a clinical trial at the moment. Publications described in this thesis on behalf of the

DMIS are the validation of the score chart to predict the risk of CMI **(Chapter 3)**, the review on the clinical management of CMI (**Chapter 1.1** is based on this publication) and the protocol for the multicenter randomized controlled trial of covered versus bare-metals stents (**Chapter 8**).

Figure 1. Map of the Netherlands showing all centers on the DMIS mailing list. The centers with a red bullet are actively participating in a clinical trial at the moment.

Several clinical studies and projects are currently pursued by the DMIS. First, a randomized controlled trial on celiac artery release versus sham procedure for patients with MALS (CARoSO) is under construction, to finally end the debate on the existence of MALS. Second, a single-center study on pre-prandial and postprandial MR blood flow measurements for the diagnosis of CMI is currently performed by our center, however multicenter implementation by the DMIS would accelerate the inclusion and increase the generalizability of the results. Thereby, endoscopic ALA-induced PpIX measurements in patients suspected of CMI will be added to the study protocol to assess the discriminative ability of these measurements for the diagnosis of CMI. Furthermore, the DMIS is implementing a patient registry and biobank initiative for

mesenteric ischemia patients. Finally, the DMIS was one of the initiators of the upcoming CMI guidelines of the UEG.

Conclusion future perspectives

The perfect future for research on CMI would be a time in which well-designed, high quality, clinical studies are conducted, prospective and if applicable in a randomized controlled setting, under the auspician of a multicenter, multidisciplinary (international) study group. Such studies should aim to find and validate a new functional test eligible as gold standard test for diagnosis of CMI and to determine the best therapeutic strategy for CMI patients in an evolving field of therapeutic innovative developments. The DMIS was established with exactly those goals in mind.


CHAPTER
12.4

Conclusion

CONCLUSION

The incidence of CMI is increasing and is expected to increase even further the upcoming years due to the aging population. The current diagnostic work-up of CMI is cumbersome and time-consuming, due to the absence of a specific test. Literature on different aspects of therapy specific for CMI is scarce. This thesis aims to provide insights in different aspects of the diagnosis and therapy of CMI to optimize the diagnostic work-up and therapy for this specific patient group. We validated a score chart to predict the risk of CMI and developed an update of the prediction model with inclusion of the cause of CA stenosis to stratify patients suspected of CMI in a low-risk, intermediate-risk and high-risk group to guide clinical decision making. We show that VLS measurements during upper GI endoscopy are reproducible with a fair to good observer reliability with intraobserver reliability being better than interobserver reliability. Since VLS measurements are performed in fasting state and CMI patients are mostly symptomatic after a meal due to increased oxygen demand, we performed VLS measurements after luminal feeding to determine the discriminative ability of postprandial VLS measurements. We show that postprandial VLS measurements have no added benefit for the diagnosis of CMI. Furthermore, we show that VLS measures the mixed venous hemoglobin oxygen saturation and not the mucosal capillary hemoglobin oxygen saturation and that the presence of bile significantly influenced the measured VLS values. Given the limitations of VLS for the diagnosis of CMI, we performed a feasibility study of a novel promising technique to measure mitochondrial oxygen levels: delayed fluorescence measurements of ALA-induced PpIX. We demonstrate that this technique is feasible and safe to perform during upper GI endoscopy and we detected an oxygen-dependent signal with this technique. In the part of the thesis on therapy for CMI we presented a study protocol for a multicenter randomized controlled trial on covered stents versus bare-metal stents for atherosclerotic CMI. Furthermore, we show in a retrospective cohort analysis that revascularization of single vessel disease of the CA or SMA in patients with GI symptoms and confirmed mucosal ischemia resulted in long-term symptom relief in 73% of patients. We assessed the feasibility and safety of TRA for mesenteric arterial endovascular procedures compared to TFA and TBA and show that TRA is a feasible and safe approach comparable to TFA. TBA was associated with a significantly higher major complication rate. We described one severe complication of a TRA procedure complicated by a total rupture of the RA. Finally, we show that intra-arterial pressure measurements performed during angiography are able to predict

the clinical significance of a mesenteric arterial stenosis. In conclusion, research on diagnosis and treatment for CMI is evolving. However collaboration in multicenter and multidisciplinary study groups is needed to conduct high-quality research with prospective inclusion of sufficient patient numbers.

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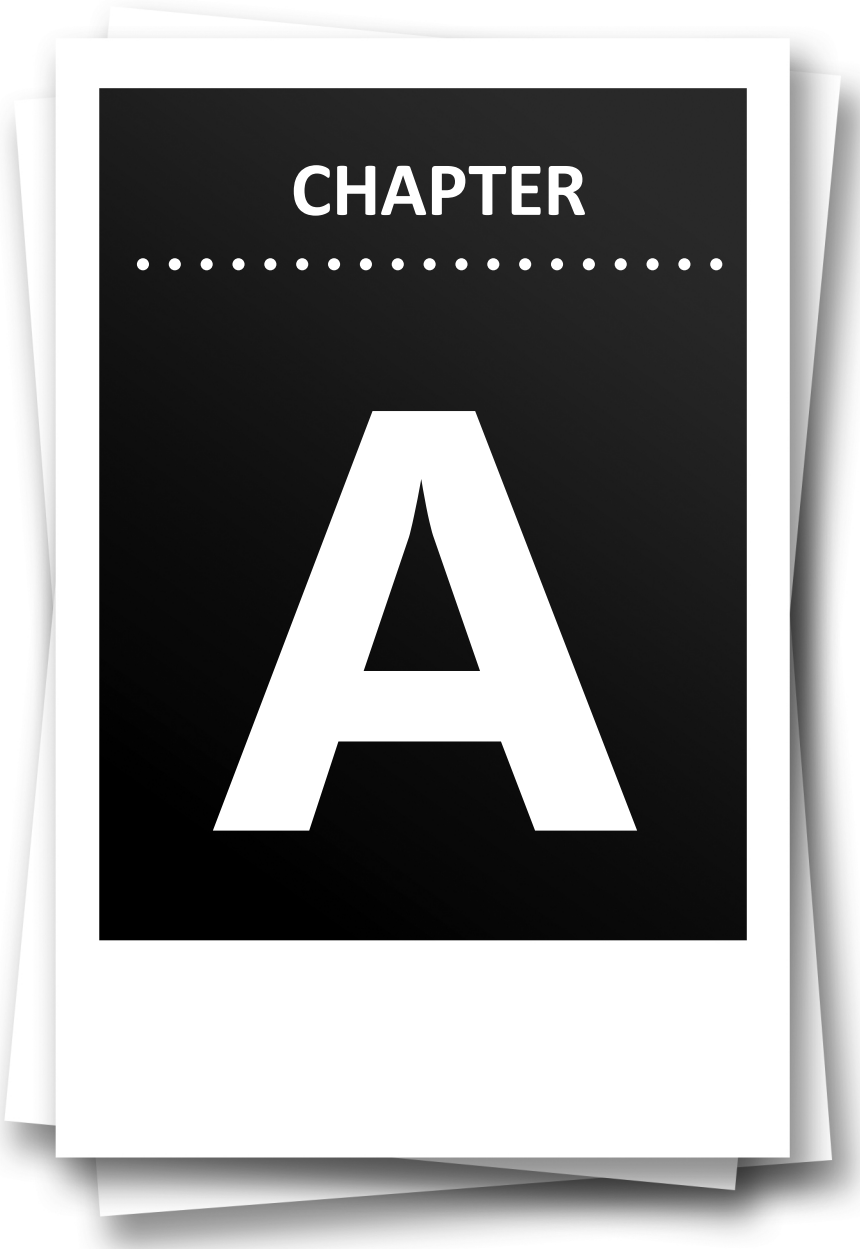
CHAPTER
A

Appendices

NEDERLANDSE SAMENVATTING

Dit proefschrift heeft tot doel inzicht te verschaffen in de verschillende aspecten van de diagnose en de behandeling van chronische mesenteriaal ischemie (CMI) om zo de diagnose en de behandeling voor deze patiëntengroep te optimaliseren. De ziekte CMI wordt geïntroduceerd in **Deel I** met een overzicht van de definitie, epidemiologie, etiologie, klinische presentatie, diagnostiek, therapie en klinische uitkomst van CMI en de anatomie van de mesenteriale vasculatuur in **Hoofdstuk 1.1**, gevolgd door de doelen en de opzet van de thesis in **Hoofdstuk 1.2**.

Diagnose

In **Deel II** worden de verschillende aspecten van de huidige diagnostische work-up voor CMI en strategieën en inzichten om de diagnostiek te optimaliseren besproken. In **Hoofdstuk 2** wordt een overzicht van de huidige beeldvormende modaliteiten voor de mesenteriale vasculatuur zoals duplex echografie, computer tomografie angiografie, magnetische resonantie angiografie en digitale substractie angiografie gegeven. **Hoofdstuk 3** beschrijft de externe validatie van een predictiemodel, reeds gepubliceerd door onze studiegroep, om het risico op CMI in te schatten op basis van 5 eenvoudige voorspellers (vrouwelijk geslacht, aanwezigheid van gewichtsverlies, aanwezigheid van hart- en vaatziekten (HVZ), mate van stenose van de arteria coeliacus (AC); en mate van stenose van de arteria mesenterica superior (AMS). Het huidige predictiemodel presteerde goed in het nieuwe validatie cohort. Deskundigen op het gebied van CMI betwistten echter de afwezigheid van de etiologie van de AC-stenose (median arcuate ligament syndrome, atherosclerose) als voorspeller in het gepubliceerde predictiemodel. Daarom hebben we het model aangepast op basis van de prestatie van het model in het gecombineerde originele en validatiecohort (totaal 666 patiënten verdacht van CMI), waarbij we nu wel de oorzaak van AC-stenose hebben meegenomen. Dit ge-update model bestaat uit de voorspellers: aanwezigheid van gewichtsverlies, aanwezigheid van HVZ, mate van AC-stenose gecombineerd met de oorzaak van AC-stenose en mate van AMS-stenose. Dit ge-update predictiemodel toont een uitstekend onderscheidend vermogen met een absoluut laag risico op CMI van 19%, een gemiddeld risico van 45% en een hoog risico op CMI van 92%. Het ge-update voorspellingsmodel is een handig hulpmiddel wat gebruikt kan worden bij de klinische besluitvorming ten aanzien van de diagnostiek. We stellen een afwachtend beleid voor bij de patiënten gestratificeerd als laag risico op CMI, bij de patiënten met een gemiddeld risico op CMI stellen we een

aanvullende functionele test voor en we stellen onmiddellijke vasculaire interventie voor bij de patiënten gestratificeerd als hoog risico op CMI. Deze strategie zou moeten leiden tot minder onnodige diagnostische procedures voor patiënten zonder CMI en een betere identificatie van patiënten met CMI met snellere behandeling, wat uiteindelijk zou moeten leiden tot minder belasting van de patiënt en lagere gezondheidskosten.

Visible light spectroscopy (VLS) uitgevoerd tijdens gastroduodenoscopie wordt in de klinische praktijk gebruikt in de diagnostische work-up van CMI. Interobserver en intraobserver validatie van endoscopische VLS wordt niet beschreven in de literatuur; daarom hebben we een observer validatie onderzoek voor VLS metingen uitgevoerd. We tonen in **Hoofdstuk 4** aan dat de observer validiteit van VLS redelijk tot goed is, waarbij de intraobserver betrouwbaarheid beter is dan de interobserver betrouwbaarheid. VLS-metingen tijdens gastroduodenoscopie zijn reproduceerbaar en onze bevindingen ondersteunen het gebruik van VLS als onderdeel van de diagnostiek naar CMI.

In **Hoofdstuk 5** hebben we gekeken of postprandiale VLS-metingen het onderscheidend vermogen van VLS-metingen verhogen omdat CMI-patiënten na een maaltijd meestal klachten ervaren door postprandiale hyperemie. Met een prospectieve cohortstudie tonen we aan dat postprandiale VLS-metingen het onderscheidend vermogen voor de diagnose van CMI niet verhogen ten opzichte van de nuchtere metingen.

Hoofdstuk 6 beschrijft de validatie van de VLS-techniek op basis van 3 experimenten in een big studie. Eerst hebben we de VLS-waarden vergeleken met gekalibreerde microvasculaire zuurstofspanning (μPO_2) meetwaarden op verschillende FiO_2-niveaus. We hebben aangetoond dat de VLS-waarden afnemen als de FiO_2 toeneemt in tegenstelling tot de µPO2-waarden die juist toenemen als de FiO_2 toeneemt waarbij een grote spreiding te zien is van de gemeten VLS-waarden en FiO_2-niveaus met een slechte lineaire correlatie. Als tweede hebben we het effect van de aanwezigheid van gal op de gemeten VLS-waarden bekeken. We hebben hierbij aangetoond dat de aanwezigheid van gal een significante invloed heeft op de gemeten VLS-waarden. Ten slotte hebben we de VLS-waarden en μPO_2-waarden vergeleken tijdens asystolie. We tonen aan dat de VLS-waarden, in tegenstelling tot de μPO_2-waarden, in de eerste 25 minuten na asystolie niet dalen naar een waarde van 0. Onze bevindingen ondersteunen het idee dat VLS de zuurstofsaturatie van het gemengd veneuze compartiment meet en niet de zuurstofsaturatie van het mucosale capillaire compartiment. Gezien het significante

effect van de aanwezigheid van gal op de gemeten VLS-waarden, adviseren wij om, voordat VLS-metingen worden uitgevoerd, vloeistof op de gastro-intestinale mucosa te verwijderen.

In **Hoofdstuk 7** hebben we een pilot-studie uitgevoerd van een nieuwe veelbelovende techniek om zuurstof te meten op mitochondriaal niveau tijdens gastroduodenoscopie: vertraagde fluorescentiemetingen van 5-aminolevulinezuur (ALA) geïnduceerd protoporfyrine IX. We tonen met deze studie in gezonde vrijwilligers aan dat zuurstofafhankelijke vertraagde fluorescentie metingen uitvoerbaar zijn tijdens gastroduodenoscopie en we detecteren met deze techniek een zuurstofafhankelijk signaal. We hebben bepaald dat de optimale orale dosis van ALA 5 mg/kg is en dat de bulbus en het duodenum descendens geschikt zijn als meetlocaties. Toediening van butylscopolamine tijdens de procedure had geen invloed op de gemeten waarden.

Behandeling

Deel III omvat verschillende therapeutische elementen van CMI met de focus op endovasculaire revascularisatie. Een retrospectieve cohortstudie heeft aangetoond dat de doorgankelijkheid van covered stents beter is dan de doorgankelijkheid van bare-metal stents in patiënten met atherosclerotisch CMI. **Hoofdstuk 8** beschrijft een studieprotocol voor een multicenter gerandomiseerde studie waarin covered stents worden vergeleken met bare-metal stents in patiënten met CMI op basis van atherosclerose om dit gevonden resultaat prospectief te bevestigen.

In **Hoofdstuk 9** hebben we middels een retrospectieve cohortanalyse de lange termijn klinische succespercentages vergeleken van revascularisatie bij eenvatslijden van de AC of AMS. We tonen met deze studie aan dat 73% van de patiënten met CMI op basis van eenvatslijden met gastro-intestinale symptomen en bewezen mucosale ischemie blijvend verbetering van symptomen heeft na revascularisatie.

Niet-coronaire endovasculaire interventies worden uitgevoerd via de arteria brachialis of arteria femoralis. Literatuur op het gebied van coronaire interventies toont echter lagere complicatie percentages voor procedures via de arteria radialis dan voor procedures via de arteria brachialis of arteria femoralis met vergelijkbare procedurele en klinische uitkomsten. We hebben in **Hoofdstuk 10.1** de haalbaarheid en veiligheid van radialis toegang voor endovasculaire mesenteriaal procedures vergeleken met

femoralis en brachialis toegang voor deze specifieke procedures. We tonen aan dat radialis toegang een veilige en haalbare benadering is voor mesenteriale procedures vergelijkbaar met femoralis toegang, terwijl brachialis toegang een significant hoger complicatiepercentage laat zien. In **Hoofdstuk 10.2** beschrijven we een ernstige complicatie van een endovasculaire procedure via de arteria radialis. Bij een jonge patiënte ontstond een ruptuur van de arteria radialis na een stentplaatsing van de arteria brachiocephalica via radialis toegang.

Intra-arteriële drukmetingen worden uitgevoerd tijdens procedures van de kranslagaders om de klinische betekenis van een stenose van de kransslagader te bepalen. In **Hoofdstuk 11** hebben we een cohortstudie uitgevoerd om de haalbaarheid te bepalen van intra-arteriële drukmetingen om een klinisch significante mesenteriaal stenose te voorspellen. We tonen aan dat we de klinische significantie van een mesenteriaal stenose kunnen voorspellen met behulp van deze drukmetingen.

In **Deel IV** vatten we de belangrijkste bevindingen van dit proefschrift samen gevolgd door de algemene discussie van dit proefschrift. Hierna wordt er richting gegeven voor toekomstig onderzoek op het gebied van CMI en het laatste deel van het proefschrift eindigt met de algemene conclusie.

ABBREVIATIONS

ACNES	Anterior Cutaneous Nerve Entrapment Syndrome
ACR	American College of Radiology
ALA	5-aminolevulinic acid
AMI	acute mesenteric ischemia
AUC	area under the curve
BMI	body mass index
BMS	bare-metal stents
CA	celiac artery
CI	confidence interval
CIRSE	Cardiovascular and Interventional Radiological Society of Europe
CMI	chronic mesenteric ischemia
CS	covered stents
CT	computed tomography
CTA	computed tomography angiography
CVD	cardiovascular disease
DMC	data monitoring committee
DMIS	Dutch Mesenteric Ischemia Study group
DSA	digital subtraction angiography
DUS	duplex ultrasound
EAGEN	European Association for Gastroenterology, Endoscopy and Nutrition
EDV	end diastolic velocity
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
ESVS	European Society of Vascular Surgery
FFR	fractional flow reserve
FMD	fibromuscular dysplasia
GFR	glomerular filtration rate
GI	gastro-intestinal
HSG	Hellenic Society of Gastroenterology
IBS	irritable bowel syndrome
I-FAPB	intestinal fatty-acid binding protein

IMA	inferior mesenteric artery
IMV	inferior mesenteric vein
INR	international normalized ratio
ICC	intraclass correlation coefficient
IQR	interquartile range
LSA	left subclavian artery
MAL	median arcuate ligament
MALS	median arcuate ligament syndrome
mitoPO_2	mitochondrial oxygen tension
µPO_2	microvascular oxygen tension
MR	magnetic resonance
MRA	magnetic resonance angiography
MDCT	multi-detector computed tomography
NA	numerical aperture
NIS	National (Nationwide) Inpatient Sample
NOMI	non-occlusive mesenteric ischemia
NVGE	Nederlandse Vereniging voor Gastro-enterologie
NVMDL	Netherlands Association of Hepatogastroenterologists
OR	odds ratio
OSMAR	open surgical mesenteric artery repair
Pa	pressure aorta
PCO_2	pressure of carbon dioxide
Pd	palladium
Pd	pressure distal
PMAS	percutaneous mesenteric artery stenting
PO_2	oxygen tension
PpIX	protoporphyrin IX
PpIX-TSLT	protoporphyrin IX-triplet state lifetime technique
PROMs	patient reported outcome measures
PSC	primary sclerosing cholangitis
PSV	peak systolic velocity
PTA	percutaneous transluminal angioplasty
PV	portal vein
RA	radial artery
RF	radio frequency

ROC	receiver-operating characteristics
RR	relative risk
SD	standard deviation
SIR	Society of Interventional Radiology
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SNR	signal-to-noise ratio
SOFDF	Singlet Oxygen Feedback-Induced mechanism
TBA	trans-brachial access
TFA	trans-feoral access
TRA	trans-radial access
UEG	United European Gastroenterology
USA	United States of America
VLS	visible light spectroscopy
WMO	Wet Medisch wetenschappelijk Onderzoek met mensen

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LIST OF PUBLICATIONS

Described in this thesis

1. Louisa J.D. van Dijk, André S. van Petersen, Adriaan Moelker. Vascular imaging of the mesenteric vasculature. *Best Practice & Research: Clinical Gastroenterology 2017;31:3-14.*

2. Louisa J.D. van Dijk, Leon M.G. Moons, Desirée van Noord, Adriaan Moelker, Hence J.M. Verhagen, Marco J. Bruno, Ellen V. Rouwet. Persistent symptom relief after revascularization in patients with single-artery chronic mesenteric ischemia. *Journal of Vascular Surgery 2018;68:779-785.*

3. Louisa J.D. van Dijk, Twan van der Wel, Desirée van Noord, Adriaan Moelker, Hence J.M. Verhagen, Daan Nieboer, Ernst J. Kuipers, Marco J. Bruno. Intraobserver and interobserver reliability of visible light spectroscopy during upper gastrointestinal endoscopy. *Expert Review of Medical Devices 2018;15(8):605-10.*

4. Louisa J.D. van Dijk, Diederik C. Bijdevaate, Adriaan Moelker. Rupture of the radial artery after brachiocephalic stent placement per transradial access. *Journal of Vascular and Interventional Radiology 2018;29:1281-1283.*

5. Rinse Ubbink*, Louisa J.D. van Dijk*, Desirée van Noord, Tanja Johannes, Patricia A.C. Specht, Marco J. Bruno, Egbert G. Mik. Evaluation of endoscopic visible light spectroscopy: comparison with microvascular oxygen tension measurements in a porcine model. *Journal of Translational Medicine 2019;17:65.* *both authors contributed equally

6. Louisa J.D. van Dijk, Jihan Harki, Desirée van Noord, Annemarie C. de Vries, Adriaan Moelker, Hence J.M. Verhagen, Ernst J. Kuipers, Marco J. Bruno. Detection of mesenteric ischemia by means of endoscopic visible light spectroscopy after luminal feeding. *Gastrointestinal Endoscopy 2019;89:94-102.*

7. Louisa J.D. van Dijk, Desirée van Noord, Annemarie C. de Vries, Jeroen J. Kolkman, Robert H. Geelkerken, Hence J.M. Verhagen, Adriaan Moelker, Marco J. Bruno - on behalf of the Dutch Mesenteric Ischemia Study group (DMIS). Clinical management of chronic mesenteric ischemia. *United European Gastroenterology Journal 2019;7(2):179–188.*

8. Louisa J.D. van Dijk, Desirée van Noord, Robert H. Geelkerken, Jihan Harki, Sophie A. Berendsen, Annemarie C. de Vries, Adriaan Moelker, Yvonne Vergouwe, Hence J.M. Verhagen, Jeroen J. Kolkman, Marco J. Bruno - on behalf of the Dutch Mesenteric Ischemia Study group (DMIS). Validation of a score chart to predict the risk of chronic mesenteric ischemia and development of an updated score chart. *United European Gastroenterology Journal 2019;7(9):1261–1270.*

9. Louisa J.D. van Dijk*, Rinse Ubbink*, Luke G. Terlouw, Desirée van Noord, Egbert G. Mik, Marco J. Bruno. Oxygen-dependent delayed fluorescence of protoporphyrin IX measured in the stomach and duodenum during upper gastrointestinal endoscopy. *Journal of Biophotonics 2019;12(10):e201900025.* *both authors contributed equally

10. Louisa J.D. van Dijk, Jihan Harki, Desirée van Noord, Hence J.M. Verhagen, Jeroen J. Kolkman, Robert H. Geelkerken, Marco J. Bruno*, Adriaan Moelker* - on behalf of the Dutch Mesenteric Ischemia Study group (DMIS). Covered stents versus bare-metal stents in chronic atherosclerotic gastrointestinal ischemia (CoBaGI): study protocol for a randomized controlled trial. *Trials 2019;20(1):519.* *both authors contributed equally

11. Louisa J.D. van Dijk, Desirée van Noord, Minke van Mierlo, Diederik C. Bijdevaate, Marco J. Bruno, Adriaan Moelker. Trans-radial access for mesenteric artery endovascular procedures: a safe and feasible technique compared with trans-brachial and trans-femoral access. *In press Journal of Vascular and Interventional Radiology.*

12. Louisa J.D. van Dijk*, Luke G. Terlouw*, Desirée van Noord, Diederik C. Bijdevaate, Marco J. Bruno, Adriaan Moelker. Endovascular pressure measurements to assess the functional severity of mesenteric artery stenoses. *In press Journal of Vascular and Interventional Radiology.* *both authors contributed equally

Book chapter

13. Louisa J.D. van Dijk, Hence J.M. Verhagen. Mesenteric vascular disease. *Encyclopedia of Gastroenterology, 2nd Edition. New York, Elsevier, 2019.*

Other publications

14. Louisa J.D. van Dijk, Bo Jan Noordman, Joris J Scheepers, Klaas A. Hartholt. A young woman with a jejuno-jejunal intussusception. *British Medical Journal Case Reports. 2015.*

15. Twan van der Wel, Louisa J.D. van Dijk, Annemarie C. de Vries. [A man with abdominal bloating] Een man met een opgeblazen gevoel. *Nederlands Tijdschrift voor Geneeskunde 2018;162.*

16. Jihan Harki, Mustafa Suker, M. Sherezade Tovar-Doncel, Louisa J.D. van Dijk, Desirée van Noord, Casper H.J. van Eijck, Marco J. Bruno, Ernst J. Kuipers, Can Ince. Patients with chronic mesenteric ischemia have an altered sublingual microcirculation. *Clinical and Experimental Gastroenterology 2018;11:405-414.*

PHD PORTFOLIO

Name PhD student:	Louisa J.D. van Dijk
PhD period:	December 2014 – Augustus 2019
Erasmus MC department:	Gastroenterology and Hepatology
	Radiology
Promotors:	Prof. dr. M.J. Bruno and Prof. dr. G.P. Krestin
Co-promotors:	Dr. D. Leemreis-van Noord and Dr. A. Moelker

Courses and workshops

	Year	Workload
BROK course, Consultatiecentrum Patiëntgebonden onderzoek (CPO), Erasmus MC, Rotterdam	2015	24 hours
EndNote workshop, Erasmus MC library, Rotterdam	2015	6 hours
Pubmed workshop, Erasmus MC library, Rotterdam	2015	6 hours
Biostatistics for clinicians, Netherlands institute for Health Sciences (NIHES), Rotterdam	2015	40 hours
Integrity in scientific research, Dept. of Medical ethics and Philosophy, Erasmus MC, Rotterdam	2015	16 hours
Basic Introduction on SPSS, Molecular medicine postgraduate school, Rotterdam	2015	23 hours
Introduction in GraphPad Prism, Molecular medicine postgraduate school, Rotterdam	2015	10 hours
Training “Omgaan met groepen voor tutoren”, Erasmus MC, Rotterdam	2015	4 hours
Photoshop & Illustrator workshop, Molecular medicine postgraduate school, Rotterdam	2015	8 hours
Presenting Skills, Molecular medicine postgraduate school, Rotterdam	2016	24 hours
Workshop “Coachen van toekomstige Erasmusartsen basis”, Erasmus MC, Rotterdam	2016	4 hours
Indesign workshop, Molecular medicine postgraduate school, Rotterdam	2016	4 hours
Biomedical English Writing Course, Molecular medicine postgraduate school, Rotterdam	2016	15 hours
English Biomedical Writing and Communication, Erasmus MC, Rotterdam	2016	84 hours
Training “Teach The Teacher – Module I”, Erasmus MC, Rotterdam	2016	24 hours
Safety course MRI	2017	4 hours
Workshop “Coachen van toekomstige Erasmusartsen vervolg”, Erasmus MC, Rotterdam	2017	4 hours

Oral presentations

	Year	Workload
Trans-radial access for endovascular interventions: a safe and feasible technique. Radiological Society of the Netherlands, Rotterdam, the Netherlands	2015	12 hours
Trans-radial access for endovascular abdominal interventions: a safe and feasible technique. Spring meeting Dutch Society of Gastroenterology, Veldhoven, the Netherlands	2016	12 hours
Postprandial flow measurements of the mesenteric arteries and portal vein using Magnetic Resonance imaging: a pilot study. Spring meeting Dutch Society of Gastroenterology, Veldhoven, the Netherlands	2016	12 hours
Covered Stents versus Bare-Metal Stents in Chronic Atherosclerotic Gastrointestinal Ischemia (CoBaGI): a multicenter randomized controlled trial. Leipzig Interventional Course (LINC), Leipzig, Germany	2017	12 hours
Sustained Symptom Relief after Revascularization of Single Mesenteric Artery Stenosis in Patients with Chronic Mesenteric Ischemia. Spring meeting Dutch Society of Gastroenterology, Veldhoven, the Netherlands	2017	12 hours
Validation of a Score Chart to Predict the Risk of Chronic Mesenteric Ischemia: a Discriminative and Useful Tool in Clinical Decision-Making. Spring meeting Dutch Society of Gastroenterology, Veldhoven, the Netherlands	2017	12 hours
Mesenteric Artery Stenting: a Covered Future? Charing Cross 2017, London, Great Britain.	2017	12 hours
Detection of Gastrointestinal Ischemia by Means of Endoscopic Visible Light Spectroscopy after Luminal Feeding. Digestive Disease Days, Veldhoven, the Netherlands	2018	12 hours
Development of an Updated Score Chart to Predict the Risk of Chronic Mesenteric Ischemia based on a Multicenter Cohort of 666 Patients. Digestive Disease Days, Veldhoven, the Netherlands	2018	12 hours
Symposium mesenteric ischemia: Clinical trials and future perspective. Digestive Disease Days, Veldhoven, the Netherlands	2018	12 hours

Poster presentations

	Year	Workload
Trans-radial access for endovascular abdominal interventions: a safe and feasible technique. United European Gastroenterology Week, Vienna, Austria	2016	12 hours
Postprandial flow measurements of the mesenteric arteries and portal vein using Magnetic Resonance imaging: a pilot study. United European Gastroenterology Week, Vienna, Austria. **Awarded with a travel grant, recognized as 'Poster of Excellence' and winner of Poster Champ Award.**	2016	12 hours
Covered Stents versus Bare-Metal Stents in Chronic Atherosclerotic Gastrointestinal Ischemia (CoBaGI): a multicenter randomized controlled trial. Controversies and updates in vascular surgery (CACVS), Paris, France. **Winner of the 2nd prize in the ePoster competition.**	2017	12 hours
Trans-Radial Access for Endovascular Abdominal Interventions: A Safe and Feasible Technique Compared with Trans-Brachial and Trans-Femoral Access. Digestive Disease Week, Chicago, United States of America	2017	12 hours
Sustained Symptom Relief after Revascularization of Single Mesenteric Artery Stenosis in Patients with Chronic Mesenteric Ischemia. Digestive Disease Week, Chicago, United States of America	2017	12 hours
Validation of a Score Chart to Predict the Risk of Chronic Mesenteric Ischemia: A Discriminative and Useful Tool in Clinical Decision-Making. Digestive Disease Week, Chicago, United States of America	2017	12 hours
Validation of a Score Chart to Predict the Risk of Chronic Mesenteric Ischemia: a Discriminative and Useful Tool in Clinical Decision-Making. United European Gastroenterology Week, Barcelona, Spain. **Awarded with a travel grant, recognized as 'Poster of Excellence'.**	2017	12 hours
Sustained Symptom Relief after Revascularization of Single Mesenteric Artery Stenosis in Patients with Chronic Mesenteric Ischemia. United European Gastroenterology Week, Barcelona, Spain. **Awarded with a travel grant.**	2017	12 hours
Observer reliability of visible light spectroscopy during upper endoscopy. Digestive Disease Week, Washington D.C., United States of America	2018	12 hours
Development of an Updated Score Chart to Predict the Risk of Chronic Mesenteric Ischemia based on a Multicenter Cohort of 666 Patients. Digestive Disease Week 2018, Washington D.C., United States of America. **Awarded as poster of Distinction top 10% best abstracts.**	2018	12 hours

Grand allocation

	Year
Gastrostart, Dutch Society of Gastroenterology (NVGE), project: 'Endoscopic Measurements of Mitochondrial Oxygen Tension: a pilot study of a promising test to diagnose Chronic Gastrointestinal Ischemia' (Endo-mitoPO2-study)'	2016
Stichting Coolsingel, project: 'Endoscopic Measurements of Mitochondrial Oxygen Tension for the Diagnosis of Chronic Gastrointestinal Ischemia'	2017
Grand for multidisciplinary and multi-center research initiatives or working groups, Dutch Society of Gastroenterology (NVGE), project: Dutch Mesenteric Ischemia Study group (DMIS)	2017

Memberships

Dutch Society of Gastroenterology (NVGE)	2015 - current
International Society of Vascular Surgery	2017 - current

Educational activities and lecturing

	Year	Workload
Tutoring first year students curriculum Medicine, Erasmus University Rotterdam, Rotterdam	2015 2016	80 hours
Lecture 'Gastrointestinal bleeding', curriculum ER and IC nurses, Zorgacademie, Erasmus MC Rotterdam	2016 2017	40 hours
Lecture 'Gastro-intestinal Ischemia' for gastroenterology nurses, Erasmus MC, Rotterdam	2016	5 hours
Supervising Journal Club first year students curriculum Medicine, Erasmus University Rotterdam, Rotterdam	2016	10 hours
Booklet practical guidelines; data management and quality for PhD-researchers	2016	12 hours
Coach professional Bachelor medicine students, Erasmus University Rotterdam, Rotterdam, The Netherlands	2016 2017 2018	72 hours
Lecture 'Mesenteric Ischemia', first year students curriculum Medicine, Erasmus University Rotterdam, Rotterdam	2017 2018	10 hours

Peer review activities

American Journal of Gastroenterology, Nederlands Tijdschrift voor de Geneeskunde, Canadian Journal of Gastroenterology and Hepatology, Scandinavian Journal of Clinical & Laboratory Investigation

DANKWOORD

Het boek is af en als allerlaatste schrijf ik dit laatste (en meest gelezen) hoofdstuk. Deze thesis vertegenwoordigt een groot deel van het werk dat ik tijdens mijn 3.5 jaar fulltime aanstelling als PhD kandidaat en daarna nog ruim een jaar naast mijn werk als arts-assistent in opleiding heb verricht. Ik zeg 'groot deel' want ik heb in deze tijd naast het werk van deze thesis ook mijn aandacht geschonken aan andere zaken zoals onderwijs, beursaanvragen, de ischemie poli, DMIS, begeleiding van studenten en congressen maar bovenal heb ik vriendschappen voor het leven gesloten. Deze thesis was er nooit gekomen en mijn tijd als PhD kandidaat was nooit zo mooi geweest zonder de betrokkenheid, ondersteuning en hulp van collega's, vrienden en familie. Een aantal wil ik hierna specifiek bedanken.

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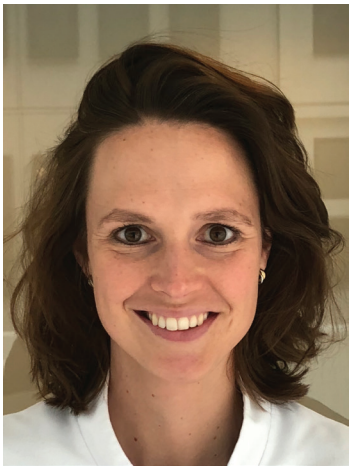
ABOUT THE AUTHOR



Louisa J.D. van de Loo - van Dijk was born on October 14, 1987 in Vught, the Netherlands. She attended secondary school at 'Gymnasium Beekvliet' in Sint Michielsgestel, where she graduated in 2006 with cum laude honors. Subsequently she started medical school at the Erasmus MC University Medical Center in Rotterdam. During medical school, Louisa worked as a data manager at the department of Pediatric Oncology at the Erasmus MC Sophia Children's Hospital. In 2010, she paused her study for one year to serve as head of the students association (Rotterdamsche Vrouwelijke Studenten Vereeniging). In the beginning of 2014 she obtained her medical degree with cum laude honors and started working as a resident not in training (ANIOS) at the department of Internal Medicine of the Ikazia Hospital, Rotterdam. In December 2014 she started her PhD trajectory as described in this thesis at the department of Gastroenterology and Hepatology under supervision of Prof. dr. M.J. Bruno and at the department of Radiology under supervision of Prof dr. G.P. Krestin. In August 2018 she started with her Internal Medicine residency in the Franciscus Gasthuis & Vlietland Hospital (program director Dr. Y.C. Schrama) as part of the training in Gastroenterology and Hepatology at the Erasmus MC University Medical Center (program director Prof. dr. C.J. van der Woude). Louisa lives in Rotterdam, together with her husband Bernt and their daughter Livia.