Detection of microcirculatory changes and treatment of patients with atherosclerotic chronic mesenteric ischemia and median arcuate ligament syndrome

PhD thesis by

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Alltid. Uansett.
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Summary

Background

Typical symptoms of chronic mesenteric ischemia (CMI) are postprandial pain and weight loss due to food aversion. The symptoms are often mild, transient, and recurrent and may go undiagnosed for many years. The symptoms in patients with CMI are caused by insufficient oxygen delivery to the gastrointestinal tract, in most cases due to occlusive mesenteric vascular disease. Atherosclerosis is the most common cause of occlusive CMI, followed by external compression of the celiac artery (CA). CMI can progress to acute mesenteric ischemia (AMI), a complication with high mortality. The diagnosis of CMI is often evident in retrospect, after patients are admitted with an acute deterioration of the disease caused by sudden occlusion of an atherosclerotic vessel. Still, CMI remains underdiagnosed and undertreated.

The prevalence of both atherosclerotic mesenteric artery stenosis and external compression of the CA is high. However, only a minority of individuals with these findings become symptomatic. Furthermore, the pathophysiology in patients with median arcuate ligament syndrome (MALS), symptomatic external compression of the CA, is unclear. The gastrointestinal tract is protected from ischemia by a redundant collateral circulation. The collateral circulation is usually sufficient to supply oxygen to the gut in patients with single-vessel pathology, even in times of increased metabolic demand. The selection of patients who would benefit from surgical intervention is difficult. The gold standard for the diagnosis of CMI is relief of symptoms after revascularization. The diagnosis is challenging, as the differential diagnoses in patients with abdominal pain are numerous. A consensus diagnosis of CMI is reached based on a compatible history, significant mesenteric artery stenosis on radiological imaging, exclusion of common differential diagnoses by means of an upper endoscopy and imaging such as a CT scan, and preferably, a functional test. Functional tests have been
developed to prove insufficiency of the usually redundant collateral circulation. Prior to this study, tonometry was the most extensively described functional test, but it has several limitations both in availability and use. Visible light spectroscopy (VLS) and laser Doppler flowmetry (LDF), investigated in this study, are easy to use, affordable, and readily available techniques which may be of value in diagnosing patients with CMI.

Treatment in patients with atherosclerotic CMI is primarily endovascular. A surgical bypass is performed in case of failed endovascular therapy or in patients unsuitable for this. Open surgery has better long-term patency, but with higher morbidity and mortality than endovascular treatment. Laparoscopic mesenteric bypass surgery can be a third therapeutic option, in addition to endovascular and open surgical treatment. A laparoscopic mesenteric bypass may offer the advantages of minimally invasive surgery, while retaining the superior long-term patency of open surgery.

Methods

In Paper I, 104 patients were evaluated for CMI during a 24-month period. A consensus diagnosis of CMI \((n = 40)\) was made based on typical symptomatology, \(\geq 70\%\) stenosis or occlusion of one or more mesenteric arteries on CT-angiography, and exclusion of common differential diagnoses. Patients with a consensus diagnosis of CMI were examined with LDF and VLS during upper endoscopy. Thirty-two patients were successfully treated and had a definitive diagnosis of CMI. Results from the preoperative microcirculatory assessment in CMI patients were compared to results from a group of individuals with normal intestinal circulation \((n = 38)\). The circulation in the control group was evaluated with duplex ultrasonography (DUS). The control group had none of the typical symptoms of CMI (weight loss, postprandial abdominal pain, or changes in eating habits). Treatment response was evaluated with DUS at one month and with LDF and VLS at three months.
In Paper II, 25 patients were evaluated for MALS. The study was designed as a single center case-control study. Patients with a consensus diagnosis of MALS ($n = 15$) underwent a gastroscopy assisted, transmucosal microcirculatory assessment with LDF and VLS. Results were compared to individuals with normal intestinal circulation ($n = 38$) evaluated with DUS, and another group of patients with atherosclerotic CMI ($n = 32$, Paper I). Treatment response was evaluated clinically at 1, 3, 6, and 12 months, and with VLS and LDF at three months. Health-related quality of life (HRQoL) in patients with MALS was assessed with the Euroqol questionnaire (EQ-5D-5L), preoperatively, and 12 months postoperatively.

In Paper III, we present an initial experience with a limited series of laparoscopic mesenteric artery revascularizations for the treatment of atherosclerotic CMI. From October 2015 to November 2018, nine patients with CMI underwent laparoscopic bypass surgery. Only CMI patients with prior unsuccessful endovascular treatment or arterial occlusions and extensive calcification, precluding safe endovascular treatment, were offered laparoscopic mesenteric revascularization. The bypasses were constructed with an 8 mm ring enforced expanded polytetrafluoroethylene (ePTFE) graft in a retrograde fashion (from the infrarenal aorta or an iliac artery) to either the superior mesenteric artery (7 cases) or splenic artery (2 cases). Graft patency was assessed with DUS at 1, 3, 6 and 12 months, and annually thereafter.

Results

A significantly lower mucosal capillary hemoglobin oxygen saturation ($SO_2$) was found in patients with atherosclerotic CMI prior to treatment, compared to controls; mean ± standard deviation (SD): $67 ± 9\%$ and $81 ± 4\%$, respectively ($p < 0.001$). Further, a significantly lower relative hemoglobin (rHb) amount, flow, and velocity ($p < 0.001$) was found. The sensitivity of $SO_2$ measured by VLS for diagnosing CMI was 94% and the specificity 72% (cut-off 78%
SO₂), calculated with receiver operating characteristics curve analysis. A combination of SO₂ and rHb increased the test sensitivity and specificity to 97% and 79%, respectively.

Eleven (92%) patients with clinical improvement after laparoscopic decompression had a definitive diagnosis of MALS. Preoperative mean transmucosal oxygen saturation was significantly lower in patients with MALS (SO₂ 76 ± 6), as compared to healthy individuals (SO₂ 81 ± 4, \( p = 0.02 \)). A borderline significant improvement in SO₂ after surgical decompression of the CA was found (SO₂ 81 ± 3.7, \( p = 0.05 \)). Median follow-up was 18 months (4 – 24 months). Four of the five dimensions investigated with EQ-5D-5L improved.

In Paper III, the technical success of the laparoscopic mesenteric bypass was 78%, and the primary open conversion rate was 22%. Median operative duration was 356 mins (range 247–492 mins). The median follow-up time was 26 months (range 18–49 months). The primary graft patency at 30 days was 78%. Primary assisted, and secondary graft patency was 78% and 100%, respectively. All laparoscopic revascularization procedures remained patent at discharge from the hospital. Median weight gain was 2 kg (range 2–18 kg), and all patients achieved relief from postprandial pain and nausea. No mortality was observed during the follow-up period.

Conclusion

A functional test with a high sensitivity and specificity is necessary for adequate patient selection in treatment of CMI. LDF and VLS can be applied to detect ischemic changes in the microcirculation in both patients with atherosclerotic CMI and patients with MALS. VLS is superior to LDF, with highly significant findings in all examined areas in patients with atherosclerotic CMI, and in the duodenum of MALS patients, as well as a significantly lower mean SO₂ (all areas combined) in both atherosclerotic CMI and MALS patients.

MALS patients had significantly lower preoperative SO₂ in the duodenum as compared to healthy controls, suggesting a possible ischemic etiology to the symptoms in these patients.
Furthermore, MALS patients displayed a borderline significant improvement in SO\textsubscript{2} after successful laparoscopic decompression.

Our results suggest that VLS during upper endoscopy should be a part of a diagnostic work-up of patients with CMI of both atherosclerotic origin and due to external compression of the CA, in combination with clinical evaluation and an imaging study, preferably CT angiography.

Laparoscopic decompression of the median arcuate ligament is a safe and effective treatment of MALS. Laparoscopic mesenteric bypass in treatment of atherosclerotic CMI may be an additional option for experienced laparoscopic vascular surgeons in case of lesions unsuitable for / after failed endovascular treatment. Due to the limited number of patients in this study, with a relevant occlusion, conversion and complications rate, further studies are needed to evaluate this novel approach adequately.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAA</td>
<td>Abdominal aortic aneurysm</td>
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<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
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<tr>
<td>AMI</td>
<td>Acute mesenteric ischemia</td>
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<tr>
<td>BMT</td>
<td>Best medical therapy</td>
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<td>CA</td>
<td>Celiac artery</td>
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<td>CABA</td>
<td>Cobolt albumin binding assay</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CMI</td>
<td>Chronic mesenteric ischemia</td>
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<td>CTA</td>
<td>Computer tomography angiography</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DALY</td>
<td>Disability adjusted life years</td>
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<td>DDx</td>
<td>Differential diagnosis</td>
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<td>DSA</td>
<td>Digital subtraction angiography</td>
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<td>DUS</td>
<td>Duplex ultrasound</td>
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<tr>
<td>EDV</td>
<td>End diastolic velocity</td>
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<tr>
<td>ePTFE</td>
<td>expanded Polytetrafluoroethylene</td>
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<tr>
<td>GALS</td>
<td>Gastroscopy assisted laser Doppler flowmetry and visible light spectroscopy</td>
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<td>GET</td>
<td>Gastric exercise tonometry</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>IFABP</td>
<td>Intestinal fatty acid binding protein</td>
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<tr>
<td>IMA</td>
<td>Inferior mesenteric artery</td>
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<tr>
<td>IU</td>
<td>International units</td>
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<tr>
<td>IVUS</td>
<td>Intravascular ultrasound</td>
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<tr>
<td>LDF</td>
<td>Laser Doppler flowmetry</td>
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<td>MALS</td>
<td>Median arcuate ligament syndrome</td>
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<td>MAP</td>
<td>Mean arterial pressure</td>
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<td>MRA</td>
<td>Magnetic resonance imaging angiography</td>
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<tr>
<td>NCD</td>
<td>Non-communicable disease</td>
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<tr>
<td>NIS</td>
<td>Nationwide (national) inpatient sample</td>
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<td>NLAST</td>
<td>Norwegian Laparoscopic Aortic Surgery Trial</td>
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<td>NOMI</td>
<td>Non-occlusive mesenteric ischemia</td>
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<tr>
<td>O2C</td>
<td>Oxygen 2 See</td>
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<tr>
<td>PCO$_2$</td>
<td>Partial pressure of carbon dioxide</td>
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<tr>
<td>PMAS</td>
<td>Percutaneous mesenteric artery stenting</td>
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<td>PSV</td>
<td>Peak systolic velocity</td>
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<tr>
<td>PTA</td>
<td>Percutaneous transluminal angioplasty</td>
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<td>rHb</td>
<td>Relative hemoglobin amount</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>ROC</td>
<td>Receiver operating characteristics curve</td>
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<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<td>SLAP</td>
<td>Superior labrum anterior posterior</td>
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<tr>
<td>SBF</td>
<td>Splanchnic blood flow</td>
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<tr>
<td>SMA</td>
<td>Superior mesenteric artery</td>
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<tr>
<td>SO$_2$</td>
<td>Oxygen saturation</td>
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<tr>
<td>Swedvasc</td>
<td>Vascular registry in Sweden</td>
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<tr>
<td>VLS</td>
<td>Visible light spectroscopy</td>
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<td>WHO</td>
<td>World Health Organization</td>
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List of publications


Preface

Aspects in diagnostics and treatment of chronic mesenteric ischemia (CMI) are presented in this thesis. Chronic abdominal pain is common in the elderly, and there is a high prevalence of atherosclerosis in the mesenteric arteries in this patient group. External compression of the celiac artery (CA) is found in 10 – 24% of the population and is usually asymptomatic (2, 3). It has been difficult to identify the individuals whose symptoms are caused by arterial insufficiency and hence would benefit from arterial revascularization. The utility of laser Doppler flowmetry (LDF) and visible light spectroscopy (VLS) in detection of transmucosal microcirculatory changes in the stomach and duodenum of patients with atherosclerotic CMI or median arcuate ligament syndrome (MALS) is investigated.

Furthermore, the technical approach and possible advantages and limitations of a laparoscopic aorto-mesenteric bypass in the treatment of atherosclerotic CMI are elucidated.

General aspects of mesenteric ischemia are considered, with a special focus on atherosclerotic CMI and MALS.
Introduction

Background

Chronic mesenteric ischemia (CMI) is defined as a disease caused by insufficient oxygen delivery to the gastrointestinal tract causing ischemic symptoms with a duration of three months or more (3). Typical symptoms are postprandial abdominal pain and weight loss due to food aversion (4, 5). Furthermore, diarrhea is frequently seen in these patients. The classical triad of abdominal pain, weight loss and an abdominal bruit on auscultation, is, however, found in only 16–22% of the cases. In 90% of the patients, CMI is caused by a gradual narrowing of one or more of the blood vessels supplying the gastrointestinal tract due to atherosclerosis (3, 6). The three major branches of the aorta supplying the gastrointestinal tract are the celiac artery (CA), the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA). Less frequently, an external, compression of the CA and/or the celiac ganglion by the median arcuate ligament, may cause symptoms (7).

The median arcuate ligament syndrome (MALS) has been a controversial diagnosis since Pekka Tapani Harjola first reported on the syndrome after a surgical decompression of the CA in 1963 (8). The controversy is based on the unclear pathophysiological mechanisms causing the symptoms. The prevailing theory is that symptoms are caused by insufficient oxygen delivery, in parallel to atherosclerotic narrowing of the vessel. However, a neuropathic genesis is also hypothesized, where a chronic irritation and compression of the celiac ganglion may cause the patients symptoms (7). In most patients, the mesenteric vessels share an abundant collateral circulation, and stenosis or occlusion of one vessel will be compensated by blood flow through the remaining two. In MALS, the stenosis is not constant as is the case with atherosclerotic CMI, but intermittent, as the compression is exacerbated during expiration. Furthermore, radiological studies have shown that compression of the CA can be found in 10-24% of the
population, whereas only a limited number of patients develop symptoms (2). Vasculitis as in Takayasu or Behçet disease, arterial dissection, fibromuscular dysplasia, and chronic non-occlusive mesenteric ischemia (NOMI) due to e.g. cardiac or pulmonary insufficiency, are other, less frequent causes of CMI (3).

Mesenteric ischemia

Diagnosing CMI is a challenge, as the typical symptoms of CMI are frequently seen in other, more common diseases such as ulcer disease, gall bladder pathology, gastritis, pancreatitis, inflammatory bowel disease and malignancy (3). Typical symptoms in combination with stenosis or occlusion of two of the three mesenteric arteries warrants revascularization. However, in case of single vessel stenosis, the collateral circulation is often thought to be sufficient, and revascularization is only performed when common differential diagnoses have been excluded. The prevalence of asymptomatic stenosis of one or more mesenteric vessels is reported to be 3% in patients under 65 years of age, but as the patients get older, the frequency increases and is found to be around 18% in patients older than 65 years (9). In recent years, imaging investigations are often performed early in the diagnostic work-up of patients with abdominal pain, and an increasing number of patients are referred on suspicion of CMI prior to exclusion of common differential diagnoses. This is particularly challenging in patients with single-vessel pathology. Further investigations are warranted in these patients to evaluate whether the collateral circulation is adequate. A consensus diagnosis of CMI is usually reached by a multidisciplinary panel consisting of vascular surgeons, interventional radiologists, and gastroenterologists (3). However, a definitive diagnosis cannot be made until treatment response is evaluated. Concerning a disease with unspecific symptoms and a radiological finding not uncommon in the elderly, a more specific diagnostic test is warranted (10).
Vascular diseases of the mesentery are divided in categories based on clinical presentation (acute, sub-acute or chronic), vessel involvement (arterial, venous) and etiology (atherosclerotic / thrombotic / external compression / non-occlusive) (Figure 1).

**Figure 1**: Classification of the most common diseases of the mesenteric arteries and veins. Mesenteric vascular disease is classified according to presence of symptoms, clinical presentation (acute, acute-on-chronic or chronic) and involvement of vessel, as well as disease pathology (arterial or venous, atherosclerotic, embolic, thrombotic, or external compression). Only the most common causes of mesenteric disease are presented in the figure. Acute mesenteric ischemia is caused by an abrupt cessation of blood flow with development of symptoms within minutes-hours and is most often caused by arterial embolism from the heart or plaque-rupture leading to thrombosis. Chronic mesenteric ischemia is defined as symptoms of vascular insufficiency with a duration of at least three months. Atherosclerosis is accountable for approximately 90% of the cases of chronic mesenteric ischemia. Acute-on-chronic mesenteric ischemia is acute mesenteric ischemia in patients with a prior history of chronic disease, with a deterioration over the last weeks.

Symptoms of acute mesenteric ischemia (AMI) can develop within minutes of onset (embolism) or hours (atherothrombosis). AMI is caused by an abrupt cessation of blood flow through the
mesenteric arteries or veins. Prompt diagnosis and treatment are required for a favorable clinical outcome. The typical clinical presentation is intense abdominal pain “out of proportion” to the clinical findings in the early stage of occlusion. Acute-on-chronic mesenteric ischemia is found in patients with a prior history of CMI, with a deterioration of symptoms over the last days to weeks.

Epidemiology

Population based studies on the incidence of CMI are scarce. Recently, the Dutch Mesenteric Ischemia Group found the annual incidence of CMI (all cause) in their region to be 9.2/100 000 (11). A steady increase in number of interventions due to CMI is reported and could reflect an increasing number of cases (3). The National (nationwide) Inpatient Sample (NIS) database reported an increase from 1.8 interventions per million inhabitants due to CMI in 2000, to 5.6 per million in 2012 (p < 0.01) (12). An increased recognition of the disease as a differential diagnosis in patients with abdominal pain and improved therapeutic options could also have contributed to the increasing number of cases.

The incidence of AMI increases with age and is estimated to be the cause of acute abdomen in up to 10% of patients older than 70 years (13). An autopsy study from Malmö (Sweden), 1970-1982, found an annual incidence of AMI of 12.9/100 000 inhabitants, which is higher than the incidence of ruptured abdominal aortic aneurysms (14). More recent reports found the incidence to be 5.4 – 7.3/100 000 (15, 16).

An external compression of the CA is found in 10-24% of the population, and is the most common cause of single vessel stenosis in the mesenteric arteries (2). It is, however, usually asymptomatic, and the incidence of symptomatic MALS, also known as Dunbar syndrome, is 1.3 – 2/100 000 (11, 17).
Anatomy and physiology

Three ventral branches of the aorta supply the gastrointestinal tract with blood. The CA is the most cranial mesenteric artery, followed by the SMA and IMA. The CA originates from the ventral wall of the aorta, at the level of the diaphragm, and runs distally with a more than 20 degrees angle to the aorta in the proximal two centimeters before it divides into the splenic, left gastric and common hepatic arteries. A low insertion of the crura of the diaphragm or a high origin of CA may result in external compression of the CA by the median arcuate ligament. The right gastric artery, a branch of the hepatic artery, and the left gastric artery supply the lesser curvature of the stomach. The greater curvature is supplied by the right- and left gastroepiploic arteries, originating from the gastroduodenal and splenic arteries, respectively. The blood supply to the small intestine, ascending, and transverse portion of the colon is derived from the SMA. The IMA supplies the descending and sigmoid colon and upper part of the rectum, and branches of the internal iliac arteries supply the lower part of the rectum. AMI caused by acute thromboembolic occlusion most frequently affects the SMA, which is considered the most important artery for intestinal circulation (3). Acute occlusion of the CA or IMA infrequently cause symptoms due to the excellent collateral circulation from the SMA.

The mesenteric circulation has a redundancy of multiple interconnecting vessel branches (Figure 2). This extensive collateral circulation between the three major branches ensures excellent perfusion to the bowel during digestion, and in most cases an adequate blood supply even in the presence of an atherosclerotic lesion on one of the three vessels. The fetal blood supply is initially dual. In subsequent differentiation, much of the dual vasculature (double aortas and dorsal and ventral arterial supply of the viscera) regresses. Many of the variations seen in mesenteric circulation derives from varying degrees of persistence of this dual blood supply (18).
The pancreaticoduodenal arcade formed by the superior and inferior pancreaticoduodenal arteries connects the CA and SMA (Figure 2).

Figure 2: Abdominal aorta with major branches. Three major branches provide the arterial blood supply to the mesenteric circulation. The celiac artery (CA), the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA). The mesenteric circulation is characterized by its redundancy in arterial blood supply. There are several anatomical variances in blood supply to the viscera. The CA divides into the splenic artery (SA), often with a tortuous path towards the spleen, the left gastric artery (LGA) supplying the stomach, and the hepatic artery (HA) supplying the liver. Branches of the CA also supply the duodenal bulb, the descending duodenum and pancreas. The SMA supplies duodenum from the major papilla, jejunum, ileum, ascending colon, and proximal two-thirds of the transverse colon. The CA and SMA are interconnected through the pancreaticoduodenal (PDA) and gastroduodenal arteries (GDA). In some patients a persistent embryonic anastomotic branch between the 10th (CA) and 13th (SMA) ventral segmental arteries result in another connection between CA and SMA, known as arc of Bühler. The SMA and IMA are connected by the marginal arcade of Drummond in the periphery, close to the intestine, and the arc of Riolan (also known as mesenteric meandering artery of Moskowitz), often described as connecting the middle colic artery of SMA to the left colic artery of the IMA. LRA: Left renal artery. Figure adapted from van Petersen et al. (1).

This is a relatively constant interconnection, whilst others are of persistent embryologic origin, such as the arcade of Buhler. The arcade of Riolan connect SMA and IMA centrally, and the arcade of Drummond in the periphery. Drummonds marginal artery is the major collateral
arcade between these two vessels, and is composed of branches from the right, middle and left colic arteries. The IMA connects to the internal iliac arterial circulations through superior and middle rectal arteries.

The wall of the small intestine is made up of the mucosa, submucosa, muscularis propria and serosa. The wall is $2.9 \pm 0.8$ mm thick in the antrum) and $1.6 \pm 0.3$ mm in the duodenum (19). The mucosal capillary circulation can be divided into a deep mucosal circulation and a superficial supplying the villi and microvilli. The villi and microvilli are the most metabolically active layer of the intestine. Anastomoses between the arterioles and venules at the base of the villi permit a shunting of blood away from the mucosa, in case of a compromised circulation, while maintaining perfusion to the muscularis and serosa. This permits to some extent a preservation of the integrity of the bowel wall in case of ischemia. At rest, 10 – 20% of the cardiac output (CO) is received by the viscera. Postprandially, this increases to 35% of the CO.

MALS is a congenital disorder in which the insertion of the diaphragm to columna, the median arcuate ligament, is slightly caudal to its normal location, or the CA has a slightly more cranial origin of the aorta (Figure 3). This causes a compression of the CA by the crus of the diaphragm which exacerbates with expiration. During inspiration, the ligament moves in a cranial direction and will relieve the compression in a variable degree.
Atherosclerosis

In contrast to a local extrinsic compression of a vessel seen in MALS, atherosclerosis is a systemic vascular disease. It is a chronic disease, with only a partially known etiology wherein both inflammatory and immunological mechanisms partake in the development (20, 21). Untreated, it has a malignant prognosis. The treatment is directed at known risk factors such as hypertension, diabetes, kidney failure, dyslipidemia, and lifestyle factors like smoking, diet, exercise, and obesity. Histologically there are four stages; (1) focal thickening of the intima with lipid accumulation, (2) development of an atheroma, a well-defined lipid core covered by
a fibrous cap, (3) development of a fibrous plaque with accumulation of collagen and smooth muscle cells and (4) advanced lesions with development of microvasculature from both luminal and medial aspects, with a necrotic, lipid rich core and in the end, calcified lesions. The pathogenesis starts with qualitative changes to the endothelium, the inner vessel wall, due to dyslipidemia, hypertension, and pro-inflammatory mediators. This leads to expression of adhesion molecules, binding of leucocytes and migration of these into intima where they mature to macrophages. After entering the vessel wall, lipids from the blood stream cause an inflammation, further attracting leucocytes. Monocytes migrate to remove the lipids, transforming to foam cells and eventually leading to apoptosis. Further, pro-inflammatory mediators stimulate migration of smooth muscle cells forming the fibrous plaque. The plaque protrudes into the vessel lumen and cause a stenosis or occlusion. With a rupture of the plaque and expression of its lipid and necrotic core to the blood stream, a thrombus is formed causing different clinical manifestations depending on its location: myocardial infarction, stroke, claudication, acute limb ischemia or mesenteric ischemia.

Global burden of disease

Cardiovascular disease (CVD) is among the top ten threats to global health identified by the World Health Organization (WHO) (22). The burden of CVD as a cause of mortality increases worldwide as life expectancy increase and fertility rates decline resulting in an aging population. Non-communicable diseases (NCD) such as CVD and cancer are the main cause of death globally (23). In 2016 NCD accounted for 71% of the world’s 57 million deaths. CVD was the leading cause. In the literature, CVD is predominantly referred to as ischemic heart disease and stroke, but also other vascular diseases, as peripheral arterial insufficiency and mesenteric ischemia is categorized as a CVD.
There are significant variances in disease distribution globally. Acute myocardial infarction and stroke has historically been diseases with highest incidence in high-income countries, while trauma and communicable diseases (infectious or transmissible diseases) have been the main burden of disease in low- and middle-income countries (24). With regards to CVD in low- and middle-income countries, rheumatic heart disease and cardiomyopathies were the leading causes in the middle of the last century, with a shift towards atherosclerotic disease in the last 30 years, particularly in urban areas (25). This is partly a consequence of urbanization and lifestyle changes.

Life expectancy at birth provides an indication of mortality patterns between countries. A girl born in Norway, in 2019, have a life expectancy of 84.2 years (26). Women live approximately four years longer than men, a figure applicable globally. However, there are significant differences between regions. WHO reports the life expectancy to be 61.2 years in the African Region, with an increasing trend (27). In some areas the increase is rapid. In Nepal there has been a 10 year increase in life expectancy in the last 10 years (28). As people live to be older and fertility rates decline, the population ages. In 2050 there will be 2.5 times more people over the age of 65 than children below 5 years of age (28).

Improvement in pharmaceutical therapy and changing lifestyles have driven a decline in mortality from CVD in the western countries, and Norway especially. This gave rise to cancer as the leading cause of death in the last years according to the Norwegian Cause of Death Registry.

The main etiology of CVD is atherosclerosis. Atherosclerosis is also the main cause of CMI, responsible for 90% of the cases. The remaining 10% is caused by external compression of vascular structures (muscle fibers, tumors), vasculitis, dissection, aneurysms, and fibromuscular dysplasia. Some infectious diseases such as HIV and intestinal tuberculosis are associated with mesenteric ischemia due to HIV-associated vasculitis and granulomas in the
vessel wall respectively (29, 30). Schistosomiasis, endemic in sub-Saharan Africa, a disease more known for its affection of the urogenital tract with increased risk of cancer and potentially increased susceptibility of HIV infection, has been reported as a cause of acute mesenteric ischemia (31, 32). These are rare causes of mesenteric ischemia and display a connection between the NCDs and communicable diseases.

High blood pressure, tobacco smoking (including second-hand smoke) and household air pollution from solid fuels are the three leading risk factors for global disease, representing 7%, 6.3% and 4.3% respectively of disability-adjusted life years (DALYs) globally in 2010 (24). In 1990 the top three risk factors for global disease were childhood underweight, air pollution and tobacco. Urbanization and change in lifestyle are two major reasons for the shift towards NCD. Further, improved water/sanitation with a reduction in children at risk of communicable diseases is important. In addition, access to new medical therapy for communicable diseases, as anti-retroviral therapy for HIV result in an older population with, both increased prevalence of e.g. HIV / AIDS, and increased prevalence of non-communicable diseases (33). This is referred to as double burden of disease.

Treatment of CVD has evolved dramatically the last 50 years. The introduction of percutaneous coronary angiography with intervention on stenotic or occluded vessels contributes significantly to the declining mortality rates due to CVD. Percutaneous coronary interventions are performed approximately 12 000 times every year in Norway.

The access to surgical care is unevenly distributed across the globe (34). At least 4.8 billion people do not have access to operating theaters or specialists in surgery. This is the case for less than 5% in high-income countries in western Europe and North America, while the population lacking these essential treatment options is as high as 95% in regions in sub-Saharan Africa and South Asia. Treatment of AMI requires urgent surgical treatment within hours of debut to improve the prognosis.
The history of mesenteric ischemia

The first description of an arterial occlusion of a mesenteric artery originates from Firenze in the 16th century, but it was not until 300 years later, towards the end of the 19th century, true studies with ligation of mesenteric vessels and its consequences were examined and published (35, 36). The access to corpses for research in form of obduction and identification of common pathology in patients with similar symptoms improved after creation of the hospitals at the end of the 18th century. Hospitals at the time, were mainly for the poor, where communicable diseases caused a high mortality in the admitted. For a disease such as acute mesenteric ischemia, in which severe abdominal pain is the only symptom in the early phase, a postmortem examination of the patients was needed to reveal the cause of death.

In 1901, Schnitzler drew a parallel between intermittent claudication, atherosclerosis and hypoxia of the tissue in the lower extremities and atherosclerosis of the mesenteric arteries and mesenteric ischemia (35). Schnitzler’s patient had postprandial abdominal pain and an acute on chronic deterioration with necrotic bowel to follow. This is the first description of the course of the disease as we recognize it today. Fourteen years after this description, Ingebrigtsen wrote an article about thrombosis of a mesenteric vessel in Norsk Magazin for Lægevidenskap (37). Two world wars with funneling of research funding towards traumatology and wound care and scarce focus on chronic diseases of the elderly, is partly an explanation for the lack of improvement in mortality after acute intestinal ischemia. The mortality was reported to be 70% by Hibbard in 1933 and was unchanged some 30 years later. The idea of revascularization before removal of ischemic bowel was introduced by Klass around 1950 (38). Further, he introduced the concept of a timely diagnosis before infarction has occurred which is the principle we act by today, especially in patients with acute-on-chronic CMI. These patients often present with a deterioration of their postprandial abdominal pain and have a high risk of developing AMI if left untreated. In patients with AMI, a prompt diagnosis and
revascularization are paramount for the outcome. A recognition of the value of angiography in acute mesenteric artery embolism, published in British journal of Surgery in 1966 by Aakhus, was a contribution towards improvement in care in these patients (39). In 1967 a case-report on a successful embolectomy of the superior mesenteric artery, first of its kind in Norway, performed by Liavåg, was published (40).

The mortality rate in patients with AMI was 70-90% in the late 1960s (35). A more aggressive approach to these patients with both earlier and more liberal use of angiography was initiated in the 1970s, with a consequent reduction in reported mortality to 50% (41). A survival of 67% was observed in patients with a short doctor’s delay (<12 hours) at the time. 40 years later, the 30-day mortality rate for embolic and thrombotic AMI reported in Swedvasc (Vascular registry in Sweden) was 37% and 40%, respectively (42).

CMI was first reported in 1894 by Councilman (43). Following Schnitzler’s description in 1901, Dunphy reconfirmed the disease entity in 1936, but the first reported successful endarterectomy for CMI was performed in 1958 (44). In the 1960s bypass surgery due to CMI was first performed (35). The transabdominal open repair was in 1980 complemented by endovascular repair, which has been a minimally invasive treatment option for CMI since then (45).

Diagnostic tools

Ultrasound

Duplex ultrasound (DUS) is recommended as the first line examination in patients with suspected CMI. Duplex ultrasound is the simultaneous use of two modalities of ultrasound: Doppler and B-mode. B-mode provides an anatomic image and color Doppler utilizes and applies the Doppler effect to interpret movement (flow) within the vessels. It is, however, operator dependent, and may be technically challenging. In our institution, a highly skilled
ultrasound specialist and professor in physiology performs all examinations on patients with suspected or established CMI. The DUS technique allows for a dynamic, functional assessment of flow through a stenosis. Peak systolic velocity (PSV) and end diastolic velocity (EDV) are used to evaluate the degree of stenosis. Different cut-off levels have been used (3). In our institution we have adopted Moneta’s interpretation criteria of significance, with 200 cm/s as a 70% stenosis of CA, and 275 cm/s as a 70% stenosis of the SMA (46). Generally, CA and SMA (6-7 mm diameter) are possible to evaluate on DUS. IMA, with a 1 mm diameter is on the other hand hard to visualize. Gas in the intestines is one factor that may impede visualization on DUS. Endoscopic ultrasound is proposed as a test to avoid the limitations of trans-abdominal ultrasound and is currently being explored in our research group.

Angiography

Digital subtraction angiography (DSA) has historically been considered as the gold standard for diagnosing arterial occlusive disease. This technique has the advantage of permitting endovascular therapy at the same time as the diagnostics, but has, as an invasive procedure, potential complications as bleeding and infection. In our center, DSA is reserved for endovascular therapy after the diagnosis is made, and for cases in which significance of the stenosis is disputed. In such cases a trans-stenotic pressure gradient measurement may be performed. Intra-arterial pressure measurements are performed proximal and distal to a stenosis. This is considered to be the most accurate method in diagnosing a significant SMA lesion (47). A 10 mmHg pressure gradient across a SMA stenosis is deemed significant (3). After stenting, the aim is to reduce the mean arterial pressure gradient towards 0 mmHg.
Computer tomography angiography and magnetic resonance angiography

In our center, CT-angiography (CTA) is performed in patients with a suspicion of CMI. This technique’s major advantage over DSA is the non-invasive nature and the visualization of other abdominal organs for exclusion of differential diagnosis. Biphasic CT with mesenteric CTA has a sensitivity of 96% and specificity of 94% for the diagnosis of occlusions in AMI (48). The sensitivity and specificity for AMI is high as additional findings to the occlusion (pneumatosis intestinalis, venous gas) can be seen. The sensitivity and specificity for significant stenosis or occlusions on CTA in evaluation of patients with CMI is 100% and 95 – 100%, respectively (10). However, in patients with single-vessel disease, or in patients with atypical presentation, functional tests are required. This is because asymptomatic stenoses are frequently observed in the population and might give a false positive diagnosis.

In patients with MALS, the CTA should be taken in deep inspiration and deep expiration as the severity of the stenosis is significantly influenced by respiration (Figure 4) (10).

According to the guidelines, magnetic resonance angiography (MRA) may be considered an alternative to CTA (3). The main advantage of MRA over CTA is the lack of radiation. IMA and peripheral mesenteric vessels are better visualized on CTA, and image quality of mesenteric vessels is superior.
Figure 4: A sagittal CT-angiography image of patient with external compression on the celiac artery. Notice the post-stenotic dilatation (arrow). The image is taken in deep expiration. The caudal movement of the ligament during expiration exacerbates the external compression. The superior mesenteric artery is displayed inferior to the celiac artery.

Functional tests

Gastric tonometry

Gastric tonometry is the measurement of carbon dioxide (CO₂) in the stomach, performed to assess the circulation to the area examined. Ischemia causes an increase in tissue PCO₂ due to the buffering of acids, as demonstrated in the equation H⁺+HCO₃⁻→H₂CO₃→H₂O+CO₂. In the stomach, the increase in CO₂ will first start in the mucosa before diffusing into the lumen (49).

Early studies found tonometry to be a reliable indicator for ischemic stress ulcerations, colonic ischemia (after aortic surgery), complications in intensive care unit (ICU) patients, and complications related to acute pancreatitis (49). However, the technique is cumbersome,
influenced by several factors such as meals, and the effect on outcome has been questionable in ICU patients (50).

The Dutch Mesenteric Ischemia Group has successfully applied tonometry in diagnosing CMI (51). In their study, a stress test is used, gastric exercise tonometry (GET), wherein the subject exercises to mimic the effect of a meal on the gastrointestinal circulation and elicit ischemia. A redistribution of flow to skeletal musculature during exercise reduces hepatic and mesenteric blood flow with 25 – 50% (52). The exercise tonometry consists of a 10-minute exercise on a bicycle, aimed at a submaximal intensity evaluated with arterial blood lactate measurements. A 78% sensitivity and 92% specificity were established in 102 patients with chronic abdominal pain and suspected CMI (CMI patients \( n = 38 \)) (51). The same test has later been used to identify patients with MALS (53). Of the treated patients with a positive GET, 83% \( (n = 24) \) were free of symptoms and had improvement in tonometry at follow-up. Gastric tonometry after food provocation has been explored as a diagnostic test for CMI but has yielded varying results (51, 54, 55).

The catheters used for the GET are to the best of our knowledge unfortunately no longer commercially available. The GET is therefore, for the time being, not available for investigation of CMI.

Splanchnic blood flow

Splanchnic blood flow (SBF) is used to investigate the splanchnic oxygen uptake. The hepatic and splanchnic blood flow may be quantified using the Fick principle with the continuous infusion of an indicator, catheterization of the liver vein and subsequent blood sampling (56). With regards to CMI it has been used as a diagnostic tool by measuring SBF at baseline and after a meal to quantify the response in blood flow (57). The ability to increase the blood flow to the intestines after a meal decline in patients with CMI, and an increase of less than 250mL/min is considered pathological (56). SBF may also be used to evaluate the liver
metabolism. The major limitations to the SBF as a diagnostic tool for CMI are the invasive and time-consuming manner of the test.

*Laser Doppler flowmetry*

Laser Doppler flowmetry is based on the principle of illuminating the observed tissue with a monochromatic laser and measurement of the change in frequency that lights undergo when reflected by moving objects (58). This change in frequency is referred to as the Doppler shift. Most of the light from the laser is either absorbed or backscattered. The backscattered light from the tissue is collected by an optical detector. All moving elements in the illuminated tissue influence the output of the LDF. Red blood cells are the most abundant moving element and hence, LDF produces an output signal proportional to the number of red blood cells moving in the illuminated tissue, and their velocity. The signal produced is independent of the direction of flow and reflects all movement. It is therefore fundamentally different from ultrasound Doppler, which is affected by the direction of the flow, and unaffected by the number of moving particles. The LDF produces a value referred to as flow (red blood cell flux) expressed as mL/min/100g tissue. The LDF measurement values varies due to a spatial variation in perfusion (59). Repeated measurements can to some extent compensate for the variation. Furthermore, LDF results are affected by motion artefacts. On the skin, appliances to hold the probe in place can be used to partly overcome this, but it is more challenging during endoscopy. Several studies on LDF used during aortic surgery and acute mesenteric ischemia have reported good results (60). One study found 100% sensitivity, specificity and predictive value (percentage of ischemic segments scored as non-viable) for evaluation of the intestinal viability in 13 patients with AMI and laparotomy, compared to 87% specificity and 69% predictive value based solely on clinical evaluation (61).
Visible light spectroscopy

Microfiber techniques combining a light source and external spectrometer is used in the reflectance spectrophotometer known as visible light spectroscopy (VLS). Benaron et al. were first to publish a study on endoscopic measurements in 10 patients undergoing upper endoscopy in 2004 (62). While reflectance spectroscopy has been used in various settings for three decades, the use in an endoscopic setting requires microfiber techniques. VLS is hence a relatively new technique and enables a non-invasive measurement of mucosal capillary hemoglobin oxygen saturation during upper endoscopy. The technique is based on the principle of a shallow penetrating (2 mm) visible light (475-625 nm wavelength) for measurement of intra-mucosal combined arterial and venous hemoglobin oxygen saturation. The calculation of the oxygen saturation relies on the difference in absorption spectra of oxygenated and deoxygenated hemoglobin (Figure 5).

In 2007, Friedland et al. published a preliminary study suggesting CMI could be detected with VLS during upper endoscopy after examining 30 healthy individuals and 3 patients with CMI (63). Mucosal oxygen saturation is distinct from arterial oxygen saturation (64). The arterial oxygen saturation is measured by pulse oximetry and is generally unchanged by local events as vasoconstriction and arterial occlusion. Mucosal oxygen saturation is indicative of tissue capillary oxygenation and declines rapidly in response to local hypoxic or ischemic events.
Different biological tissues have selective scattering capabilities, and as light traverse tissue it undergoes multiple scattering events. In addition, absorption occurs in various degree by multiple molecules. Each molecule has its own absorption spectrum. The absorption spectra between oxygenated and deoxygenated hemoglobin are significantly different, as shown in Figure 5. By virtue of its abundance and strong absorption, hemoglobin accounts for most of the absorption in the gastrointestinal mucosa and enables the assessment of hemoglobin oxygenation by VLS. Notably bile and stool have high absorptive capabilities and can interfere with the measurements.
VLS was in 2011 validated through a prospective cohort of 121 patients with suspected CMI (65). A sensitivity of 90% and specificity of 63% was determined using ROC-curve analysis, with a cut-off of <63% in antrum, <62% in the duodenal bulb and <58% in the descending duodenum. A T-Stat 303 Microvascular Oximeter (Spectros, Portola Valley, Calif, US) was used in this study. Improvement was detected in 80% of the patients with CMI after intervention. The authors concluded that the technique was easy to perform, in contrast to other, more cumbersome techniques, previously described in detection of ischemia in CMI patients.

In 2018, intra-observer reliability was assessed by van Djik et al., and found to be excellent, whereas inter-observer reliability was fair to good (66).

Treatment

There are two main options when treating mesenteric ischemia: open surgical revascularization with an antegrade or retrograde bypass, using a biological (great saphenous vein autograft) or prosthetic (Dacron / expanded polytetrafluoroethylene (ePTFE)) material, or endovascular therapy with or without stenting (3, 10). Percutaneous mesenteric artery stenting (PMAS) is the primary treatment option in thrombotic AMI (67). Retrograde open mesenteric artery stenting is an alternative, hybrid option, for the 20% of patients with AMI in which PMAS is not feasible, with a high technical success rate of 93% (68). The SMA is the most frequently affected vessel in patients with AMI and is also the primary target for revascularization in patients with CMI (3).

With regards to CMI, the open surgical revascularization has superior long-term results, with a five-year primary patency of 80-81% compared to 51-52% for endovascular treatment (review article 2010, n = 1939 patients, open surgery n = 1163, endovascular repair n = 776) (69). A more recent systematic review (2018, n = 18 726) also found a lower risk of recurrence (RR 0.47; 95% confidence interval (CI) 0.34 - 0.66) with open surgery compared to endovascular
However, there was a statistically significant higher risk of in-hospital complications (RR 2.2; 95% CI 1.8-2.6) and a nonsignificant increase in mortality at 30 days (RR 1.57; 95% CI 0.84-2.93). The significantly higher primary patency must be weighed against the inferior results with regards to in-hospital complications and 30-day mortality. As the general population with CMI are older and with more comorbidities, guidelines prefer endovascular therapy as the treatment of choice, when possible, despite the superior long-term patency of open surgical revascularization (3, 10, 71). Hence, the open mesenteric bypass should be reserved for those patients in whom endovascular therapy has failed or is unsuitable or be considered in patients <50 years of age and otherwise fit for open surgery.

The differences between the patient populations receiving the two different treatment options are increasing. As open surgery is reserved for patients unsuitable for endovascular therapy, they are often older, have more comorbidities and a more extensive atherosclerotic disease. Naturally, these differences may affect the results of the chosen therapy.

Endovascular treatment

Endovascular therapy is performed through an access in either the femoral or brachial artery. Fewer complications have been reported through femoral access. The majority of the lesions are ostial and heavily calcified. Consequently, there is a high risk of recoil from the artery after a mere PTA. Hence a PTA + stent is recommended (3). Bare metal stents are most frequently applied, but covered stents have been used due to the high rate of intimal hyperplasia leading to demand for reintervention. The quality of evidence favoring covered stents are low, and there are no comparative data available on drug eluding stents. Results from the ongoing CoBaGI trial (Covered stents versus Bare-metal stents in chronic atherosclerotic Gastrointestinal Ischemia) are expected this year (72).
Postoperative management

Following endovascular treatment with stenting of mesenteric arteries, dual antiplatelet therapy is in the latest guidelines recommended for 4 weeks, followed by lifelong monotherapy. As in all patients with atherosclerotic disease, best medical treatment (BMT) is recommended. BMT comprises of platelet therapy, statin, optimization of comorbidities / other risk factors (antihypertensive treatment, good blood sugar control, diabetes, and weight reduction), physical activity, adjustment in nutrition and smoking cessation.

Treatment of median arcuate ligament syndrome

Treatment of MALS is surgical division of the median arcuate ligament and the neuro-fibrous bands crossing ventral to the CA. The decompression can be performed by laparoscopy, retroperitoneal videoscopy or laparotomy with open decompression (73). Evidence to the superiority of one procedure is lacking (10). However, laparoscopic release has the advantage of smaller scars, lower rates of gastroesophageal reflux disease, and shorter hospital stay. Laparoscopic decompression is the treatment of choice at our institution.

Immediate failure is reported after attempts on primary endovascular treatment of visceral stenosis due to extrinsic compression as seen in MALS (74). Primary endovascular treatment in patients with MALS is not recommended due to high risk of stent fracture (Figure 6) (75). Endovascular therapy is albeit in some cases required after surgical division of the median arcuate ligament.

With a small operative field, robot assisted surgical release of the median arcuate ligament has been explored and is found to be a feasible option (76-78). It offers superior three-dimensional visualization, and improved operator controls. The short- and intermediate-term results are similar for the conventional laparoscopic decompression and robot assisted surgical release.
However, no true advantage for the patient has been found, as some studies report longer operating time with the robot, others shorter.

Figure 6: Female patient with primary endovascular treatment of median arcuate ligament syndrome at a hospital abroad. Image shows the aorta with the major branches to the mesentery: the celiac artery and superior mesenteric artery. A fractured stent in the celiac artery is shown. Image shown with patient’s permission.

Post-treatment follow-up

Following mesenteric artery revascularization, clinical follow-up is important to detect in-stent restenosis and symptom recurrence to prevent AMI. There is no clear consensus on how frequent patients should be controlled. We have decided to monitor these patients closely. The re-intervention rate at mid-term follow up is in one study as high as 33%, and mortality after stent occlusion is significant (79, 80). The first follow-up, 4 weeks postoperative, is with the vascular surgeon, and is primarily to identify postoperative complications. The effect of treatment is evaluated at three months. At 3, 6 and 12 months, and yearly thereafter, DUS is
performed. In the most recent guidelines, the expert panel recommends the use of DUS and/or CTA to review stent patency in patients with recurrence of symptoms. DUS has recently been evaluated in a prospective study using trans-stenotic mean arterial pressure gradient as reference in patients with stented SMA (81). In this material, the combination of PSV >3.0 m/s and EDV >0.5 m/s gave both a specificity and positive predictive value of 100%, for diagnosis of significant in-stent stenosis. The sensitivity was 31.8%. However, the finding of a significant stenosis on DUS should, based on this study, be regarded as a true stenosis and has the advantage of being non-invasive in contrast to a conventional digital subtraction angiography (DSA), and without radiation, in contrast to CTA and DSA. Grading of endoprosthesis stenosis with CTA after SMA stenting had a sensitivity and specificity of 52.4% and 87.5%, respectively, in a recent study using trans-stenotic mean arterial pressure (MAP) gradient as a reference (47).

Prognosis

The 30-day mortality rate for embolic AMI reported in Swedvasc is 33% and 37% for endovascular and open surgery, respectively (82). In patients with thrombotic AMI the 30-day mortality rate is 23% and 56% for endovascular and open surgery, respectively. Endovascular treatment should be performed as soon as possible after the diagnosis is made, and preferably before intestinal infarction occurs, when the ischemia is still reversible (67). In patients in need of bowel resection, open surgical revascularization is more frequently performed. Patients with compromised bowel integrity have a poor prognosis, leading to a difference in mortality between open and endovascular treatment. One-year mortality following acute occlusion of the SMA was reported to be 58% and 39% in Swedvasc (1999 – 2006), for open and endovascular surgery, respectively (42). The long-term survival at five years was 30% and 40% for open and
endovascular surgery, respectively. The European Society for Trauma and Emergency Surgery reports only 26% of patients admitted with AMI to be alive one year later (67).

A meta-analysis found more in-hospital complications and a non-significant increase in 30-day mortality in patients with CMI after open surgical repair, compared to endovascular repair. The RR for in-hospital complications was 2.2 (95% CI 1.8-2.6) and RR for 30-day mortality was 1.57 (95% CI 0.84-2.93). The long-term results are, however, superior with open surgical repair, with lower risk of recurrence (3-years: RR 0.47: 95% CI 0.34-0.66) and a similar three-year survival. The pooled 30-day mortality after open revascularization for CMI was in this meta-analysis 5.5%, and 1.3% for endovascular repair, largely based on a study with data from the NIS database with 8011 included patients of a total 9167 patients in the meta-analysis (83). In the NIS-study, an overall mortality from CMI was 2.9%, with a gradual reduction from 7.3% mortality in 2002 to 2.2 in 2012. There is a difference in indication, patient population and disease stage in the open surgery group and endovascular therapy group making a true comparison of the two methods challenging.

Several studies report good results after surgical division of the median arcuate ligament. A large systematic review from 2016 reported symptomatic relief in 83% of 400 patients treated with CA release (open surgical release n = 279, laparoscopic n = 121) (84). Eighty percent experienced sustained symptom relief. There are fewer complications in this patient group compared to patients with atherosclerotic CMI. Of the 121 patients receiving laparoscopic treatment, an open conversion was performed in 9.1% (n = 11) due to bleeding. Postoperative complications reported were pancreatitis (0.8%) and gastroparesis (0.8%). There were no procedure-related deaths in the laparoscopic or in the open surgical release group.
Aims of the thesis

There are no population based, cross-sectional studies on CMI, and the prevalence is unknown. The incidence is reported to be 9.2 / 100 000 inhabitants / year in one recently published study (11). We have observed an increasing number of referrals to our department on suspicion of CMI in recent years. This observation is reflected in the literature as an increasing number of endovascular procedures due to CMI over the last two decades (12). Atherosclerotic CMI is a disease of the elderly. With increased life expectancy in Norway, and improvement in therapeutic options, we expect the number of patients treated for CMI to increase in the coming years. Both a timely diagnosis and treatment of CMI is important to avoid development of acute-on-chronic mesenteric ischemia.

Treatment in patients with atherosclerotic CMI is primarily endovascular. A surgical bypass is performed in case of failed endovascular therapy or in patients unsuitable for this. Open surgery has better long-term patency, but with higher morbidity and mortality than endovascular treatment. As such, a laparoscopic bypass could offer some of the benefits of minimally invasive surgery, while retaining the superior long-term patency of open surgery.

The executive aim of the thesis was to provide insight in diagnostic and therapeutic options in patients with CMI, with focus on the disease with atherosclerotic etiology, and that caused by external compression (MALS). The utility of laser Doppler flowmetry and visible light spectroscopy was examined to evaluate whether the use of these tests influenced the sensitivity and specificity in diagnosing atherosclerotic CMI or MALS. Furthermore, we aimed to investigate and further develop laparoscopic mesenteric revascularization techniques beyond the level of two previously published case reports (85, 86). The advantages, limitations, and outcomes of the laparoscopic bypass procedure for atherosclerotic CMI were assessed.

The following studies were designed to reach the aims of the thesis:
- *Gastroscopy assisted laser Doppler flowmetry and visible light spectroscopy in patients with chronic mesenteric ischemia* (Paper I). We aimed to explore the utility of LDF and VLS during upper endoscopy as a diagnostic tool in patients with CMI. Furthermore, we aimed to validate VLS and explore the simultaneous use of LDF and VLS with regards to sensitivity and specificity in diagnosing CMI. We hypothesized that patients with CMI have reduced microcirculation in the stomach and duodenum.

- *Perioperative microcirculatory changes detected with gastroscopy assisted laser Doppler flowmetry and visible light spectroscopy in patients with median arcuate ligament syndrome* (Paper II). We aimed to explore the utility of VLS and LDF in diagnosing MALS. The external compression of the CA by the median arcuate ligament is found in almost a quarter of the population. As only a minor portion develop symptoms, it is regarded as a disease of controversy. We hypothesized that patients with MALS have reduced microcirculation in the stomach and duodenum. Furthermore, we hypothesized that the microcirculation would improve after laparoscopic decompression of the artery.

- *A short series of laparoscopic mesenteric bypasses for chronic mesenteric ischemia* (Paper III). We explored the feasibility of a laparoscopic mesenteric bypass in patients with CMI. The long-term patency of open surgical revascularization for CMI has shown to be superior to that of endovascular procedures. The perioperative morbidity is however higher for open surgery. A laparoscopic mesenteric bypass could possibly reduce perioperative morbidity compared to open surgery, with the benefits of the long-term patency of open surgical revascularization.
Hypothesis

The main hypothesis of the thesis is:

Patients with atherosclerotic CMI or MALS have an impaired microcirculation detectable with VLS and / or LDF.

Further, we hypothesize that the use of LDF and / or VLS in examination of the microcirculation of patients with atherosclerotic CMI or MALS will increase the sensitivity and specificity in diagnosing the diseases.

H$_0$: There is no difference in the microcirculation in patients with CMI as compared to individuals with normal intestinal circulation.
Material and methods

Design

This thesis consists of two studies on atherosclerotic chronic mesenteric ischemia and one study on median arcuate ligament syndrome.

The studies in Paper I and II were designed as single center, analytic observational studies. Patients with atherosclerotic CMI or MALS were compared to healthy individuals with no narrowing of the mesenteric vessels. The main outcome measures were saturation, rHb, flow and velocity in the mucosa of the ventricle and duodenum. The outcome measures were recorded in both groups at one time point. The CMI and MALS patients were followed over time, recording the results of the therapy, under the assumption that the controls remain healthy.

The study design in both Paper I and II is a case – control study. An algorithm for classification of types of clinical research is presented in Figure 7.

Paper III is a descriptive observational case series. There is no comparative analysis. A schematic presentation of the study design in Paper I-III is found in Table 1.

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*Table 1: Study design of Paper I-III. Paper I and II are designed as case-control studies, where patients with atherosclerotic CMI are compared to individuals with normal intestinal circulation (evaluated with duplex ultrasound). Paper III is a case series without comparison. Abbreviations: MALS: Median arcuate ligament syndrome, CMI: Chronic mesenteric ischemia.*
Figure 7: Algorithm for classification of types of clinical research. There are two major branches of clinical research: experimental and observational. In experimental studies the researcher assign exposure such as treatment. Observational studies with a control group are termed analytical. If no control or comparison is made, the observational study is termed descriptive. In observational analytical studies the temporal direction of the studies outcome and exposure is identified for further subdivision into study designs. Figure adapted from Grimes et al. (87).
Study population

All included patients were referred to the department of vascular surgery, Heart, Lung and Vascular Clinic, Oslo University Hospital from other hospitals or primary health care. The vascular surgery department specializes in investigation and treatment of CMI and is a tertiary referral center.

The suspicion of MALS or CMI was based on symptomatology, a positive CT angiography (≥50% stenosis in deep expiration for MALS and ≥70% for CMI) and exclusion of common differential diagnosis such as ulcer disease, cholelithiasis, pancreatitis, inflammatory bowel disease and malignancy. The stenosis was graded by an intervention radiologist. The percentage of stenosis is calculated as (1 - L/R) x 100, where L is the diameter of the vessel at the lesion and R is the diameter of the vessel at the reference site. Inclusion and exclusion criterion for Paper I are presented in Table 2.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A CT angiographic verification of atherosclerotic stenosis (≥70%) of ≥1 intestinal arteries, and ≥2 of the following three symptoms</td>
<td>Acute mesenteric ischemia</td>
</tr>
<tr>
<td></td>
<td>MALSS</td>
</tr>
<tr>
<td></td>
<td>Unable to obtain consent</td>
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<td></td>
<td>Unwilling or unable to perform endoscopy</td>
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<td></td>
<td>Weight loss</td>
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<tr>
<td></td>
<td>Postprandial pain</td>
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<tr>
<td></td>
<td>Change in eating habits</td>
</tr>
</tbody>
</table>

Table 2: Inclusion and exclusion criteria (Paper I). All patients were evaluated with CT-angiography and clinical evaluation prior to a multidisciplinary discussion. Patients with a significant stenosis on one or more intestinal arteries in addition to typical symptoms were included. Abbreviations; MALSS: median arcuate ligament syndrome. CT: Computer tomography.

Control patients were randomly included from a list of patients awaiting upper endoscopy.
The inclusion and exclusion criteria for Paper II were a CT angiographic verification of external compression (≥50% stenosis) in deep expiration and ≥2 of the following three symptoms: weight loss, postprandial pain and/or change in eating habits. Exclusion criterion were AMI, atherosclerotic CMI, unable to obtain consent or perform endoscopy. Inclusion and exclusion criterion for Paper II are presented in Table 3.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A CT angiographic verification of external compression of the celiac artery (≥50%), and ≥2 of the following three symptoms</td>
<td>Unable to obtain consent</td>
</tr>
<tr>
<td>- Weight loss</td>
<td>Unwilling or unable to perform endoscopy</td>
</tr>
<tr>
<td>- Postprandial pain</td>
<td></td>
</tr>
<tr>
<td>- Change in eating habits</td>
<td></td>
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</tbody>
</table>

In Paper III patients with CMI and a prior unsuccessful endovascular treatment or extensive atherosclerotic lesions in the mesenteric arteries precluding safe endovascular treatment were included and offered a laparoscopic revascularization procedure.
Gastroscopy assisted laser Doppler flowmetry and visible light spectroscopy

We utilized O2C (“oxygen to see”, LEA Medizintechnik GmbH, Giessen, Germany), a diagnostic device for non-invasive evaluation of the microcirculation (88). The device has many fields of application, including diabetic foot, wound healing, transplantation (flap surgery) and assessment of peripheral arterial insufficiency. Different probes are developed for the different areas of application. With flexible glass fiber probes, the gastrointestinal tract can be evaluated through an endoscope. An endoscopic evaluation of the mucosa is also performed; however, this is mainly of value to exclude differential diagnosis unless an ischemic ulcer is found. The device relies on a combination of laser Doppler technique and tissue spectrometry (VLS) and emits both white light and a laser beam. A stable recording is acquired during a lead time of some seconds, wherein the signal is evaluated before the measurements are recorded. The O2C uses 25 milliseconds per measurement and provides a mean of the measurements over time. With 10 seconds recording time a total of 400 measurements are recorded per measurement point. The LM-10 microprobe (LEA Medizintechnik GmbH, Giessen, Germany) is 2.6 mm in diameter and can pass through the working channel of an Olympus flexible gastroscope (Olympus corporation, Tokyo, Japan) (Figure 8). The white light in the O2C illuminates the tissue in an area of approximately 0.8 mm³. The wavelength of the laser is 820 nm.

Figure 8: A O2C LM-10 microprobe (O2C, LEA Medizintechnik GmbH) (blue) seen through a gastroscope (left). The microprobe is passed through the working channel of the gastroscope and contains flexible glass fiber optics emitting white light, and a laser beam and is connected to a machine which allows for simultaneous use of laser Doppler flowmetry and visible light spectroscopy. The black orifice in the bottom of the image is the pylorus. Right: Distal end of the LM-10 microprobe.
The O2C allows for the simultaneous measurement of flow (red blood cell flux), velocity, a combined arterial and venous capillary oxygen saturation of hemoglobin, as well as a relative hemoglobin amount (Figure 9). A view of the spectrum of oxyhemoglobin is used as a visual aid to evaluate the quality of the measurements, and to identify artifacts. With the O2C an ambient light correction prior to recording is performed, which allows the examined area to be illuminated and maintain a visual contact of the O2C microprobe throughout the examination. Minor adjustments in placement of the probe against the mucosa are made in case of loss of contact or if it is pressed too hard against the mucosa. In case of a change in ambient light during a recording, the recording automatically restarts with a new ambient light correction.

Figure 9: Image of the screen of the O2C during microcirculatory measurements in the stomach of a healthy control subject. The absorption spectrum of oxyhemoglobin is found on the left-hand side (red), with saturation, relative hemoglobin, flow, and velocity from top to bottom on the right-hand side. The four curves are made from the 400 measurements during the 10 second measurement time. A 4 second lead time is applied to evaluate the quality of the recording (to the left of the red vertical line).
The measurement points were chosen considering the arterial supply of the stomach and duodenum by the branches of the CA and SMA (Figure 10).

![Figure 10: A schematic view of the distal esophagus, stomach, and duodenum. The red dots represent the approximate localization of the measurement points. The points were chosen considering the arterial supply of the stomach and duodenum by the CA and SMA.](image)

**Intervention**

In paper I, patients with atherosclerotic CMI were treated with PTA + stent \((n = 26)\) or open / laparoscopic surgery with aortomesenteric bypass \((n = 7)\). In paper II, patients with MALS were treated with a laparoscopic decompression \((n = 12)\) of the celiac artery. In paper III patients with failed endovascular therapy, or unsuitable anatomy for an endovascular approach were treated with a laparoscopic mesenteric bypass using an 8 mm ring-enforced heparin-bonded ePTFE (Propaten graft, W. L. Gore & Associates, Flagstaff, AZ, USA) in a retrograde fashion from the infrarenal aorta or iliac artery to either the SMA or splenic artery \((n = 9)\) (Figure 11).
Endovascular treatment

Access point was primarily through the femoral artery in all patients. However, in case of an unfavorable angle of the target vessel of the aorta, a brachial artery access was employed. The Seldinger technique was used for arterial access under duplex ultrasound guidance (89). Patients received a weight adjusted dose of heparin intravenously. A hydrophilic wire was used to traverse the stenosis in the target vessel, and a nitinol (metal alloy of nickel and titanium), balloon mounted stent was inserted. An Angioseal (Terumo Medical Corporation, Somerset, NJ, USA) was used on the femoral artery or manual compression on the brachial artery for hemostasis after completion of the procedure.
Open surgery

The patients were under general anesthesia and in a supine position. Intravenous antibiotic prophylaxis (Cephalothin 2g) was administered every 90 minutes until a total of four doses, with the first dose being administered 30 minutes before the start of the surgery. The procedure was performed through a traditional midline laparotomy. The aorta and mesenteric artery distal to the stenosis / occlusion was dissected free. Intravenous heparin (5000 IU) was administered before cross-clamping of the infrarenal aorta. An 8 mm ePTFE graft was the preferred graft material, and Optilene (B. Braun, Hessen, Germany) 4-0 was used for the proximal anastomosis, in an end-to-side fashion, sutured with a hanging-loop technique. Optilene 6-0 polypropylene sutures were used for the distal anastomosis, also in an end-to-side fashion, and with the vessel secured with vessel loops or vascular bull-dog clamps. Only one mesenteric vessel in each patient was revascularized in this study population. Inflow and retrograde blood flow through the arteriotomy were evaluated before irrigation with heparin sodium chloride solution before completion of the anastomosis. Peroperative ultrasound or flow measurements were performed to evaluate graft patency. The graft was covered with omentum / or retroperitoneum overlying the aorta. The abdominal fascia was closed with synthetic monofilament absorbable sutures and skin incision was closed with metal clips.

Laparoscopic decompression

The patients were under general anesthesia and in a supine position with the surgeon placed between the legs of the patient. A 12 mm trocar was placed under visual guidance between the xiphoid process and umbilicus. The abdominal cavity was insufflated with CO₂, three additional trocars (5 mm) were placed, one on the right side, and two on the left side of the patient's abdomen. The left liver lobe was elevated using Nathanson's liver retractor (Cook Medical, Bloomington, Indiana, United States). The omental bursa was opened through the division of the hepatogastric ligament. The common hepatic artery or splenic artery was identified and
followed proximally to the celiac trunk bifurcation. The CA was dissected free using a monopolar hook until the median arcuate ligament was identified. The left gastric artery and the small diaphragmatic branches from the CA were preserved. The median arcuate ligament was divided with either the monopolar hook or Ultracision Harmonic (Ethicon Endo-Surgery, Cincinnati, OH, USA). Care was taken to clear the cranial surface of the CA and its origin from the aorta, from any neuro-fibrous tissue. The aorta was free dissected 2-3 cm cranially and on both sides of the origin of the celiac artery. After removing the Nathanson's liver retractor, exsufflation was done, and trocars were removed.

Laparoscopic mesenteric bypass

Patients were under general anesthesia and prophylactic antibiotics (Cephalothin 2g) was administered intravenously, every 90 minutes. The patient was positioned supine on a split-leg table, and the surgeon stood between the legs. A surgical nurse stood on the right side of the patient, and an assistant on each side. Pneumoperitoneum was achieved through a trocar placed under direct visualization of the peritoneum. A pressure of 12 mmHg was maintained during the surgery. The small intestine was mobilized to the patient’s right side of the abdominal cavity using 1-2 fan retractors (Covidien Endo Retract II, Ethicon Endo-Surgery, Cincinnati, OH, USA) if necessary, to keep the intestine separated from the surgical field. The abdominal aorta and iliac arteries were approached by directly opening the overlying peritoneum. The SMA was approached in the area just below the conjunction of the superior and inferior mesenteric veins. Ligament of Treitz was divided and duodenum mobilized to dissect free an adequate length of the SMA. In one case, the right iliac artery, and in another, the left graft limb of a previously laparoscopically operated aortobifemoral bypass, was dissected. A ring-enforced 8 mm ePTFE was spatulated at one end and introduced into the abdominal cavity through a 12 mm trocar (Figure 12). With regards to the bypass from the infrarenal aorta to the splenic artery, a laparoscopic iliac clamp (Karl Storz, Tuttlingen, Germany) was carefully passed through an
opening in the retroperitoneum between the aorta and vena cava inferior, ventral to the left renal vein, in a cranial direction, dorsal to the pancreas, towards the omental bursa (Figure 11). Care was taken to keep the clamp parallel to the aorta. The graft (a spatulated 8 mm ring enforced ePFTE graft) was grasped with the iliac clamp and carefully tunneled from the omental bursa, dorsal to the pancreas, towards the infrarenal aorta. A CTA was examined preoperatively to avoid any venous structures along the suprarenal aorta to avoid any injury during graft tunneling. Intravenous heparin (5000 IU) was administered before clamping of the SMA.

Figure 12: Left: 3D reconstruction of a laparoscopically performed retrograde aorto-mesenteric bypass (arrow) to the superior mesenteric artery, using 8 mm ring-enforced heparin-bonded expanded polytetrafluoroethylene graft (image included with patient’s permission). Right: A 6 mm heparin-bonded expanded polytetrafluoroethylene graft, end-to-side anastomosed to an 8 mm ring-enforced heparin-bonded polytetrafluoroethylene graft with gradual length markings and a spatulated end.
An end-to-side anastomosis was performed with two hemi-circular 6-0 polypropylene sutures of 12-15 cm length and with a beforehand tied Teflon pledget (BD, BARD peripheral vascular, AZ, USA) to the end. The graft was flushed after confirmation of backflow and a suitable length of graft was used to avoid graft kinking. The infrarenal aorta was clamped and after aortotomy and spatulation of the graft end, an end-to-side anastomosis was constructed using 4-0 polypropylene sutures, also with Teflon pledgets. The aortic clamps were removed, and blood flow restored.

Outcome measures

Paper I: SO$_2$, relative hemoglobin amount, velocity, and flow (flux) were evaluated before and after revascularization in patients with CMI and compared to healthy controls with normal intestinal circulation.

Paper II: SO$_2$, relative hemoglobin amount, velocity, and flow (flux) were evaluated before and after laparoscopic decompression in patients with MALS and compared to healthy controls and to patients with CMI. Health-related quality of life was assessed using EQ-5D before and after treatment.

Paper III: Patients with previous unsuccessful endovascular treatment or with arterial occlusion and extensive calcification precluding safe endovascular treatment were offered laparoscopic mesenteric revascularization. Demographic data and perioperative results were recorded, and a descriptive analysis of the data was performed.

Quality of life

There are limited data on the effect of treatment of CMI on patient’s quality of life. Patients in Paper II completed a validated and Norwegian translated questionnaire EuroQol (EQ-5D-5L) before and after treatment (90). EQ-5D provides a descriptive profile and a single index value
for health status based on five dimensions; mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each of the five are divided into five levels of perceived problems from 1 (no problems) to 5 (indicating extreme problems). The second part of the questionnaire is a visual analogue scale (VAS) from 0 (worst imaginable health state) to 100 (best imaginable health state).

Statistical methods

Sample size

In Paper I and II sample size was calculated with a significance level of $\alpha = 0.05$ and a power of 0.8. In Paper I, a clinically significant difference between the two groups was estimated to be 10%, and the standard deviation was estimated to 15% based on a pilot study. The sample size was calculated using the formula $n = \frac{2\sigma^2}{\Delta^2}k$, ($\sigma =$ standard deviation, $\Delta =$ clinically significant difference, $k =$ constant; 7.9 (given $\alpha = 0.05$ and $\beta = 0.2$)). This gives a sample size of 36 in each group.

In Paper II, G*power Version 3.1.9.6 (Franz Faul Universität, Kiel, Germany), was used for sample size calculation, given an estimated clinically significant difference of 5% and a standard deviation of 4% in healthy controls (based on Paper I, 81±4) and 6.5% in MALS patients. We found it likely that the MALS group would be more heterogenous than was the case with patients with atherosclerotic CMI (67±9) as all had single vessel stenosis, and we expected the difference between healthy controls and MALS patients to be less pronounced than what was the case for patients with atherosclerotic CMI. We found it unlikely to acquire as many MALS patients as control patients and adjusted the allocation ratio accordingly (2/3 controls, 1/3 MALS).
Receiver operating characteristic curve

In study I and II test performance at different cut-off levels were explored using receiver operating characteristics curve (ROC). This test is applied to find the optimal point of sensitivity and specificity for a test at different cut-off levels. The test provides an easy-to-read plot with an area under the ROC curve indicating the robustness of the methods examined.

The test was developed by engineers during World War II to detect enemy objects on the battlefield (91). In medicine the ROC curve was first applied in the 1960s and has since been employed in a wide variety of disciplines.

The basic measures of the accuracy of a test are its sensitivity and specificity. A perfect test would have both 100% sensitivity and 100% specificity. A compromise must often be made between the two, and as sensitivity increases, specificity declines. A ROC curve is a plot of the true positive against the false positive (1-specificity) for different cut-off points. A test with no discrimination, 50/50, a coin toss, will yield a plot on a diagonal line $y = x$. Furthermore, the area under the curve will in this case be 0.5. A perfect test would yield an area under the ROC curve of 1. To determine the cut-off value, there are different approaches (92). One must define whether the sensitivity, specificity (or both) is more important for the diagnostic test in question. The Youden’s Index can be applied if both sensitivity and specificity is equally important. Youden’s index is the sum of sensitivity + specificity -1, and the cut-off point giving the highest value is chosen, which will provide the cut-off point farthest from no discrimination regarding test capabilities. In Paper I, we chose the cut-off point closest to (0,1) on the ROC curve, the point with the highest sensitivity, while maintain as high a specificity as possible; the point closest to perfect differentiation (93). This cut-off will be the point located in the upper left corner of the ROC figure. In Paper II, we first present the sensitivity and specificity using the same cut-off value as in Paper I. This cut-off point would not necessarily be closest to (0,1), as
the calculations were made on a different material. The cut-off value represented by the point closest to (0,1) was thus presented as well.

Student’s t-test

Student’s t-test is one of the most widely used test for statistical analysis of medical data. It is a parametric test, suitable for normally distributed data (94). It requires a larger data set than a nonparametric test, as a nonparametric test make no assumption of normal distribution. By comparing the means of two data sets, the student’s t-test is used to determine if the data is equal. In that case, no difference exists between the data sets. Student’s t-test was used both in Paper I and Paper II.

Mann-Whitney U test and Wilcoxon signed ranks test

In Paper I, a nonparametric test (Mann-Whitney U test) was applied for data with skewed distribution. This is the nonparametric analogue to the unpaired student’s t-test. The nonparametric analogue of a paired student’s t-tests is Wilcoxon signed ranks test. A paired test is applied where, for instance, the same individual is examined before and after treatment. The disadvantage of a nonparametric test is the lack of power compared to the parametric tests. Larger variations are needed to find a difference, but nonparametric tests are good with small samples and with data without normal distribution. In Paper I, Wilcoxon Signed ranks test was used to investigate the changes in outcome measures after intervention.
Ethical considerations

The study protocol was approved by the Regional Committees for Medical and Health Research Ethics in South-Eastern region of Norway (REK Sør-Øst B 2016/682) and registered in theClinicalTrials.gov Protocol Registration and Results System (NCT02914912).

Both written and oral information was given to participants in the studies. Only cognitively able patients were included. Study participants were clearly informed of their option and right to withdraw from the study at any time, without consequence for future treatment. After receiving information, all participants gave their written consent to participate in the study. The study was conducted in accordance with the Helsinki declaration (95).

In study I and II an upper endoscopy was performed to examine the microcirculation in the stomach and duodenum. Upper endoscopy is a common initial investigation in patients with upper abdominal complaints and would not impose an unwarranted burden to the patient as it is a necessary part of the diagnostic evaluation to exclude other, more common causes of abdominal pain. However, as most of the patients already had performed an endoscopy prior to referral to our center, a second endoscopy had to be performed preoperatively, and a third postoperatively. Patients experienced discomfort during the procedure, but risk of complications were low. It was considered unethical to base therapy decision on an unvalidated diagnostic test, therefore, the results of the VLS and LDF did not influence the therapeutic decisions. Most patients regarded the extra follow-up both in the out-patient clinic and gastroenterology laboratory to be an extra service, rather than a burden.

Control patients were randomly included from a list of patients awaiting upper endoscopy. A standard flexible gastroscope (Olympus Corporation, Tokyo, Japan) was used, and the examination was planned prior to inclusion in the study. The examination time for the control patients was prolonged by 5-10 minutes as compared to what was expected from the scheduled
examination, to allow time to evaluate the microcirculation with VLS and LDF. Not all patients would necessarily have been examined in the duodenum, as was the case when they agreed to participate in the study. It was considered that the prolonged examination time and the duodenoscopy did not impose an unwarranted burden to the control patients.

With regards to study III several ethical issues were raised. Advances in surgery are often based on innovation. Technical and procedural innovations have resulted in declining morbidity and mortality and has been beneficial to patient care over the years. An example relevant to this thesis is that endovascular therapy is recommended over open surgery in CMI, due to reduced perioperative morbidity (3). The foremost ethical dilemma with a novel surgical technique is the uncertainty with regards to risks and benefits to the patient. As a new procedure is implemented, the real risks may not be known at the time (96). Complications like postoperative infection and bleeding occur soon after intervention. These complications are recorded and related to the procedure, while other complications may develop months or years after the procedure and may not be affiliated with the intervention.

All our patients gave an informed consent both to participate in the study, and to the surgical procedure, as is the case with all surgical procedures performed in an elective setting. However, in this case not all risks or benefits related to the procedure were known at the time and were therefore explained in more general terms. This included common surgical complications as infections, bleeding, postoperative pain, graft thrombosis, and cardiovascular incidences. All patients were given the alternative of the traditional procedure (open surgical bypass) or the choice of no surgery, as this was performed in an elective setting. However, the consent given, based on the physician and patients shared decision making, was based on the innovators and his colleague’s potential optimism bias. The information was invariably based on our expectations that this procedure would lead to a better patient outcome and the patients probably expected the same benefit of the new procedure.
With all surgical innovations a detailed record of patient outcome measures should be kept. Although publication bias often may lead less successful techniques to be tucked away rather than published, the publishing and sharing of information, following both successful and unsuccessful procedures, is important.

The safety of the laparoscopic technique in vascular surgery had been thoroughly studied through the NLAST (Norwegian Laparoscopic Aortic Surgery Trial) at our, and collaborating institutions, prior to inclusion of patients (97, 98).

With regards to the laparoscopic mesenteric bypass, all procedures were performed by Kazmi, a surgeon with a long and extensive experience in laparoscopic vascular surgery, with several publications on laparoscopic aortobifemoral bypasses as part of NLAST spanning over the last 15 years.

The novel aspect of this study was the application of the laparoscopic vascular surgery technique on a new indication, CMI, and to our knowledge, the first laparoscopic bypass to the splenic artery. In case of complications, the patient’s legal rights were not compromised in any way by participation in the study.

All patients willingly sought surgical treatment for their disease. Patients could withdraw their consent to participate at any time and were not required to provide a reason to do so. In case of a request to withdraw from the trial, efforts were made to solve any practical issues, if any, to retain the patient. If this could not be done, the patient would have been treated as per center guidelines.
Summary of the results

Paper I

The utility of LDF and VLS in detecting microcirculatory changes in patients with CMI during upper endoscopy was evaluated in a single center, case-control study (99). One hundred and four patients were evaluated for mesenteric ischemia during a 24-months period. Patients with a consensus diagnosis of CMI (n = 40) were examined with LDF and VLS during upper endoscopy. Thirty-two were successfully treated and had a definitive diagnosis of CMI. Results were compared with a group of individuals (n = 38) with normal intestinal circulation evaluated with duplex ultrasonography (DUS) and without the typical symptoms of CMI (weight loss, postprandial abdominal pain).

A significantly lower mucosal capillary hemoglobin oxygen saturation (SO2) was found in CMI patients, compared to controls, before treatment; mean ± SD: 67 ± 9% and 81 ± 4%, respectively (p < 0.001). A significantly lower relative hemoglobin (rHb) amount, flow and velocity (p < 0.001) were also found. The sensitivity of SO2 measured by VLS for diagnosing CMI was 94% and the specificity 72% (cut-off 78%), calculated with ROC curve analysis (Figure 13). However, a combination of SO2 and rHb increased the test sensitivity and specificity to 97% and 79%, respectively (Figure 13, Table 4).

In conclusion: Patients with atherosclerotic CMI have significantly reduced microcirculation in the stomach and duodenum compared to controls with normal intestinal circulation.
Figure 13: Receiver operating characteristics (ROC) curve of a mean of all measurements in the stomach and duodenum for \( \text{SO}_2 \) (red line) and for a combination of \( \text{SO}_2 \) and \( \text{rHb} \) (blue line) after normalization in patients with atherosclerotic chronic mesenteric ischemia compared to controls with a normal intestinal circulation evaluated with duplex ultrasound. A diagonal reference line is provided (green), which is a line of no discrimination.

Table 4: Area under the curve based on ROC-curve analysis of a mean of all measurements in the stomach and duodenum for \( \text{SO}_2 \) (\( \text{SO}_2\text{tot}/11 \)) and for a combination of \( \text{SO}_2 \) and \( \text{rHb} \) (\( \text{NORMSO}_2+\text{rHbtot} \)) after normalization in patients with atherosclerotic chronic mesenteric ischemia compared to controls with normal intestinal circulation evaluated with duplex ultrasound.

<table>
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<tr>
<th>Test Result Variable(s)</th>
<th>Area</th>
<th>Std. Error(^a)</th>
<th>Asymptotic Sig.(^b)</th>
<th>Asymptotic 95% Confidence Interval</th>
</tr>
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<tbody>
<tr>
<td>( \text{NORMSO}_2+\text{rHbtot} )</td>
<td>0.958</td>
<td>0.020</td>
<td>0.000</td>
<td>0.918</td>
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<tr>
<td>( \text{SO}_2\text{tot}/11 )</td>
<td>0.927</td>
<td>0.031</td>
<td>0.000</td>
<td>0.890</td>
</tr>
</tbody>
</table>

\(^a\) Under the nonparametric assumption

\(^b\) Null hypothesis: true area = 0.5
Paper II

During a 36 month period, 25 patients were evaluated for MALS (100). The study was designed as a single center case-control study. Patients with a consensus diagnosis of MALS ($n = 15$) underwent a gastroscopy assisted, transmucosal microcirculatory assessment with LDF and VLS (GALS). Results were compared to individuals with normal intestinal circulation ($n = 38$) evaluated with DUS, and to patients with chronic mesenteric ischemia ($n = 32$, Paper I). Treatment response was evaluated clinically at 1, 3, 6, and 12 months, and with VLS and LDF at three months. Health-related quality of life (QoL) was assessed with Euroqol (EQ-5D-5L), preoperatively, and 12 months postoperatively.

Preoperative mean transmucosal oxygen saturation was significantly lower in patients with MALS ($SO_2 \ 76 \pm 6$), as compared to healthy individuals ($SO_2 \ 81 \pm 4$), $p = 0.02$. A borderline significant improvement in $SO_2$ after surgical decompression of the CA was found ($SO_2 \ 81 \pm 3.7 \ \text{CG1}, \ p = 0.05$). Eleven (92%) patients with clinical improvement after laparoscopic decompression had a definitive diagnosis of MALS. Median follow-up was 18 months (4 – 24 months). Four of the five dimensions investigated with EQ-5D-5L improved, and a statistically significant improvement in patient’s self-perceived health status using a visual analogue scale was recorded ($p = 0.02$).

In conclusion: VLS detected a significantly lower baseline transmucosal $SO_2$ in patients with MALS as compared to control subjects with normal intestinal circulation, supporting a possible ischemic etiology in our patient population. A borderline significant improvement in $SO_2$ after laparoscopic decompression was found.
This study presents an initial experience with a limited series of laparoscopic mesenteric artery revascularizations for the treatment of CMI (101). From October 2015 to November 2018, nine patients with CMI underwent a laparoscopic bypass. The bypasses were constructed with an 8 mm ring enforced expanded polytetrafluoroethylene (ePTFE) graft in a retrograde fashion (from infrarenal aorta or iliac artery) to either the superior mesenteric artery (seven cases) or the splenic artery (two cases). Median operation time was 356 minutes (range 247–492 minutes). Five patients had a history of unsuccessful endovascular treatment. The laparoscopic technical success was 78%, and the primary open conversion rate 22%. All laparoscopic revascularization procedures remained patent at discharge. The median follow-up time was 26 months (range 18–49 months). The primary graft patency at 30 days was 78%. Primary assisted, and secondary graft patency was 78% and 100%, respectively. Median weight gain was 2 kg (range 2–18 kg), and all patients achieved relief from postprandial pain and nausea. No mortality was observed during the follow-up period.

In conclusion: laparoscopic aortomesenteric revascularization procedures for chronic mesenteric ischemia are feasible but require careful patient selection. These procedures should only be performed at referral centers and by vascular surgeons with prior experience in laparoscopic vascular surgery.
Discussion

Functional testing with visible light spectroscopy and laser Doppler flowmetry

Patients with atherosclerotic CMI (Paper I) and patients with MALS (Paper II) had a significantly lower mucosal arteriovenous oxygen saturation (referred to as \( SO_2 \)), as compared to controls. The recordings were made in the intestinal mucosa of the stomach and duodenum by means of VLS. This corroborates the findings of van Noord et al. who detected ischemia in patients using VLS in patients with CMI, and the findings of Mensink et al. who found impaired circulation in 29 of 30 patients with a consensus diagnosis of MALS, examined with GET (50, 53, 65). Furthermore, in patients with atherosclerotic CMI an impaired \( SO_2 \) (67 ± 9%) was found in both patients with multi-vessel \((n = 30)\), and single vessel \((n = 2)\) disease as compared to healthy individuals \((SO_2 81 ± 4)\) \((p < 0.001)\).

In patients with MALS \((n = 11)\), all of whom had single vessel pathology, the preoperative, baseline \( SO_2 \) was significantly lower \((SO_2 76 ± 6)\), as compared to healthy individuals \((SO_2 81 ± 4, p = 0.02)\) \((\text{Figure 14})\). The findings suggest that the collateral circulation is inadequate in both these patient groups. The symptoms are thought to come from insufficient postprandial oxygen delivery. The circulation appears, however, to be more impaired in patients with atherosclerotic disease than in patients with MALS. The saturation was significantly lower in atherosclerotic CMI patients as compared to MALS patients \((p = 0.004)\). Three patients (9%) with atherosclerotic CMI had ischemic ulcers visible during upper endoscopy. Histological examination of biopsy samples, however, has been reported to be of little value in diagnosing CMI (102). The transmucosal oxygen saturation increased and the velocity declined after decompression of the CA in eight of the eleven patients with symptom relief (one patient declined the second endoscopy). No change in saturation was found in the patient without clinical response to treatment. This increase in transmucosal oxygen saturation in 80% of the
controlled patients with symptom relief may help to conclude a successful laparoscopic decompression of the CA.

The vascular disease in patients with atherosclerotic CMI is more advanced and generalized than is the case in patients with isolated compression of the CA. The vessels in patients with MALS, who are significantly younger, are overall in a better state, and this could also be the case for the collateral circulation. CMI patients had more ischemic heart disease, hypertension, and diabetes mellitus, which are known risk factors of atherosclerotic disease. The findings do, however, suggest a possible ischemic etiology in MALS patients.

![Figure 14: Box plot of preoperative combined arterial and venous oxygen saturation in CG1 (Healthy) (n = 38), CG2 (CMI, n = 32) and patients with MALS (n = 11). The thick black line represents the median, the blue box represents the 25–75th percentile and the bars are minimum and maximum points (excluding outliers). Abbreviations: CG1, control group 1 (normal intestinal circulation evaluated with duplex ultrasound); CG2, control group 2; CMI, chronic mesenteric ischemia; MALS, median arcuate ligament syndrome.](image)

The therapeutic approach to single vessel atherosclerotic CMI and MALS is disputed (10, 103). In most patients, the collateral circulation is redundant and provide an adequate blood supply to the intestines in case of single vessel pathology. In selected patients, however, the collateral
circulation is inadequate. To identify the individuals with single vessel pathology who would benefit from revascularization, a functional test is required.

The pathophysiology in MALS is unclear. Both a neuropathic and ischemic etiology are proposed (104). Until recently, no diagnostic test has been able to verify an arterial insufficiency, and it has been considered a diagnosis of exclusion.

Our hypothesis was that both atherosclerotic CMI and MALS lead to insufficient oxygen delivery to the gastrointestinal tract. The insufficient oxygen delivery could in turn cause the patients’ symptoms. We explored the utility of laser Doppler flowmetry and visible light spectroscopy during upper endoscopy in these patients, hypothesizing that the insufficient oxygen delivery would be detectable in the stomach and duodenum, regardless of which of the mesenteric arteries were involved. Although VLS has been utilized for the detection of microcirculatory changes in CMI patients, this is the first study to apply the simultaneous use of VLS and LDF in the examination of patients with atherosclerotic CMI or MALS.

Using ROC curve analysis of a mean of all examination points, an area under the curve of 0.93, a sensitivity of 94% and specificity of 72%, with a cut-off value of 78% SO2 was found (Figure 13). The sensitivity and specificity found using VLS with the O2C is higher than previously reported by Van Noord et al. (65). They found a sensitivity of 90% and specificity of 60% for VLS in detection CMI using T-stat 303 Microvascular Oximeter (Spectros, California, USA). Further, Sana et al. evaluated treatment response in a large cohort of patients with clinical suspicion of CMI (105). A corpus mucosal oxygen saturation below 56% was one of the strongest predictors of treatment response. The recorded measurement values in the data set of van Noord and Sana et al. are lower than in our patient group, which could be due to differences in patient population, and use of a different apparatus, albeit with the same technique.
One major limitation of the VLS technique has been the lack of data with regards to its applicability in CMI patients. Most of the published data is from one center, the Dutch mesenteric ischemia group, and the present study is one of the first to corroborate their results.

A combination of the two variables examined by VLS (SO$_2$ and rHb) after normalization gave an area under the curve of 0.96, with an increase in sensitivity to 97% and specificity of 79% for diagnosing CMI compared to SO$_2$ alone. Normalization is performed to adjust values measured on different scales to a notionally common scale, and hence a mean or a single value can be deduced from the two variables.

A low specificity of VLS has been a debating point in the application of this method for patient selection in CMI (63). Our SO$_2$ cut-off levels in Paper I were chosen to increase the sensitivity at the disadvantage of specificity. This decision was made after consideration of the negative consequences of a false negative test (patients going untreated), in comparison to the negative consequences of a false positive test (patients receiving a diagnostic angiography, and possibly unnecessary treatment).

In patients with MALS, a ROC curve analysis was performed, and an area under the curve of 0.70, and sensitivity and specificity of 82% and 60%, respectively was found with a SO$_2$ cut-off of 80%. The 80% cut-off was found using the ROC curve, and this was found to be the point closest to (0,1) which is considered the optimal trade-off between sensitivity and specificity. Using the same cut-off of 78% as in the atherosclerotic CMI group, resulted in a 54% sensitivity and 64% specificity. This is regarded as too low for the test to be utilized for patient selection alone. However, it could be of value as part of the decision basis in a multidisciplinary meeting for consensus diagnosis. A positive and negative predictive value is not possible to calculate, as the prevalence of MALS is unknown. However, a high negative predictive value would be appreciated, to utilize the test as a diagnostic tool to exclude MALS, as most patients referred on suspicion of MALS in fact have another cause to their complaints. To increase the negative
predictive value, a high specificity is required. Reducing the cut-off further will increase the specificity but this comes at the expense of the sensitivity. If the sensitivity is too low, many patients will be left untreated. If the cut-off is too high, some patients will be treated unnecessarily. At 80%, which is the optimal cut-off for this test based on the ROC analysis, there is a significant overlap with the control subjects (81 ± 4%). At 78%, the sensitivity is as low as 54%. The timing of the test in the investigation of these patients must also be considered. If VLS is utilized on patients in which all other common, likely differential diagnosis already have been excluded, the probability that MALS is the reason for their complaints is higher. In our population 11 of 12 patients experienced symptom relief after treatment, suggesting that the multidisciplinary evaluation of patients has reduced the likelihood of other causes of the patients’ symptoms. A high positive predictive value, and a high sensitivity would be appreciated if VLS was applied in this setting, suggesting a cut-off of 80% is preferable. The relatively low sensitivity and specificity found on all cut-off levels does however lead to conclude that the test capabilities are inadequate for patient selection.

The sensitivity is reported as 100% for CT angiography detecting ≥50-70% stenosis of one or more mesenteric arteries, but gives little information regarding the physiological consequences of the flow-limitation, especially in single vessel disease (106). The prevalence of intestinal artery stenosis is increasing with age and is around 18% in patients aged 70 years or more, hence a functional test is in some patients required to evaluate the implications of the stenosis (107).

The celiac artery was involved in 97% (n = 31 of 32 patients) of the patients with atherosclerotic CMI, the SMA in 88% (n = 28) and IMA in 44% (n = 14). In patients with MALS (n = 11), the CA was involved in all patients, and no other vessel was found to be affected. It could be argued that measurements in the colon may give a better test performance because of the importance of the SMA in colonic perfusion. Patients do, however, in most cases (75%, n = 22 of patients
with atherosclerotic CMI, and 82%, \( n = 9 \) of MALS patients) describe pain within the first 30 minutes of a meal. At that time point, the food is still in the stomach, suggesting this to be a more accurate anatomical localization for the measurements. Measurements in the colon could be explored in future studies, and it would be interesting to see the effect of a meal on the colonic perfusion, as a stress test in the form of a meal is more feasible in colonoscopy than upper endoscopy. The colon is, as the small bowel, protected from ischemia by a redundant collateral blood supply through the collateral vessels. The anatomy varies, and in some individuals, the splenic flexure and sigmoid colon are watershed-areas caught between the branches of two major vessels, and hence has a higher risk of ischemia. The right colon may be especially vulnerable in individuals with a poorly developed marginal artery of Drummond, which is the case in 50% of the population (108). Furthermore, the right colon has a thinner mucosa, and may therefore be more susceptible to ischemia (109). Friedland et al. performed an animal study on the applicability of VLS in colonic ischemia in 2003 (110). Studies have later examined the use of trans-serosal VLS in evaluating colon anastomosis following colorectal resection (111). Previous studies have also used LDF in evaluation of colonic perfusion during aortic surgery (60). The applicability of VLS during colonoscopy in patients with CMI would be interesting, but in our population the significant findings with lower mucosal oxygen saturation in the stomach and duodenum suggest this was an adequate anatomical localization for the measurements.

A simultaneous use of VLS and LDF has not previously been reported, and this study is to our knowledge, the first to apply this strategy. In our study, LDF was inferior to the more recently developed technology of visible light spectroscopy. VLS measurements (\( \text{SO}_2 \) and \( \text{rHb} \)) were highly significant in all examined areas in patients with atherosclerotic CMI. This was only the case for \( \text{SO}_2 \) (mean of all examination points and duodenum) in MALS patients. The
microcirculation in MALS patients was found to be better than in patients with atherosclerotic CMI (Figure 14).

The demonstrated improved sensitivity and specificity for the combination of rHb amount and SO₂ suggest a possible clinical value of VLS measurements performed during upper endoscopy at an earlier stage in the diagnostic evaluation of patients with chronic abdominal pain. The mean age of patients with CMI is reported by Alahdab et al. to be 69 years (73 years in Paper I), and the disease has an unequal gender distribution as 62% of the patients were female (63% in Paper I) (70). Furthermore, 66% had a smoking history (91% in Paper I). Hence, VLS measurements during upper endoscopy could be particularly of value in female patients over 60 years of age with a smoking history and abdominal pain, even in patients without prior imaging diagnostics. In case of a positive VLS (impaired microcirculation, low SO₂), patients should be referred to a specialist in vascular surgery for further diagnostic work-up.

VLS measures (indirectly) the oxygen extraction in the cells. The first compensating mechanism in the cells following insufficient oxygen delivery is an increased oxygen extraction rate. This may explain why VLS was superior to LDF in the diagnostics. A comparison of VLS and microvascular oxygen tension in vitro in a porcine model was performed in 2019 (112). This was performed to compare VLS to a validated measurement technique, i.e., the microvascular oxygen tension. Measurements were performed on the small intestine on five pigs at different FiO₂ (fraction of inspired oxygen) values (18-100%), with and without bile, and before a lethal dose of potassium chloride was administered. Atmospheric FiO₂ is 21%. The results suggested that VLS measures the mixed oxygen saturation rather than mucosal capillary hemoglobin oxygen saturation. The authors conclude that further investigations are needed to evaluate if mixed oxygen saturation is the best method to evaluate ischemia. The manufacturer of the O2C used in our studies claim that we measure the combined (mixed) arterial and venous capillary hemoglobin oxygen saturation, with 75% overweight on venous
side, which is in accordance with the results mentioned above. We hypothesize that the capillary venous oxygen saturation indeed is the better variable compared to arterial oxygen saturation, as the amount of oxygen bound to hemoglobin after distribution of oxygen to the tissues is measured, which gives an indication of the balance between oxygen delivery and consumption.

Another interesting study performed compared the sublingual microcirculation in patients with CMI and healthy controls with a Cytocam incident dark field illumination videoscope device, before and after a caloric challenge (113). An impaired microcirculation both at baseline, and a significant response after caloric intake compared to healthy controls with a normal baseline circulation, was found. This method may offer a rapid, noninvasive method to identify patients at risk of having CMI.

The main objective of a functional test is to reveal an insufficiency in the collateral circulation. In the case of multi-vessel disease, the need of a functional test is not evident. Patients may be treated based on typical symptoms, exclusion of common differential diagnosis, and a CTA. However, in case of borderline significant stenosis on CTA or single vessel pathology in atherosclerotic CMI and in MALS, a functional test is warranted for discriminative purposes. Herein are the consequences of over- and undertreatment important. There is a risk of overtreating patients with suspected single-vessel CMI without a discriminative test. Overtreatment may cause potential complications without any benefit to the patient. In case of multi-vessel pathology, the risk of overtreatment is low, as the mesenteric disease more frequently is symptomatic, and clinical success ranges from 90-100% (11). Furthermore, the burden and possible consequences of leaving a patient with atherosclerotic CMI untreated are critical, with the possible development of AMI.

For a functional test to have clinical value, it should be readily available, affordable, easy to use, fast and fail-safe. VLS (and in part LDF) fulfil these criteria. The sensitivity for VLS in detecting CMI in this study is higher than the specificity. However, as the implications of
overtreatment are less serious than under treatment, VLS could be valuable in the diagnostics and patient selection for treatment also in its current state, especially for CMI of atherosclerotic origin as a progressive disease. In patients with MALS, a diagnostic test with a high specificity would be preferable, leading to a high negative predictive value. This would mean that a high proportion of patients with a suspicion of MALS, but a negative VLS, can be excluded from surgery. The clinical implications of under treatment are less serious in patients with MALS, a single vessel disease, as no patients to the best of our knowledge, have developed AMI.

A functional test is, however, not necessary in all patients. In patients with multi-vessel pathology and typical clinical presentation the symptom relief after revascularization is high. In a 2019 review by the Dutch mesenteric ischemia group, a functional test is recommended in patients with single vessel stenosis; in patients with typical symptomatology but without significant stenosis on CTA, and in case of atypical symptomatology in patients with multi-vessel pathology (103). The clinical management and diagnostic work-up of patients with suspected CMI is summarized as an algorithm in Figure 15. In our study, only two patients with atherosclerotic CMI had single vessel disease, and further studies are needed to corroborate the results in this patient group. The over-all excellent results of treatment in our study on patients with atherosclerotic CMI and typical symptoms supports the conclusion that a functional test is not necessary in all patients. 94% (n = 30) of our patient had multi-vessel disease. There were 24 patients who were excluded based on <70% stenosis. In retrospect, inclusion and evaluation of the microcirculation in this sub-group would have been particularly interesting.
Figure 15: Flowchart over the most important steps and criteria of the diagnostic work-up of patients with suspected CMI. Patients with typical symptoms are examined to exclude common differential diagnosis before imaging is performed. In case of atypical symptomatology in patients with multi-vessel pathology, in patients with single vessel stenosis and in patients without stenosis, but with typical symptoms, a functional test is recommended prior to a multidisciplinary evaluation consisting of vascular surgeons and gastroenterologist. Adapted from van Dijk et al. (103)

The patients with MALS were relatively young (median age 45 (range 24-72)), and otherwise healthy. Still, a significantly lower transmucosal combined arterial and venous capillary hemoglobin oxygen saturation in MALS patients compared to controls with normal intestinal circulation ($p = 0.02$) was found. A borderline significant increase in this variable was found
after intervention ($p = 0.05$). A lower oxygen saturation was found in both the stomach and duodenum in MALs patients compared to healthy controls. This supports the prevailing theory that the patient’s symptoms are a result of ischemia due to insufficient oxygen delivery. This could be by means of direct compression of the CA and following reduction in blood flow through the CA, or due to a neurogenic irritation leading to splanchnic vasoconstriction (73). A solely neuropathic etiology seems less likely in our population even though neurolysis was performed. The present results suggest that there is an insufficient collateral network in these patients, and not the common collateral redundancy, to an extent that cause lower oxygen saturation even in a fasting state. The reduction in oxygen saturation in the duodenum could be a consequence of a steal phenomenon from the SMA leading to ischemia. Despite the lack of consensus regarding disease pathophysiology, most studies have reported good results of either laparoscopic or open median arcuate ligament release (104).

Supporting a neurogenic etiology in MALs patients a percutaneous celiac plexus block was performed in five MALs patients by Weber et al. (114). Weber et al. reported temporary symptom relief in four of these patients and one patient without response to the blockade. A clinical response was, however, reported in all five patients after laparoscopic decompression of the celiac artery. First, the results presented by Weber suggest a possibly good positive predictive value for diagnostic blockade in MALs patients, and secondly, they argue that it was the neurolysis of the celiac plexus which led to symptom relief in this patient group. One patient reported symptom relief, although the celiac artery was occluded both pre- and postoperatively. Six patients (23.1%) had persistent stenosis and one had an occlusion but were symptom free. There was no significant difference in persistent compression of the CA on postoperative DUS between responders and non-responders (responders had more frequently residual stenosis). Unfortunately, evidence supporting this conclusion is scarce (104). A recently published retrospective cohort of 96 patients who underwent celiac plexus block, demonstrated findings
of a celiac artery compression in 22 patients and normal anatomy in the remaining (115). A dedicated inspiratory and expiratory phase CT was available in 9 patients. A clinical improvement was reported in 90% of the patients, with no difference between the group with normal anatomy and the group with external compression of the CA. 44 patients (46%) underwent resection of the MAL and celiac plexus, with significant improvement in pain scores. They conclude that the primary etiology of the patients’ symptoms is neuropathic. The retrospective design and the lack of imaging data are major limitations to the report.

The high prevalence of asymptomatic patients with external compression on the CA, as well as a redundant collateral circulation in most patients, and the consideration of the SMA to be the most important mesenteric vessel, are all arguments in disfavor of an ischemic etiology.

Van Petersen et al. performed a retroperitoneal endoscopic (videoscopic) CA release, for MALS in 46 patients (116). With this approach only the left crus of the MAL is divided, and keeps the celiac plexus almost completely intact. Their excellent results, despite the lack of neurolysis, contradicts the notion of MALS as a neurogenic disease.

Our findings of a significantly lower preoperative SO₂ in MALS patients as compared to controls, supports a possible ischemic etiology. This is further supported by a borderline increase in saturation after intervention accompanied by symptom relief. Columbo et al. reported that 33% of their patients reported recurrent or unresolved symptoms after laparoscopic decompression, requiring a PTA and stent in the CA (117). This is corroborated by van Petersen et al. (116). The necessity for an endovascular stent placement or aortoceliac bypass to achieve symptom relief, even after surgical division of the MAL and neurolysis, is indicative of an ischemic etiology. Furthermore, the positive results after the endovascular procedure, and not after the decompression, makes a placebo effect less likely in these patients.
One patient with relief of symptoms had an increase in velocity on DUS post-intervention, but this could be due to an erroneous ultrasound measurement, as the patient displayed an improvement in SO₂ after decompression. Mensink et al. reported a positive GET in 97% (n = 29) of patients with a consensus diagnosis of MALS prior to intervention, suggesting a possible ischemic etiology in their material. Of the 29 treated patients, 24 had symptomatic relief, and of the patients who underwent a repeat GET (n = 16), all had a normal GET, in contrast to only one of the patients (25%) with persisting complaints. Unfortunately, 13 symptomatic patients were excluded from surgery due to a normal GET, which would have been an excellent control group.

The evidence supporting a clear pathophysiology is weak for both an ischemic and neurogenic etiology. It is not clear if the patients suffer from ischemic induced pain as a result of primary insufficiency in the celiac artery, with insufficient collateral circulation or steal from the SMA, or ischemic induced pain due to celiac plexus overstimulation leading to vasoconstriction or a pure celiac plexus irritation mediating a neuropathic pain.

In Paper II we conclude that there is a possible ischemic etiology in MALS patients. The data available is divided; it could be a vascular etiology to the MALS patients’ symptoms, and it could be purely caused by irritation of the celiac plexus (leading to vasoconstriction and ischemia in some patients) and hence a neuropathic disease.

Treatment

There are currently two methods to treat atherosclerotic CMI. Open surgical release, or endovascular treatment (with or without stenting and / or in combination with IVUS or laser atherectomy). However, laparoscopic mesenteric bypass surgery could be a third therapeutic option. Laparoscopic mesenteric bypass surgery may offer the advantages of a minimally
invasive surgical technique which, for an experienced laparoscopic surgeon, may be of value in selected patients.

Treatment of atherosclerotic chronic mesenteric ischemia

Thirty-three patients were referred to treatment based on a consensus diagnosis of atherosclerotic CMI. Treatment was PTA + stent (n = 26) or open surgery with aortomesenteric bypass (n = 7). An aortomesenteric bypass was performed in case of failed endovascular therapy, or in patients with unsuitable anatomy, as is the strategy in most vascular centers (3). The superior long-term patency of open surgical bypass is offset against the early benefit of endovascular therapy with lower post-operative in-hospital morbidity and 30-day mortality (70). Open mesenteric bypass surgery can be performed safely in the hands of an experienced surgeon, with contemporary reports of mortality rates of < 3% (118). There has been an improvement in outcomes of mesenteric reconstructions in the last decades. Advances in medical, anesthetic, and intensive care management, in addition to technical refinements and better patient selection, could be responsible for the improvement in outcome.

In our material, symptom relief was reported in 97% (n = 32) of the treated patients at one-month follow-up. One patient with three-vessel pathology underwent an unsuccessful endovascular procedure and was unsuitable for further attempts both open and endovascular due to comorbidities. Three successfully treated patients died prior to post-intervention microcirculatory assessment at three months; one stent-occlusion, one occluded bypass after open surgical revascularization, and one of unrelated cause. Two patients referred to treatment died prior to intervention. The results reflect the seriousness of this disease, and the severe consequences of delayed therapy and therapeutic failure.

A post-operative VLS and LDF were performed in 69% (n = 22) of the patients. All patients reported symptom relief, and an increase in \( \mathrm{SO}_2 \) was found in 73% (n = 16) of the patients.
Repeated measurements at six and 12 months would have been interesting, to see if the microcirculation improved further by time and especially if the microcirculation in the six patients without improvement in SO₂ at three months changed over time. SMA is the preferred target vessel for treatment, and as the CA was affected in 97% (n = 31) of the patients, this could explain the lack of improvement in the stomach and duodenum. A pre- and postoperative measurement in the colon would have been interesting in this patient group based on the arterial supply of the colon by IMA and SMA. Follow-up duplex ultrasound did not show any residual stenosis, and all by-passes were patent at one month. There is a time-gap between the evaluation of the treatment patency and the microcirculatory assessment which could be a confounding factor.

In the 2020 guidelines on CMI, a SMA stenosis over 50% is suggested to be relevant in patients with multivessel disease (10). This comes as a recommendation, with expert agreement of 78%, and is based on a comparison of surface area and blood flow volumes through the SMA and CA, which revealed the surface area and postprandial flow to be 33% higher in the SMA. The current practice in our institution is to consider a 70% stenosis to be significant on either SMA or CA. The Dutch Mesenteric Ischemia Group propose ≥70% stenosis to be significant in single-vessel disease, as they found the probability of CMI in case of an isolated intermediate (50-70%) stenosis to be 0% and 10% for the CA and SMA, respectively (11). They also argue that a ≥50% stenosis is suitable for patients with affection of both CA and SMA. The probability for CMI was 83% in this group. These new guidelines, although with evidence grade 2B, appear to be reasonable and adherence to the guidelines means treating more patients for atherosclerotic CMI in the future.

Recently, laser atherectomy has been explored as a treatment option in patients with in stent restenosis of the SMA in patients with atherosclerotic CMI (119). As the laparoscopic mesenteric bypass surgery is reserved for patients with unsuitable anatomy or failed
endovascular treatment, the laser atherectomy could reduce the number of patients suitable for this technique further, however, this need to be explored further.

Intravascular ultrasound (IVUS) has been used in complex cases where conventional endovascular treatment has failed (119-121). Guidance with IVUS may further increase the spectrum in which an endovascular approach is feasible. IVUS may also have a part in evaluation of grade of stenosis, as an alternative to pressure gradient measurements, or as an option to demonstrate the dynamic nature of the obstruction in MALS (122).

A laparoscopic mesenteric bypass was performed with informed consent in nine patients with CMI from October 2015 to May 2018 and found feasible (Paper III). It was performed by means of a transabdominal direct approach to the abdominal aorta and the mesenteric vessels. This approach does not require dissection for medial mobilization of the splenic flexure, descending and sigmoid colon as is required with a retro-colic or retro-renal approach. Besides, a longer length of SMA and its branches can be dissected free with this approach in comparison with the retro-renal approach. The retro-renal approach allows for access to the full aortic length from diaphragm to left iliac artery laparoscopically. However, the dissection is more extensive and the peripheral segments of SMA and CA branches remain inaccessible.

Three of the nine patients treated with laparoscopic mesenteric bypass suffered from complications; two graft thrombosis and one ureter injury. Two of the complications (graft thrombosis) were related to the novel laparoscopic technique, and the technique was adjusted during the course of the study based on experience from these complications. Graft thrombosis is a well-known complication in all vascular bypass-surgery. One conversion to open surgery was done due to a venous bleeding from the inferior mesenteric vein, and one conversion was done due to difficulties to maintain a stable visual of the mesenteric vessel during anastomosis. None of these patients suffered any complications. All patients were treated by an experienced team in laparoscopic surgery (97). The three complications were in the four first patients in this
study. The last two patients treated had no complications related to the technique indicating a learning curve with fewer complications with increasing experience, although the number of patients is low. Several technical challenges and possible solutions are presented. Primary assisted patency was 78% and secondary patency at 30 days was 100%. The secondary patency after a median postoperative follow up of 26 months (range 18-49 months) was 100%. Many technical details, such as a routinely use of a laparoscopic ultrasound probe to evaluate graft patency per-operatively, or the use of a side graft to allow safe and effective route for flushing the main graft during the surgery or for a per-operative angiography were discovered. A careful patient selection and meticulous operative technique were identified as key factors for success through this early experience. Yet, based on the current relevant occlusion and complication rate, further investigations and studies are necessary to evaluate this novel approach adequately. The laparoscopic mesenteric bypass surgery technique is an advanced procedure which should only by performed at vascular centers with experienced surgeons in laparoscopic aortic surgery.

There are few trained vascular surgeons with skills in laparoscopic vascular surgery, and the improvement in endovascular techniques have led to the question if laparoscopic vascular surgery techniques are necessary. Despite much experience in laparoscopic surgery, our team experienced several complications in this feasibility study. The development and improvement in endovascular techniques have reduced the number of patients eligible for the most common laparoscopic procedures in vascular surgery; treatment of aortoiliac occlusive disease and abdominal aortic aneurysms (123). The traditional open bypass for aortoiliac occlusive disease is now reserved for patients with complex occlusions or failed endovascular therapy. This reduction in case load, also reduces the training volume, and increases the technical challenges of laparoscopic surgery, a technique which requires much training to master and maintain.

Some of the intriguing advantages of a minimally invasive approach are easier and faster recovery in combination with the durable results of open surgical repair. Survival freedom from
composite events (all-cause mortality, graft thrombosis, and systemic morbidity) was found to be significantly lower in patients treated with laparoscopic aortobifemoral bypass for aortoiliac occlusive disease compared to open surgical bypass, by Krog et al. (97). However, the results of NLAST, a large randomized controlled trial comparing open and laparoscopic surgery in treatment of aortoiliac occlusive disease, are pending.

The laparoscopic mesenteric bypass procedure should be reserved for selected, tertiary referral centers in vascular surgery. We believe there are subsets of patients, unsuitable for endovascular therapy, who would benefit from a minimally invasive surgical approach. Laparoscopic surgery has also been shown to be a cost-effective option (124).

Treatment of median arcuate ligament syndrome

The existence of MALS is still debated, and many argue that the data available are of low quality, inconclusive and may be affected by publication bias. However, one systematic review referred to in the recent guidelines on CMI found an 80% sustained symptom relief after CA release for MALS in 400 patients (10, 84). This corresponds with our study population with 91% sustained symptom relief.

In the present study, laparoscopic decompression of the CA was found to be safe and without major complications. Laparoscopy has been the treatment of choice for more than a decade in this patient group, with good results. Sustained symptom relief has been reported to be 90% after laparoscopy, compared to 75% after open surgical release (84). None of the patients in our study had any adverse events or reported worsening of preoperative symptoms. In total, 92% of the treated \( n = 11 \) patients reported postoperative symptom relief (median follow-up 18 months, range: 4 – 24 months), suggesting an adequate patient selection. Cienfuegos et al. have distinguished patients with >70% stenosis from those with 50-70% and found better results in the first group (125).
In one patient, there was an increase in velocity measured postoperatively by transabdominal duplex ultrasound. This patient reported symptom relief and had an increase in oxygen saturation after intervention. Furthermore, one patient had clinical effect, but had a reduction in oxygen saturation. Errors in measurements may occur; both with DUS and VLS. The patients could also have a placebo effect of the treatment. There are no studies available comparing the results of sham surgery and decompression of the CA in patients with MALS. The placebo effect has, however, been demonstrated through sham surgery on other patient populations. Schröder et al. found a significant improvement in objective and subjective shoulder scores, without any group differences, for two surgical approaches and sham surgery for SLAP (superior labrum anterior posterior) II lesions of the shoulder (126). A similar approach to patients with MALS, comparing decompression of the celiac artery (with neurolysis of the plexus), to bypass-surgery leaving the celiac plexus intact, and sham surgery would have clarified both the pathophysiological aspect of the disease, as well as resulting in a conclusion towards the existence of the disease, however it is possible that this in fact is two different diseases with the same angiographic finding.

Studies have reported a high incidence of psychiatric disease in MALS patients, which could influence the patient’s response to surgery (127, 128). Two patients (18%) had a history of psychiatric disease (anxiety / depression) in our study population.

Quality of Life

Nine of the 11 successfully treated patients completed a validated and Norwegian translated questionnaire EuroQol (EQ-5D-5L). A statistically significant improvement on the visual analogue scale, from 44 preoperatively to 62 postoperatively, was recorded ($p = 0.02$) (Table 5). Improvement was found in four of the five health dimensions explored (mobility, self-care, usual activities, pain / discomfort, and anxiety / depression). An improvement in the EQ-5D
index score was found, although not statistically significant. The results give an indication of the benefit of treatment in this patient group. Careful patient selection is nonetheless paramount to obtain adequate results.

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Table 5: EQ-5D index score and visual analogue scale (VAS) before and after treatment in patients with median arcuate ligament syndrome (Paper II).

In 2019, the Dutch Mesenteric Ischemia Study Group published an article evaluating the impact of revascularization in patients with atherosclerotic CMI on health-related quality of life (HRQoL) (84). Fifty-five (69.6%) patients returned their questionnaire (EQ-5D), however, only 23 (29%) completed the questionnaire. Furthermore, there was a long time (mean 20 months) between revascularization and completion of the postoperative questionnaire, which also adds to the limitations of the study. However, this study was the first to demonstrate improvement in HRQoL (median EQ-index score from 0.70 preoperative to 0.81 (p = 0.02) postoperative) in patients with CMI after mesenteric artery revascularization.

Methodological considerations

The absence of a gold standard clinical test to diagnose CMI is an expected limitation of the studies. A consensus diagnosis is reached based on typical symptomatology, exclusion of differential diagnosis and typical findings on CT-angiography interpreted within the range of current guidelines for stenosis grade. A definitive diagnosis is established based on symptom relief after treatment. In the present study, symptom relief was, however, reported to the same team of physicians who were responsible for treatment and bias cannot be excluded (129).
Despite being a tertiary referral center, the size of the center did not permit blinding of patients or examiners and may have contributed to measurement bias. In paper I, the number of patients with a definitive diagnosis of CMI ($n = 32$) did not reach the required sample size calculated in our power analysis ($n = 36$ in each group). In paper II we expected the difference between the MALS and control group to be less pronounced than was the case in atherosclerotic CMI compared to controls. Further, we reduced the expected standard deviation, as we found it likely that the MALS group would be more heterogenous than patients with atherosclerotic CMI with a variability in affected vessel and disease progression. Under these premises, a sample size of 10 patients in MALS group and 32 in the control group was found, and this sample size was reached for both groups. The assumption proved to be close to the results found, but a slight increase in expected standard deviation would have markedly increase the required number of patients in the study. Considering the rarity of the disease, we accepted the relatively low number of patients, but a higher number of patients could have resulted in a statistically significant improvement in saturation post-intervention, which would have improved the paper.

In paper I, patients evaluated on suspicion of CMI were significantly older than the controls, had a higher prevalence of cardiovascular disease and smoking. This is a limitation to the study, as both age and smoking may have affected the measurements. Smoking is a major risk factor of atherosclerotic disease, and a common denominator in many patients with vascular disease. Patients were fasting prior to investigation and were instructed not to smoke in the 6 hours prior to the endoscopy. The effect of nicotine was hence low during examination, as $t/2$ of nicotine is 2 hours (130). The chronic effects of cigarette smoking were not considered to be a confounding factor, rather in part a consequence of the atherosclerotic disease which in some patients affect the mesenteric arteries. Furthermore, matching the patients with CMI to control patients with regards to smoking was not done as we were not privy to that information prior to inclusion. With regards to a higher prevalence of cardiovascular disease in the CMI group, this
was considered unlikely to interfere with the results in a resting state. No patients had symptoms of ischemic heart disease during the examinations.

We have attempted to obtain an even gender distribution between the groups, (63% \( n = 20 \)) female in CMI group, 63% \( n = 7 \) female in the MALS group, and 55% \( n = 21 \) in control group), but as the inclusion of patients was performed parallel to the inclusion of control patients an exact even distribution was not achieved. There was no statistically significant difference between the two groups with regards to gender. The same control group was used in Paper I and II, but as patients with atherosclerotic CMI in general are older than patients with MALS, a matching of a control group to both patient groups was challenging. In retrospect, a separate control group for each of the two different entities, MALS and atherosclerotic CMI, with matching age would have been preferable as, to the best of our knowledge, no studies with VLS have been performed with an even age distribution (63, 131).

A limitation to the study in both paper I and II was the lack of a common radiological diagnostic procedure, as the controls were examined with duplex ultrasound, and not CT angiography. We did not obtain approval from the ethics committee for performing CT angiography of the patients in the control group since they were relatively young and we would not expose them to radiation and contrast.

The gastroscopy assisted VLS and LDF was performed in fasting, resting patients. They were asymptomatic at the time of examination, but a reduction in mucosal circulation was detected, nonetheless. After a meal, the metabolic demand is higher, and the deficit in the microcirculation would intuitively be more pronounced. A meal would increase the metabolic demand, but as a stress test during upper endoscopy, it increases risk of aspiration and may affect both the endoscopist’s overview and the measurements performed. One study on VLS after luminal feeding found an increase in duodenal oxygen saturation in patients with atherosclerotic CMI (131). However, an increase was found in both non-CMI patients and
healthy controls as well, and neither the postprandial oxygen saturation levels nor their absolute or relative difference from pre-prandial measurements provided any additional discriminative potential for the diagnosis of CMI.

We found that a significant stenosis or occlusion in the intestinal arteries caused an on average global reduction in microcirculation of the stomach and duodenum in patients with CMI. The reduction found was regardless of the localization of the stenosis and despite the presence of an extensive collateral network. This has been a debating point of the applicability of VLS, as ischemia may be patchy and measurements may miss the anatomical localization of the ischemic tissue (63). Repeated measurements on several points in the stomach and duodenum seems to compensate for this. The microprobe (LM-10) used in this study requires a stable position with light contact to the mucosa and is dependent on an experienced endoscope operator. The same team of physicians performed all endoscopies to ensure reproducibility. It would be beneficial if a probe (or several) could be somehow attached to the mucosa at different locations. The O2C would with an attached probe be able to give continuous readings over a longer period, in a way like previously reported for tonometry.

The study in paper III was designed as a descriptive observational case series. A limitation to the study was that no comparison between the new technique and established therapeutic alternatives was made. A completion angiography or flow measurement of the reconstruction might have improved the results and should have been performed. The patients with atherosclerotic CMI often have many comorbidities. Hypertension, chronic obstructive pulmonary disease, diabetes mellitus, heart disease, and smoking increase the risk of complication in surgical patients. The patients in our study suffered from complications related to technical aspects of the new surgical approach. A comparison with the open surgical approach will in future studies add to interpretation of the clinical implications of the new technique.
Conclusion

Main conclusion

A functional test with a high sensitivity and specificity is necessary for adequate patient selection in treatment of CMI. The hypothesis “Patients with atherosclerotic CMI or MALS have an impaired microcirculation detectable with VLS and / or LDF” was tested. Based on our findings we reject the null hypothesis (no difference in microcirculation between patients with MALS or atherosclerotic CMI and control group). LDF and VLS can be applied to detect ischemic changes in the microcirculation in both patients with atherosclerotic CMI and patients with MALS. VLS is superior to LDF, with highly significant findings in all examined areas in patients with atherosclerotic CMI, and in the duodenum of MALS patients, as well as a significantly lower mean SO$_2$ (all areas combined) in both atherosclerotic CMI patients and MALS patients.

A significantly lower SO$_2$ in the duodenum of MALS patients ($p = 0.006$) suggest a possible ischemic etiology to the symptoms in this patient group. A borderline significant improvement in SO$_2$ after successful laparoscopic decompression support this theory. However, as a division of the celiac plexus was performed during laparoscopic decompression, the patients’ symptoms could partially have been of neurogenic etiology.

Our results suggest that VLS during upper endoscopy should be a part of a diagnostic work-up of patients with CMI of atherosclerotic origin. VLS may play a role in future diagnostics of MALS, in combination with clinical evaluation and an imaging study, preferably CT angiography.

The combination of VLS and LDF did not improve the sensitivity and specificity in diagnosing CMI. The sensitivity of VLS for diagnosing CMI was found to be 97%, and the specificity 79%,
which is higher than in previously published reports. With regards to MALS, the sensitivity and specificity was found to be too low to be utilized for patient selection.

Laparoscopic decompression of the median arcuate ligament is a safe and effective treatment of MALS. Laparoscopic mesenteric bypass in treatment of atherosclerotic CMI may be an additional therapeutic option for experienced laparoscopic vascular surgeons in case of lesions unsuitable for, or after failed endovascular treatment. Based on the small material in this study, with a relevant occlusion, conversion and complications rate, further studies are needed to evaluate this novel approach adequately.
Concluding remarks and future perspective

A functional test, such as discussed in this thesis, is essential in patients with single vessel pathology or atypical symptomatology. VLS has a high sensitivity, but there is still room for improvement with regards to specificity to prevent unnecessary invasive treatments in case of false positive tests. Further studies are needed to corroborate the results of this thesis, and explore other, possible diagnostic tools to improve patient selection in both atherosclerotic CMI and MALS.

The SMA is the most important vessel with regards to flow to the mesentery and hence, placement of a probe in the mid ileum would be particularly interesting. There is a redundant collateral circulation to the bowel, but a mid-ileum probe placement would give a more targeted measurement of the SMA. Given the physical location distal to the stomach, a mid-ileum probe placement might permit the examinator to do a stress test in form of a meal in the patients. A stress test might yield more pronounced differences between healthy subjects and patients, and one might hypothesize that both the sensitivity and the specificity of the diagnostic test would increase. A remotely controlled endoscopic capsule with ability to adhere to the mucosa at a point of interest before performing measurements, or a continuous recording through the GI-tractus would also be interesting, as previously mentioned.

Microdialysis is a minimally invasive in vivo sampling technique used for continuous measurement of local biochemical substances and molecules in the extracellular fluid of specific organs or compartments, aiming to detect ischemia. It is applied in several clinical areas, including microvascular surgery and transplantation for early detection of ischemia. Several animal studies have been conducted and verified the applicability in detection of intestinal ischemia, however, few human studies have been performed (132). This technique, although invasive, could aid in the diagnostic evaluation of patients with single-vessel CMI or patients with atypical symptomatology.
A biomarker sensitive and specific for CMI obtained through a blood sample, such as IFABP (intestinal fatty acid binding protein) or CABA (cobolt albumin binding assay), plasma citrulline, immune modified albumin and alfa glutathione s-transferase, which have been previously investigated for its utility in diagnosing AMI, could also be investigated as non-invasive tests to detect CMI.

The utility of endoscopic ultrasound for evaluation of mesenteric artery stenosis is currently examined by our research group as minimally invasive alternative diagnostic test in cases where transabdominal DUS visibility and interpretation is limited by gas, artefacts, or obesity.

With regards to MALs, a major debating point is the very existence of the disease. Despite several studies displaying good results from surgical release of the CA from the median arcuate ligament, a consensus on this rare disease has been difficult to obtain. A blinded, randomized controlled trial comparing release of the CA to a placebo surgery / sham operation in patients with suspected MALs, would aid in clarifying this, if performed at a large center and with an adequate number of patients. With regards to detection and diagnostics, the same applies for MALs as CMI in general, and it would be interesting to see if biomarkers for identification of CMI can be used in MALs as well, assuming ischemia is the cause of the patients’ complaints.

CMI is a disease with many unanswered questions. The epidemiology is still unclear, and incidence and prevalence ought to be mapped through cross-sectional studies. At Oslo University Hospital, we have debated the possibility of including DUS of the mesenteric arteries in the screening program for abdominal aortic aneurisms. The main objection to this protocol adjustment to the screening is the difference in gender distribution, as AAA screening is currently performed only in men. Given the relative rarity of the disease, a national center for diagnosing and treating chronic mesenteric ischemia might be necessary for a proper diagnostic work-up including a functional test prior to treatment.
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Papers I-III
Perioperative Microcirculatory Changes Detected with Gastroscopy Assisted Laser Doppler Flowmetry and Visible Light Spectroscopy in Patients with Median Arcuate Ligament Syndrome

Purpose: Physiological tests may aid in diagnosing median arcuate ligament syndrome (MALS). MALS is a symptomatic compression of the celiac artery causing symptoms similar to chronic mesenteric ischemia (CMI) of atherosclerotic etiology. Simultaneous use of visible light spectroscopy (VLS) and laser doppler flowmetry (LDF) during upper endoscopy may detect microcirculatory changes in these patients.

Patients and Methods: In a single-center, prospective comparative cohort, 25 patients were evaluated for MALS. In patients with a consensus diagnosis of MALS (n=15) underwent a gastroscopy assisted, transmucosal microcirculatory assessment with LDF and VLS. Results were compared to individuals with normal intestinal circulation (n=38) evaluated with duplex ultrasonography, and to patients with chronic mesenteric ischemia (n=32).

Treatment response was evaluated clinically at 1, 3, 6, and 12 months, and with ultrasound, VLS and LDF at three months. Health-related quality of life (QoL) was assessed with Euroqol (EQ-5D-5L), preoperatively, and 12 months postoperatively.

Results: Preoperative mean transmucosal oxygen saturation was significantly lower in patients with MALS (SO₂ 76±6), as compared to healthy individuals (SO₂ 81±4), p=0.02. An overall significant improvement in SO₂ after surgical decompression of the celiac artery was found (SO₂ 81±3.7, p=0.05). Eleven (92%) patients with clinical improvement after laparoscopic decompression had a definitive diagnosis of MALS. Median follow-up was 18 months (4–24 months). Four of the five dimensions investigated with EQ-5D-5L improved.

Conclusion: VLS detected a significantly lower baseline transmucosal SO₂ in patients with MALS as compared to control subjects with normal intestinal circulation. An improvement in SO₂ after laparoscopic decompression was found, supporting a possible ischemic etiology in our patient population.

Keywords: mesenteric ischemia, functional test, endoscopy, vascular surgery, abdominal pain

Introduction

Median arcuate ligament syndrome (MALS) is caused by compression of the celiac artery (CA) by the median arcuate ligament and was first described anatomically by Lipschutz in 1917. The median arcuate ligament is a fibrous band that crosses over the aorta and connects the right and left crura of the diaphragm. The anatomical variant with compression of the CA due to either a high origin of the artery or a low insertion of the crura is present in 10–24% of the population. This is the most
common cause of single-vessel stenosis in the mesenteric arteries. Although this external compression is usually asymptomatic, it can, in some patients, cause postprandial epigastric pain or nausea, weight loss, and an epigastric bruit.4,5

The diagnosis is controversial, mainly because the pathophysiology of MALS remains unclear. The prevailing theory is that insufficient amounts of blood pass through the compressed CA in times of increased metabolic demand, leading to ischemia.5,6 Another theory is that a neuropathic compression of the vessel may lead to irritation of sympathetic pain fibers causing pain, much like in the case of other nerve compression diseases, such as a carpal tunnel.6

The clinical presentation of MALS is variable.4 The diagnosis depends on exclusion of other possible causes of abdominal pain, and patients often undergo extensive examinations. Upper endoscopy is a standard initial investigation in patients with postprandial upper abdominal complaints.5,7 Using gastric exercise tonometry (GET) as a functional test, one study has demonstrated ischemia in patients with MALS.8 The test is, however, somewhat cumbersome, the required equipment is no longer available, and alternative functional tests hence need to be explored.

Gastroscopy assisted laser Doppler flowmetry (LDF) and visible light spectroscopy (VLS) (GALS) have successfully been utilized to examine transmucosal microcirculatory changes in the gastrointestinal tract both in healthy individuals and patients with chronic mesenteric ischemia (CMI) due to atherosclerosis of the mesenteric arteries.9,10 Even in the case of a single vessel pathology, GALS has been able to detect ischemic changes in the stomach and duodenum.10,11

Traditionally, the treatment of MALS has been an open surgical release of the compression on the celiac artery, but for the last decade, a laparoscopic approach has been utilized.12,13

This study aimed to examine the transmucosal microcirculation of the stomach and duodenum in the patients with MALS utilizing GALS before and after the laparoscopic decompression of the CA.

We hypothesized that patients with MALS have reduced microcirculation in the stomach as compared to subjects with healthy intestinal circulation and that the microcirculation and symptoms improve in patients after the surgical procedure. Furthermore, we hypothesized that the patient’s health-related quality of life (QoL) improved after surgery.

Patients and Methods
The study was designed as a single-center prospective comparative cohort. It was conducted at Oslo University Hospital during a 36 months period from September 2016 to September 2019. Patients included were referred from either primary health care or other hospitals. The suspicion of MALS was based on symptomatology, CT angiography findings (≥ 50% stenosis in deep expiration phase (Figure 1)), and exclusion of common differential diagnoses such as ulcer disease, cholelithiasis, pancreatitis, inflammatory bowel disease, and malignancy. All patients were subjected to a detailed clinical examination and CT angiography before discussion in a multidisciplinary panel comprising of vascular surgeons and interventional radiologists. Patients were required to have at least two of the three following criteria; postprandial pain, unintentional weight loss, and changes in habits of food intake (reduced amount and/or increased frequency of meals, the exact frequency and composition of each meal was not recorded). CT angiography in deep inspiration and deep expiration phase was undertaken. A reconstruction in axial, sagittal, and coronal planes was examined to confirm

Figure 1 CTA sagittal plane of a patient with MALS taken in deep expiration. An external compression of the celiac artery and a normal anatomy of the superior mesenteric artery is demonstrated.

Abbreviations: MALS, median arcuate ligament syndrome; CTA, computed tomography angiography.
MALs. A consensus diagnosis of MALs was made based on the above.

In patients with a consensus diagnosis of MALs, a transmucosal microcirculatory investigation with GALS was performed. The investigation was repeated after surgical treatment, and results were compared to data from individuals with healthy intestinal circulation (Control Group 1 (CG1) n=38). The individuals in CG1 were recruited from a list of patients awaiting upper endoscopy due to dyspepsia, control of Barrett’s esophagus, or controls after ulcer disease. None of these had postprandial abdominal pain or weight loss. A transabdominal duplex ultrasound (Vivid E95, General Electric Healthcare, Chicago, IL) with a curvilinear probe C1–6 was performed after a minimum of six hours fasting to evaluate the patency of the intestinal arteries in these control individuals. An experienced specialist in ultrasonography performed all examinations. Significant stenosis (>70%) was defined as a peak systolic velocity of the superior mesenteric artery (SMA) ≥275 cm/s and CA ≥200 cm/s.14

Additionally, data from MALs patients were compared to previously published data on patients with chronic mesenteric ischemia (CMI), (Control Group 2 (CG2), n=32) due to atherosclerosis.10 In this previous study, the inclusion criterion was stenosis ≥70% or occlusion of ≥1 mesenteric artery on CT angiography in addition to symptom relief after intervention with percutaneous transluminal angioplasty with or without stenting or aortomesenteric bypass.

Symptom relief was defined as either a complete or partial disappearance of symptoms. A definitive diagnosis of MALs was thereby based on a complete or partial relief of symptoms after an intervention.

Measurements
All patients were investigated with upper endoscopy at the gastric laboratory before and three months after the laparoscopic surgical treatment. All endoscopies were performed by the same team of examiners, comprising an experienced gastroenterologist and two vascular surgeons. The patients were examined in a fasting state and in a left, lateral decubitus position. Peripheral oxygen saturation was monitored in all patients receiving benzodiazepines or analgesics and kept >95%. Air insufflation was kept at a minimum, and no spasmolytic agent was administered.

The measurement points were chosen based on the arterial supply of the stomach and duodenum by the branches of the CA and superior mesenteric artery (SMA) (Figure 2). A mean of the four measurements in the duodenum (descending and horizontal part), the four measurements at the lesser curvature and pylorus, and three measurements at the greater curvature were calculated.

A 2.6 mm “Oxygen 2 See” (O2C) microprobe, LM-10 (O2C, LEA Medizintechnik, Giessen, Germany), was passed through the working channel of an Olympus flexible gastroscope. The O2C utilizes both LDF and VLS to make simultaneous measurements of flow (i.e., red blood cell flux), velocity, combined venous and arterial saturation of capillary hemoglobin (μHbSO2) and a relative hemoglobin-amount (μHbcomb).15

The machine detected movement and pressure artifacts, and visually assessed unstable, or fluctuating recordings were discarded, and the measurements were automatically or manually repeated.

The study patients were followed up at 1 (clinical evaluation), 3 (upper endoscopy with microcirculatory measurements, clinical evaluation, duplex ultrasound), 6 (clinical evaluation), 12 (clinical evaluation, QoL assessment) months, and yearly (clinical evaluation) thereafter.

Health-Related Quality of Life
At inclusion and 12 months postoperatively, patients completed a validated and Norwegian translated questionnaire...
EuroQol (EQ-5D-5L).\textsuperscript{16} EQ-5D provides a descriptive profile and a single index value for health status based on five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the five dimensions is divided into five levels of perceived problems from 1 (indicating no problems) to 5 (indicating extreme problems). The second part of the EQ-5D-5L is a visual analog scale from 0 (worst imaginable health state) to 100 (best imaginable health state).

Operative Technique
All patients were treated laparoscopically, and the same vascular surgeon performed all procedures. The patients were under general anesthesia and in a supine position with the surgeon placed between the legs of the patient. A 12 mm trocar was placed under visual guidance between the xiphoid process and umbilicus. The abdominal cavity was insufflated with CO\textsubscript{2}, three additional trocars (5 mm) were placed, one on the right side, and two on the left side of the patient’s abdomen. The left liver lobe was elevated using Nathanson’s liver retractor (Cook Medical, Bloomington, Indiana, United States). The omental bursa was opened through the division of the hepatogastric ligament. The common hepatic or splenic artery was identified and followed proximally to the celiac trunk bifurcation. The CA was dissected free using a monopolar hook until the median arcuate ligament was identified. The left gastric artery and the small diaphragmatic branches from the CA were preserved. The median arcuate ligament was divided with either the monopolar hook or Ultracision Harmonic (Ethicon Inc., Somerville, New Jersey, United States). Care was taken to clear the cranial surface of the CA and its origin from the aorta, from any fibrous, muscular or nervous tissue. The aorta was free dissected 2–3 cm cranially and on both sides of the origin of the celiac artery. After removing the Nathanson’s liver retractor, exsufflation was done, and trocars were removed. Patients were discharged after a median hospital stay of 2 days (range 2–3 days).

Ethics and Trial Registration
Informed written consent was obtained from all patients and control subjects. The study protocol was approved by the Regional Committees for Medical and Health Research Ethics in the South-Eastern region of Norway (REK sor-ost B 2016/682) and registered in the ClinicalTrials.gov Protocol Registration and Results System (NCT02914912). The study was conducted in accordance with the Declaration of Helsinki.

Statistics
Normally distributed data are presented as mean values with standard deviations or median values with range unless otherwise stated. For continuous outcome variables, the independent Student’s \( t \)-test was applied, and Fisher’s exact test was applied to categorical data. Wilcoxon signed ranks test was used to investigate the change after intervention. The statistical significance was set at 5\% (\( p < 0.05 \)).

A power analysis was performed based on the results from our previous study on CMI with a mean oxygen saturation of 81±4\% in the individuals with healthy intestinal circulation and an anticipated saturation of 76\% in patients with MALs (CMI 67±9\%). With the study power set at 80\%, a sample size of 10 patients was calculated.

Test performance at different cut-off levels was explored using receiver operating characteristics (ROC) curve, and sensitivity and specificity for diagnosing MALs were calculated.

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM Corp. Armonk, NY).

Results
From September 2016 to September 2019, a total of 25 patients were referred from primary health care and from other hospitals to the Department of Vascular Surgery, Oslo University Hospital, for the evaluation of MALs (Figure 3). Of these, eight were excluded based on ≤50\% stenosis on CTA in the deep expiration phase. Two had ≥50\% stenosis, but no symptoms and the findings were regarded as incidental. Fifteen patients were hence included in this study, and based on the standard diagnostic workup, they were diagnosed with MALs and offered surgical treatment. Laparoscopic decompression was the treatment of choice in all patients; however, three patients chose to decline surgery and are being followed-up in the out-patient clinic. Twelve patients underwent a successful laparoscopic decompression of the CA. Of these, 11 reported clinical improvement on follow-up. These 11 patients have been considered as having a confirmed diagnosis of MALs and are included in the statistical analysis. Patient characteristics are presented in Table 1.

All patients with a confirmed diagnosis of MALs described postprandial abdominal pain upon referral, nine (82\%) of them reported pain debut within 30 minutes of
a meal, two (18%) experienced pain 30–60 minutes after a meal. The pain lasted for more than 60 minutes in six (55%) of these patients. A mean weight loss of 5kg (±7kg) was reported in seven patients (64%). The time from debut to diagnosis varied, with a median of 96 months (16–600). Baseline characteristics of CG1 and CG2 are presented in Table 2.

GALS could be performed in all patients with MALS. All endoscopies were negative with regard to the concomitant disease. The mean total examination time was 12 minutes (±6 minutes). Ten patients (91%) agreed to go through a second upper endoscopy three months after surgical intervention. One successfully treated patient with symptom relief refused a second upper endoscopy due to discomfort during the endoscopic procedure.

The preoperative mean transmucosal oxygen saturation was significantly lower in patients with MALS (SO₂ 76 ±6%), as compared to healthy individuals (CG1, SO₂ 81 ±4%, p=0.02, Table 3, Figure 4). There was no statistically significant difference in relative Hb amount, flow, or velocity between the groups. The results of the preoperative measurements in CMI patients (CG2, SO₂ 67±9%) were, however, significantly lower than in both healthy individuals (CG1) and MALS patients (p<0.001, p=0.004 respectively).

Five patients with MALS (45%) had oxygen saturation (SO₂) below the cut-off of 78% from our study on CMI. Using ROC analysis, we found the sensitivity for identifying an individual with MALS was 54% and specificity 66% with SO₂ cut-off of 78% (Figure 5). A cut-off of 80% increases the sensitivity to 82% with a specificity of 60%.

After a median follow up of 18 months (4–24 months), eleven (92%) of the 12 patients treated with laparoscopic
decompression reported complete or partial improvement in their symptoms compared to pre-intervention status. A partial recurrence of preoperative complaints was reported in four patients (36%). However, they still reported improvement in their symptoms compared with the preoperative status. All of these had an open CA on follow-up duplex ultrasound.

Table 1 Patient Characteristics in the Study on Visible Light Spectroscopy and Laser Doppler Flowmetry During Upper Endoscopy in Patients with Median Arcuate Ligament Syndrome

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>n=11</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting weight loss</td>
<td>7 (64)</td>
<td></td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>5±7</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11 (100)</td>
<td></td>
</tr>
<tr>
<td>Debut &lt;30 minutes after a meal</td>
<td>9 (82)</td>
<td></td>
</tr>
<tr>
<td>Debut &gt;30 minutes after a meal</td>
<td>2 (18)</td>
<td></td>
</tr>
<tr>
<td>Duration of abdominal pain &lt;30 minutes</td>
<td>2 (18)</td>
<td></td>
</tr>
<tr>
<td>Duration of abdominal pain 30–60 minutes</td>
<td>3 (27)</td>
<td></td>
</tr>
<tr>
<td>Duration of abdominal pain &gt;60 minutes</td>
<td>6 (55)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea/obstipation/nausea</td>
<td>9 (81)</td>
<td></td>
</tr>
<tr>
<td>Changes in eating habits</td>
<td>8 (73)</td>
<td></td>
</tr>
<tr>
<td>Abdominal bruising</td>
<td>8 (73)</td>
<td></td>
</tr>
<tr>
<td>Time from debut until diagnosis (months)</td>
<td>96 (16–600)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Values are presented as *mean±SD, b median (range) or absolute numbers with percentages.

At three months, a second upper endoscopy was performed. An overall significant improvement in SO2 after surgical decompression of the CA was found (preoperative SO2 76±6, postoperative SO2 81±3.7, p=0.05). On an individual basis, an improvement in transmucosal SO2 was found in eight (72%) of the MALS patients postoperatively (Figure 6). Two patients had no change in saturation (including one patient without symptom relief). Both rHb and flow increased after intervention, whereas velocity declined (Table 4). With regards to velocity, there was an on average higher pre-interventional velocity in MALS patients compared to controls (CG1 and CG2) (Table 3). A reduction in velocity was observed postoperatively, however, not being statistically significant.

A normalization of peak systolic velocity on duplex ultrasound was found postoperatively in ten patients (Table 5). One had an open CA, but PSV>2,0m/s postoperatively.

EQ5D-5L was completed pre- and postoperatively by 9 of the 11 successfully treated patients. The visual analog scale showed an overall improvement from a score of 44 preoperatively to 62 postoperatively. Improvement after surgery was recorded in all patients except one. Four of the five dimensions investigated with EQ-5D-5L

Table 2 Baseline Characteristics of Patients with MALS and Control Subjects with Normal Intestinal Circulation (CG1), and Control Subjects with Chronic Mesenteric Ischemia (CMI, CG2)

<table>
<thead>
<tr>
<th>Variables</th>
<th>MALS n=11</th>
<th>CG1 (Healthy) n=38</th>
<th>p-value</th>
<th>CG2 (CMI) n=32</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45 (24–72)</td>
<td>60 (20–82)</td>
<td>0.01</td>
<td>73 (53–89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172±6</td>
<td>169±9</td>
<td>0.22</td>
<td>168±9</td>
<td>0.20</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62±9</td>
<td>74±16</td>
<td>0.02</td>
<td>64±16</td>
<td>0.89</td>
</tr>
<tr>
<td>BMI</td>
<td>21±2</td>
<td>26±5</td>
<td>0.001</td>
<td>22±5</td>
<td>0.43</td>
</tr>
<tr>
<td>Female</td>
<td>7 (63)</td>
<td>21 (55)</td>
<td>0.73</td>
<td>20 (63)</td>
<td>0.52</td>
</tr>
<tr>
<td>Smoking history</td>
<td>8 (73)</td>
<td>22 (58)</td>
<td>0.49</td>
<td>29 (91)</td>
<td>0.16</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0 (0)</td>
<td>7 (18)</td>
<td>0.33</td>
<td>13 (4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1</td>
<td>5 (16)</td>
<td>0.30</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>0 (0)</td>
<td>3 (8)</td>
<td>1</td>
<td>5 (16)</td>
<td>0.30</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0)</td>
<td>5 (13)</td>
<td>0.57</td>
<td>12 (38)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (9)</td>
<td>10 (26)</td>
<td>0.41</td>
<td>22 (69)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lung disease</td>
<td>2 (18)</td>
<td>6 (16)</td>
<td>1</td>
<td>7 (22)</td>
<td>1</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>–</td>
<td>12 (38)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

| Medication                 |           |                    |         |                |         |
| Single platelet            | 0 (0)     | 8 (21)             | 0.41    | 23 (72)        | <0.001  |
| Double platelet            | 0 (0)     | 1 (3)              | 0.49    | 7 (22)         | 0.40    |
| Statin                     | 0 (0)     | 10 (26)            | 0.15    | 28 (88)        | <0.001  |

Note: Values Presented as Mean (SD) or Median (Range) or Absolute Numbers with Percentages.

Abbreviations: MALS, median arcuate ligament syndrome; CG1, control group 1; CG2, control group 2.
improved. One dimension (self-care) was not affected prior to intervention and remained unchanged.

**Discussion**

To our knowledge, this is the first study to investigate the transmucosal microcirculation in patients with MALS using a gastroscopy assisted LDF and VLS. The results of this study support the hypothesis that MALS has an ischemic etiology. We observed a significantly lower transmucosal oxygen saturation in patients with MALS compared to healthy individuals at baseline. Further, a borderline significant increase in transmucosal oxygen saturation was observed after the intervention. In addition, an increase in rHb and flow after the laparoscopic surgical

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**Table 3** Mean Values of Combined Arterial and Venous Oxygen Saturation (SO₂), Relative Hemoglobin Amount (rHb), Flow and Velocity for the Three Examined Areas in the Stomach and Duodenum, and a Mean of All Areas in Patients with MALS, CG1 and CG2.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Duodenum</th>
<th></th>
<th>Pylorus and Lesser Curvature</th>
<th></th>
<th>Greater Curvature</th>
<th></th>
<th>Total All Areas</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>p-value</td>
<td>Mean±SD</td>
<td>p-value</td>
<td>Mean±SD</td>
<td>p-value</td>
<td>Mean±SD</td>
<td>p-value</td>
</tr>
<tr>
<td>SO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALS (n=11)</td>
<td>67±8</td>
<td>0.006</td>
<td>83±8</td>
<td>0.76</td>
<td>78±11</td>
<td>0.13</td>
<td>76±6</td>
<td>0.01</td>
</tr>
<tr>
<td>CG1 (n=38)</td>
<td>75±8</td>
<td></td>
<td>84±6</td>
<td>0.01</td>
<td>82±6</td>
<td>0.07</td>
<td>81±4</td>
<td>0.02</td>
</tr>
<tr>
<td>CG2 (CMI) (n=32)</td>
<td>57±14</td>
<td></td>
<td>74±10</td>
<td></td>
<td>70±12</td>
<td></td>
<td>67±9</td>
<td></td>
</tr>
<tr>
<td>rHb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALS</td>
<td>82±9</td>
<td>0.09</td>
<td>82±6</td>
<td>0.85</td>
<td>87±5</td>
<td>0.76</td>
<td>84±5</td>
<td>0.45</td>
</tr>
<tr>
<td>CG1</td>
<td>87±7</td>
<td></td>
<td>83±8</td>
<td>0.006</td>
<td>86±8</td>
<td>0.005</td>
<td>85±5</td>
<td>0.001</td>
</tr>
<tr>
<td>CG2 (CMI)</td>
<td>76±8</td>
<td></td>
<td>74±9</td>
<td></td>
<td>78±9</td>
<td></td>
<td>76±6</td>
<td></td>
</tr>
<tr>
<td>Flow</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALS</td>
<td>308±66</td>
<td>0.72</td>
<td>306±86</td>
<td>0.84</td>
<td>277±55</td>
<td>0.21</td>
<td>297±50</td>
<td>0.001</td>
</tr>
<tr>
<td>CG1</td>
<td>316±64</td>
<td></td>
<td>311±72</td>
<td>0.06</td>
<td>317±98</td>
<td>0.10</td>
<td>314±57</td>
<td>0.37</td>
</tr>
<tr>
<td>CG2 (CMI)</td>
<td>285±61</td>
<td></td>
<td>260±65</td>
<td></td>
<td>240±65</td>
<td></td>
<td>262±52</td>
<td></td>
</tr>
<tr>
<td>Velocity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALS</td>
<td>39±4</td>
<td>0.36</td>
<td>38±5</td>
<td>0.47</td>
<td>39±5</td>
<td>0.59</td>
<td>39±4</td>
<td>0.90</td>
</tr>
<tr>
<td>CG1</td>
<td>40±4</td>
<td></td>
<td>37±3</td>
<td>0.005</td>
<td>38±5</td>
<td>0.006</td>
<td>38±3</td>
<td>0.90</td>
</tr>
<tr>
<td>CG2 (CMI)</td>
<td>39±4</td>
<td>0.82</td>
<td>33±4</td>
<td></td>
<td>34±4</td>
<td></td>
<td>35±3</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** MALS, median arcuate ligament syndrome; CG1, control group 1 (normal intestinal circulation); CG2, control group 2; CMI, chronic mesenteric ischemia.

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**Figure 4** Box-plot of preoperative combined arterial and venous oxygen saturation in CG1 (n=38), CG2 (CMI, n=32) and patients with MALS (n=11). The thick black line represents the median, the blue box represents the 25–75th percentile and the bars are minimum and maximum points (excluding outliers).

**Abbreviations:** CG1, control group 1; CG2, control group 2; CMI, chronic mesenteric ischemia; MALS, median arcuate ligament syndrome.
干预措施表明局部血流得到改善。

两个主要假说被提出以解释MAL的病理生理学。

1. 血流不足导致的疼痛。这可能是由于供血不足引起的，或者由于神经性成分导致的血管收缩引起的。

splanchnic vasoconstriction. The reduction in blood flow through the CA could cause a steal effect from the SMA, leading to small bowel ischemia. The other theory is that a neuropathic compression of the vessel may lead to inflammation and irritation of sympathetic pain fibers causing pain, much like in the case of other nerve compression diseases, such as carpal tunnel.6 The celiac plexus is a hub for abdominal visceral afferent nerve fibers with pain sensation. Blocking the transmission of pain sensation through this hub has been performed with the injection of anesthetic agents for relief of intractable pain associated with malignant disease and chronic pancreatitis. Limited data on its efficacy are available. One review reports a favorable outcome of the procedure with pain relief in 72% (celiac plexus neurolysis) of the patients with

### Table 4 Combined Arterial and Venous Oxygen Saturation (SO₂), Relative Hemoglobin Amount (rHb), Flow and Velocity Before and After Laparoscopic Decompression of the Celiac Artery in Patients with Median Arcuate Ligament Syndrome

<table>
<thead>
<tr>
<th>Variables (n=11)</th>
<th>Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO₂Preoperative</td>
<td>76.6±6.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Postoperative</td>
<td>81.0±3.7</td>
<td></td>
</tr>
<tr>
<td>rHbPreoperative</td>
<td>83.8±4.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Postoperative</td>
<td>85.9±3.5</td>
<td></td>
</tr>
<tr>
<td>FlowPreoperative</td>
<td>299.9±49.8</td>
<td>0.65</td>
</tr>
<tr>
<td>Postoperative</td>
<td>313.45±52.6</td>
<td></td>
</tr>
<tr>
<td>VelocityPreoperative</td>
<td>38.47±4.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Postoperative</td>
<td>37.4±4.1</td>
<td></td>
</tr>
</tbody>
</table>

2. 由于手术相关的因素导致的疼痛。例如，由于手术相关的因素导致的疼痛。例如，由于手术相关的因素导致的疼痛。例如，由于手术相关的因素导致的疼痛。例如，由于手术相关的因素导致的疼痛。例如，由于手术相关的因素导致的疼痛。例如，由于手术相关的因素导致的疼痛。


**Table 5 Pre- and Post-Intervention Demographics and Characteristics in Patients with Median Arcuate Ligament Syndrome**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Gender</th>
<th>Age (Years)</th>
<th>BMI (kg/m²)</th>
<th>Preoperative Ultrasound</th>
<th>Preoperative CTA</th>
<th>Preoperative Saturation (%)</th>
<th>Treatment</th>
<th>Conversion</th>
<th>Postoperative Ultrasound (mV/s)</th>
<th>Postoperative Saturation (%)</th>
<th>Effect of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>28</td>
<td>19.1</td>
<td>Not performed</td>
<td>CA stenosis</td>
<td>82.0</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>1.7</td>
<td>82.0</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>69</td>
<td>23.0</td>
<td>1.7 m/s</td>
<td>CA stenosis</td>
<td>73.4</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>3.0</td>
<td>83.1</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>22</td>
<td>22.5</td>
<td>2.5 m/s</td>
<td>CA stenosis</td>
<td>73.7</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>1.7</td>
<td>81.0</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>36</td>
<td>19.5</td>
<td>Not performed</td>
<td>CA occlusion</td>
<td>76.0</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>1.9</td>
<td>Not willing</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>60</td>
<td>21.3</td>
<td>0 m/s</td>
<td>Not performed</td>
<td>71.0</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>1.5</td>
<td>77.7</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>40</td>
<td>20.0</td>
<td>1.8 m/s</td>
<td>CA stenosis</td>
<td>77.7</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>Not performed</td>
<td>82.3</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>46</td>
<td>22.7</td>
<td>Technical difficulties</td>
<td>CA stenosis</td>
<td>84.6</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>1.8</td>
<td>74.2</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>24</td>
<td>21.6</td>
<td>2.1 m/s</td>
<td>CA stenosis</td>
<td>83.8</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>1.8</td>
<td>84.0</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>45</td>
<td>19.8</td>
<td>2.9 m/s</td>
<td>CA stenosis</td>
<td>79.4</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>2.0</td>
<td>87.0</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>62</td>
<td>16.9</td>
<td>4.0 m/s</td>
<td>CA stenosis</td>
<td>66.0</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>1.5</td>
<td>75.8</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>65</td>
<td>22.6</td>
<td>Not performed</td>
<td>CA stenosis</td>
<td>80.5</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>1.5</td>
<td>84.27</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>65</td>
<td>23.2</td>
<td>Not performed</td>
<td>CA stenosis</td>
<td>78.8</td>
<td>Laparoscopic decompression</td>
<td>No</td>
<td>1.5</td>
<td>78.2</td>
<td>No</td>
</tr>
</tbody>
</table>

**Abbreviations:** CA, celiac artery; CTA, CT angiography; BMI, body mass index.

In our previous study, CMI patients had significantly reduced microcirculation compared to control individuals, suggesting that VLS could play an essential diagnostic role in the diagnostic process. The sensitivity of VLS (SO$_4$-Rho) for identifying CMI was 97%, and specificity 79%. VLS made use of a more sensitive diagnostic test for ischemia than LDF. As ischemic changes could be reliably detected in both healthy individuals and CMI patients, the provocation study with CFI on patients with MALD, physical exercise and fasting state could be used as a stress test and resulted in the detection of ischemic changes in these patients. However, in a recently published study with VLS after luminal feeding in patients with CMI, reduced oxygen saturation increased in both healthy individuals and CMI patients, and the provocation study with CFI on patients with MALD, physical exercise, and fasting state could be used as a stress test and resulted in the detection of ischemic changes in these patients.

The excellent collateral circulation of the bowel and pancreas with chronic pancreatitis of the bowel and patients with chronic pancreatitis should intuitively permit an adequate supply to the microcirculation in the intestinal anastomosis. In our previous study, the excellent collateral circulation of the bowel and patients with chronic pancreatitis should intuitively permit an adequate supply to the microcirculation in the intestinal anastomosis. A detailed understanding of the microcirculation before and after surgical intervention is therefore needed.
The improvement in the transmucosal saturation in the patients with symptomatic improvement may help to conclude a successful laparoscopic decompression of the CA. In our study, we were not able to reproduce the diagnostic accuracy of VLS during upper endoscopy with regards to CMI. With a cut-off 80% SO2, the sensitivity is 82% but according to our results, sensitivity and specificity are still too low for this test to be utilized for patient selection.

A common view is that stenosis of a single mesenteric artery is insufficient to lead to mesenteric ischemia. However, several recent studies, including our own on CMI, suggest that ischemia can develop even with single vessel pathology.10,19,20

Follow-up with duplex ultrasound after laparoscopic decompression shows normalization of velocities in all controlled patients except one.

Although we present a material over 36 months from Norway’s largest hospital, a relatively small number of patients were included. MALS patients were significantly younger than healthy individuals (CG1) (p=0.01) and had a lower BMI. In comparison to CMI patients (CG2), MALS patients had a significantly lower prevalence of hypertension, diabetes mellitus, intermittent claudication and ischemic heart disease. Furthermore, patients with MALS and CMI were examined with CT angiography, and healthy controls were examined with color duplex ultrasound.

Laparoscopic decompression for MALS was first reported in 2000 and is now the treatment of choice in this patient group.4,21,22 The procedure requires a small operating field and is well fitted for laparoscopic surgery. The approach used in our institution has proven to be safe and to date without complications. None of the patients in this study have reported any adverse events or worsening of their preoperative symptoms.

In total, 92% of the treated patients reported symptom relief, suggesting that our patient selection was adequate. A correlation between the severity of a stenosis and outcome after surgical decompression has been described, with better clinical outcome found in patients with ≥70% stenosis.21 Our patients had ≥50% stenosis. However, as this is an exclusion diagnosis, a test with higher specificity is warranted to identify patients who might benefit from surgery.

**Conclusion**

Gastroscopy assisted VLS may detect perioperative changes in the transmucosal SO2 in patients with MALS. Laparoscopic decompression is a safe and effective treatment of patients with MALS. Improvement in transmucosal SO2 after laparoscopic decompression may support a possible ischemic etiology in patients with MALS.

**Data Sharing Statement**

Individual participant data that underlie the results reported in this article, after deidentification (text, tables and figures), will be made available at the conclusion of the ongoing study on chronic mesenteric ischemia at Oslo University Hospital, in 2022 and be available for three years. In addition to this, the study protocol will be available. Data will be shared with investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Proposals should be directed to M.D. PhD Syed Sajid Hussain Kazmi, syekaz@ous-hf.no, project leader. To gain access, data requestors will need to sign a data access agreement.

**Author Contributions**

All authors, STB, NS, AWM, JOS, JH, and SSHK made a substantial contribution to conception and design, acquisition of data, analysis, and interpretation of data; took part in drafting the article and revising it critically. All authors gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


A Short Series of Laparoscopic Mesenteric Bypasses for Chronic Mesenteric Ischemia

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Background: Laparoscopic aortomesenteric bypass may be performed to treat the chronic mesenteric ischemia patients who are not suitable for endovascular treatment. This study presents an initial experience with a limited series of laparoscopic mesenteric artery revascularization for the treatment of mesenteric ischemia.

Methods: Chronic mesenteric ischemia (CMI) patients with previous unsuccessful endovascular treatment or with arterial occlusion and extensive calcification precluding safe endovascular treatment were offered laparoscopic mesenteric revascularization. From October 2015 until November 2018, nine patients with CMI underwent laparoscopic revascularization. In addition to demographic data and perioperative results of the treatment, graft patency was assessed with Duplex ultrasound at 1, 3, 6 and 12 months, and annually thereafter. A descriptive analysis of the data was performed.

Results: All bypasses were constructed with an 8 mm ring enforced expanded polytetrafluoroethylene graft in a retrograde fashion (from infrarenal aorta or iliac artery) to either superior mesenteric artery or splenic artery (2 cases). Median operation time was 356 mins (range 247–492 mins). Five patients had a history of unsuccessful endovascular treatment. Laparoscopic technical success was 78%, and the primary open conversion rate was 22%. All laparoscopic revascularization procedures remained patent after discharge during a median follow-up time of 26 months (range 18–49 months). The primary graft patency at 30 days was 78%. Primary assisted, and secondary graft patency was 78% and 100%, respectively. Median weight gain was 2 kg (range 2–18 kg), and all patients achieved relief from postprandial pain and nausea. No mortality was observed during the follow-up period.

Conclusion: Laparoscopic aortomesenteric revascularization procedures for chronic mesenteric ischemia are feasible but require careful patient selection. These procedures should only be performed at referral centers by vascular surgeons with prior experience in laparoscopic vascular surgery.

Keywords: mesenteric ischemia, bypass, laparoscopy, chronic mesenteric ischemia, intestinal ischemia

Introduction

Revascularization procedures have been conducted for the treatment of mesenteric ischemia since 1957.1 Although endovascular procedures for the treatment of chronic mesenteric ischemia (CMI) have superseded the open revascularization procedures, the comparative results on mortality and long-time patency are shown to be better for the open procedures.2–5 Due to reduced perioperative morbidity, guidelines recommend endovascular therapy as the first choice for the treatment of CMI.6,7 However, in case of failed endovascular therapy or in patients with occlusion and extensive calcification precluding safe angioplasty and stenting, a bypass
from aorta to either superior mesenteric artery (SMA)/celiac artery (CA) or both is indicated. Laparoscopic mesenteric bypass operation techniques have been introduced to achieve the advantages of a minimally invasive surgical technique. However, no study has yet been performed to investigate the feasibility of the laparoscopic mesenteric bypass operation technique.

This small prospective non-comparative cohort aimed to assess the clinical results of an early experience with the laparoscopic revascularization, in the patients with chronic mesenteric ischemia, in addition to critically evaluate the operative technique.

Materials and Methods
Patients with a suspicion of CMI referred to the Department of Vascular Surgery, Oslo University Hospital, Aker, from October 2015 to December 2018, were included in this study. Our department is a tertiary referral hospital for the investigation and treatment of mesenteric ischemia pathology. During the same inclusion period, 72 patients with the diagnosis of CMI were treated with endovascular procedures at the vascular department. All patients in this study were investigated preoperatively with Computed Tomography Angiography (CTA). CMI was defined and diagnosed based on the following criteria:

1. Symptom duration > 3 months
2. CTA findings of stenosis or occlusion in one or more mesenteric arteries
3. Exclusion of differential diagnoses (e.g., cancer disease, peptic ulcer disease, hiatus hernia, irritable and inflammatory bowel disease, gall bladder and pancreas pathologies)

Mesenteric arteries were defined as celiac artery (CA), superior mesenteric artery (SMA), and inferior mesenteric artery (IMA). SMA was the main artery selected for revascularization even in cases where both CA and SMA had occlusion or stenosis. The splenic artery was chosen for revascularization when the atherosclerotic occlusion was only confined to CA. All patients had prior investigations (endoscopies, computed tomography, abdominal ultrasound) to exclude other causes of their symptoms of postprandial abdominal pain, weight loss, and changes in food intake patterns. Only patients with a history of prior unsuccessful endovascular treatment or extensive atherosclerotic lesions in the mesenteric arteries precluding safe endovascular treatment were offered a laparoscopic revascularization procedure. An extensive atherosclerotic lesion was defined as a heavily calcified atherosclerotic plaque in Fullen’s zone 1 and 2 on CTA, evaluated to be unavailable for catheterization or stent placement. The patients were followed-up postoperatively at 1, 3, 6 and 12 months and annually thereafter. In addition to clinical follow-up, a Duplex ultrasound was used to confirm patency of the graft, and CTA was taken to confirm graft patency if required. Data on changes in the clinical symptoms, complications of the primary surgical treatment, and secondary interventions were collected.

Completion of the laparoscopic procedure without conversion to open surgery was defined as a technical success. Primary patency was defined as patent revascularization at follow-up, confirmed by Duplex ultrasound. Primary assisted patency was defined as patent revascularization, achieved with an intervention for a failing graft (although asymptomatic). Secondary patency was patency achieved after intervention on an occluded graft.

Laparoscopic Technique
All operations were performed in general anesthesia. All patients received intravenous antibiotic prophylaxis (Cefalotin 2g) after intubation, which was repeated every 3 hrs until a total of four doses. The patient was positioned supine on a split-leg table, and the surgeon stood between the legs. A surgical nurse stood on the left side of the surgeon, and an assistant on each side of the patient. Pneumoperitoneum was achieved with carbon dioxide (CO2) insufflation through a trocar placed under direct visualization of the peritoneum. A pneumoperitoneum pressure of 12 mmHg was maintained during the surgery. If necessary, trocars were placed at anatomical positions suitable for safe peritoneal or omental adhesiolysis (Figure 1A). The small intestine was gently mobilized towards the right side of the abdominal cavity. If necessary, one or two 10 mm fan retractors (Covidien Endo Retract II Ethicon) were used to keep the intestine separated from the surgical field.

Abdominal aorta and iliac arteries were approached by directly opening the overlying peritoneum. The infrarenal aorta was dissected free for a length suitable for application of aortic clamps and the construction of an end-to-side anastomosis (Figure 1B). In one case, the right iliac artery and in another left graft limb, of a previously laparoscopically operated aortobifemoral graft, were also dissected.
Aorto/Iliac-SMA Bypass

SMA was approached in the area just below the junction of superior and inferior mesenteric veins. Treitz ligament was divided, and duodenum mobilized to free dissect the required length of SMA. Ring enforced expanded polytetrafluoroethylene (ePTFE) 8 mm (Gore-Tex Stretch Vascular Graft) was spatulated at one end and introduced into the abdominal cavity through a 12 mm trocar. Intravenous heparin was given to achieve anticoagulation, and the SMA was clamped distally with either a long vessel loop or with a small laparoscopic bulldog artery clamp. In the case of calcified SMA, a laparoscopic aortic clamp was used for proximal cross-clamping of the SMA, which also helped in keeping the greater omentum and transverse colon, separated from the operation field. Thrombendarterectomy was performed through a longitudinal arteriotomy. A partial stent resection (distal part of the stent) was performed in case of an occluded stent. An end-to-side anastomosis was performed with two hemi-circular 6–0 polypropylene sutures, each about 12–15 cm length and with a beforehand tied Teflon pledgets to their ends (Figure 1C). Artery clamps were temporarily removed from SMA and backflow

Figure 1 Different phases of a laparoscopic retrograde aorto-mesenteric bypass to the superior mesenteric artery. (A): Paramedian vertical lines are midclavicular and anterior axial lines. Upper transverse is subcostal, and lower transverse is the line joining the two anterior superior iliac spines. Trocar position 6 for 30° laparoscope, 1 and 9 for aortic clamps and 4, 5, 7 for working instruments. The rest of the trocar positions for other helping instruments. (B): Partially dissected superior mesenteric artery (a) and infrarenal aorta (g). Treitz ligament is divided, and duodenum mobilized distally and held under a retractor (a). Inferior mesenteric vein (d). (C): End-to-side anastomosis with superior mesenteric artery. (D): Completed anastomoses on superior mesenteric artery and infrarenal abdominal aorta. Ring enforced expanded polytetrafluoroethylene graft with an end-to-side anastomosed 6 mm graft. Side graft (e) is being flushed with heparinized NaCl to check the patency of anastomoses before the aortic and superior mesenteric artery clamps are removed. Laparoscopic bulldog artery clamp (g).
was confirmed through the graft, before it was flushed with heparinized NaCl. A suitable length of the graft was used to allow a generous graft loop to avoid graft kinking, and the rest of the graft length was excised and discarded. The infrarenal aorta was clamped, and after aortotomy and spatulation of the graft end, an end-to-side anastomosis was constructed with the help of 4-0 polypropylene sutures, again with Teflon pledgets at the ends (Figure 1D). Aortic clamps were removed, and mesenteric circulation established through the bypass.

**Aorto-Splenic Bypass**

In two cases, the splenic artery was used as the site of the distal anastomosis. Figure 2A–D illustrates the trocar’s positions and different phases of the aorto-splenic bypass. Nathanson liver retractor (Cook Medical) was used to elevate the left liver lobe. The hepatogastric ligament was excised to approach the splenic artery along the cranial edge of the pancreas. The artery was dissected in length suitable for cross-clamping and to construct an end-to-side anastomosis. A laparoscopic iliac clamp (Carl

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**Figure 2**

(A): Trocar positions for laparoscopic retrograde aorto-splenic bypass. Trocar positions 5 for 30° laparoscope and 1 for Nathanson’s liver retractor. Position 2, 4, and 3 for working trocars for splenic artery dissection and anastomosis. Positions 7 and 6 for infrarenal aortic dissection and anastomosis. Other positions are used for helping instruments. (B): Distal end of a tunneled ring enforced expanded polytetrafluoroethylene graft anterior to the left renal vein (Q). Cross-clamped infrarenal aorta and left gonadal vein (Q). (C): Ring enforced expanded polytetrafluoroethylene graft is being anastomosed end-to-side to a clamped splenic artery. Nathanson’s liver retractor is elevating the left liver lobe. (D): Completed end-to-side anastomosis to the infrarenal aorta.
Storz, Germany) was carefully passed anterior to the left renal vein along the right side of the aorta and progressed, cranially behind the pancreas, towards the omental bursa. Care was taken to keep the clamp parallel with the aorta. A spatulated 8 mm ring enforced ePTFE graft was grasped with this clamp and carefully, tunneled from the omental bursa, dorsal to the pancreas, towards the infrarenal aorta.

After systemic heparinization, the splenic artery was clamped with the laparoscopic aortic clamps or small laparoscopic bulldog artery clamps. Longitudinal arteriotomy was performed, and an end-to-side anastomosis was constructed with 6–0 polypropylene sutures. The graft was flushed with heparinized NaCl and cross clamped with a laparoscopic aortic clamp until the anastomosis with the aorta was constructed in an end-to-side fashion (Figure 2D). Nathanson liver retractor was removed, and the proximal portion of the graft was covered by the lesser omentum and the left liver lobe. The retroperitoneum was used to cover all grafts to the SMA.

No intra-operative imaging with either angiography or ultrasound was performed, except in one patient.

**Ethics and Trial Registration**
All included patients were participating in an ongoing clinical study on chronic mesenteric ischemia.¹¹ The study was approved by the Regional Committees for Medical and Health Research Ethics in the South-Eastern region of Norway (REK sør-øst B 2016/682) and registered in the ClinicalTrials.gov Protocol Registration and Results System (NCT02914912). The patients gave informed written consent for inclusion in the study and the operative procedure. The study was conducted in accordance with the Declaration of Helsinki.

**Statistical Analysis**
A descriptive analysis of the data was performed. Median and range were calculated.

**Results**
From October 2015 until May 2018, nine CMI patients with a median age of 60.5 years (range 47–77 years), underwent laparoscopic mesenteric revascularization. Eight patients were females. The median time for symptom duration was 24 months (range 12–48 months). Three patients had constant abdominal pain and could not even take peroral liquid food. Seven patients had previous single or multiple abdominal surgeries. All patients had extensive preoperative investigations to exclude other possible causes of their symptoms. All patients were evaluated for endovascular therapy, and when eligible, “endovascular first practice” was exercised.⁶ In most of the cases (n=8), the atherosclerotic plaque extended through the entire length of the Fullen’s zone 1 and 2 and incorporated origins of the inferior pancreaticoduodenal artery and middle colic artery. The descriptive data of the nine patients are given in Table 1.

**Table 1** Demographic Data, Risk Factors, Comorbidities, and Clinical Findings in the Group of Patients with Chronic Mesenteric Ischemia Treated with Laparoscopic Mesenteric Bypass Procedures

<table>
<thead>
<tr>
<th>Total Number = 9</th>
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<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
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<tr>
<td><strong>Female gender</strong></td>
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<tr>
<td><strong>Risk factors</strong></td>
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<td><strong>Comorbidities</strong></td>
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<tr>
<td>Prior stroke</td>
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<tr>
<td>CAD</td>
</tr>
<tr>
<td>CVD</td>
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<tr>
<td>Class 2</td>
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<tr>
<td>Class 3</td>
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<tr>
<td>Class 4</td>
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<td><strong>Median BMI kg/m² (range)</strong></td>
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<tr>
<td><strong>Prior abdominal surgery</strong></td>
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<tr>
<td><strong>Prior mesenteric PTA and Stent</strong></td>
</tr>
<tr>
<td><strong>Symptoms and findings</strong></td>
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<tr>
<td>Postprandial pain</td>
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<tr>
<td>Changes in food intake</td>
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<td>Weight loss</td>
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<tr>
<td>Constant pain</td>
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<tr>
<td>Diarrhea/Nausea</td>
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<td>Weight loss in kg, median (range)</td>
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<tr>
<td>Symptoms duration in months, median (range)</td>
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<td><strong>Endoscopy findings</strong></td>
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<td>Gastroesopagitis</td>
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<td>Irritable bowel syndrome</td>
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<td>Statin treatment</td>
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<td>Antiplatelet</td>
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<td>Anticoagulation</td>
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<tr>
<td>Proton Pump Inhibitors</td>
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<tr>
<td>Opioids</td>
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<td>Others medicines</td>
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**Abbreviations:** ASA, American Society of Anesthesiologists; BMI, body mass index; CAD, Coronary artery disease; CVD, Cerebrovascular disease; PTA, Percutaneous Transluminal Angioplasty.
Five laparoscopic retrograde aorto-mesenteric bypass operations to SMA were performed (Figure 3A–C). Two patients were operated with retrograde aorto-splenic bypass. One patient received an iliaco-mesenteric bypass to the SMA and another from the left graft limb of a previously operated aortobifemoral bypass to SMA (Figure 3B). A median hospital stay of the patients in this study was seven days (range 5–35 days). No patient died during the 30 postoperative days. Perioperative details are given in Table 2.

Two patients reoperated for graft thrombosis also had anticoagulation therapy with a daily subcutaneous, low molecular weight heparin, for three months. The laparoscopic procedure could be successfully completed in 7 patients (78%). In one patient, the laparoscopic procedure was converted to open surgery due to bleeding from the mesenteric venous confluence. In another patient, distal anastomosis on SMA was performed with laparotomy. None of the patients with laparoscopic bypass required postoperative epidural analgesia.

Figure 3 (A). 3D reconstruction of a laparoscopic retrograde aorto-mesenteric bypass to the superior mesenteric artery (yellow arrow). Occluded stent in the superior mesenteric artery (green arrow). (B). 3D reconstruction of a laparoscopic retrograde aorto-mesenteric bypass to the superior mesenteric artery (blue arrow), from the left graft limb of a prior laparoscopic aortobifemoral bypass graft (red arrow). (C). A 6 mm expanded polytetrafluoroethylene graft, end-to-side anastomosed to an 8 mm ring enforced expanded polytetrafluoroethylene graft with graduated length markings and spatulated end.
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<td><strong>CTA findings</strong></td>
<td>Stenosis Common trunk SMA and hepatic artery, Occlusion IMA</td>
<td>Oculded stent in SMA, Occlusion IMA</td>
<td>Fractured and occluded stent CA</td>
<td>Oculded stent in SMA, stenosis</td>
<td>Stenosis of an isolated origin of splenic artery direct from aorta</td>
<td>Oclusion all mesenteric vessels</td>
<td>Oclusion SMA, Stenosis CA and IMA</td>
<td>Oculded stent in SMA, Stenosis CA and IMA</td>
<td>Oclusion CA and SMA, Stenosis IMA</td>
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<td><strong>Prior mesenteric endovascular/vascular procedure</strong></td>
<td>None</td>
<td>Twice stent in SMA</td>
<td>Stent in celiac artery and open surgery for celiac artery compression syndrome</td>
<td>Stent and twice repeat PTA of SMA</td>
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<td>Unsuccessful PTA attempt</td>
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<td>Stent in SMA</td>
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<td><strong>Operative procedure</strong></td>
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<td>Laparoscopic retrograde aorto-SMA bypass</td>
<td>Laparoscopic retrograde aorto-splenic bypass</td>
<td>Laparoscopic retrograde aorto-SMA bypass</td>
<td>Iliaco-SMA bypass</td>
<td>Laparoscopic retrograde aorto-SMA bypass</td>
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<td><strong>Operation time in minutes</strong></td>
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<td>431</td>
<td>355</td>
<td>343</td>
<td>457</td>
<td>247</td>
<td>315</td>
<td>328</td>
<td>356</td>
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<td><strong>Anastomoses time in minutes</strong></td>
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<td>43/33</td>
<td>50/29</td>
<td>40/29</td>
<td>35/36</td>
<td>57/34</td>
<td>21/16</td>
<td>28/24</td>
<td>26/23</td>
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<td><strong>Bleeding in mL</strong></td>
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<td>300</td>
<td>100</td>
<td>500</td>
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<td>500</td>
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<td>250</td>
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<tr>
<td><strong>Complication and treatment</strong></td>
<td>Left ureter injury; open ureter repair</td>
<td>None</td>
<td>Graft thrombosis 2nd post-operative day; laparoscopic thrombectomy</td>
<td>Graft thrombosis 2nd post-operative day; open thrombectomy</td>
<td>Graft kinking 2nd post-operative day; laparoscopic resection of graft and revision of aortic Anastomosis</td>
<td>Mesenteric Anastomosis with open technique</td>
<td>Venous bleeding from inferior mesenteric vein; converted to open</td>
<td>None</td>
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</table>

(Continued)
two patients converted to laparotomy required epidural analgesia for three postoperative days.

Primary graft patency at 30 days was 78%. Two graft thromboses were revealed on CTA, taken on the second postoperative day. None of these patients had any clinical symptoms of postoperative intestinal ischemia. One of these underwent a successful laparoscopic thrombectomy. The other had to be operated with open graft thrombectomy. Both patients had a patent bypass during the follow-up and no recurrent symptoms of mesenteric ischemia.

Primary assisted graft patency and secondary graft patency at 30 postoperative days were 78% and 100%, respectively.

In one patient with a retrograde aorto-splenic bypass, postoperative CTA on the second postoperative day revealed graft stenosis. The patient did not have any symptoms of intestinal ischemia. However, to ensure long-term graft patency, the patient underwent a successful laparoscopic graft length correction, as well as the revision of aortic anastomosis on the 5th postoperative day (Figure 4A–C). Left ureter injury was diagnosed on the third postoperative day in the patient with a prior laparoscopic aortobifemoral bypass. This patient underwent ureter repair and had after almost four years of follow-up, no symptoms from the repaired ureter.

Duplex ultrasound at 1, 3, 6, 12 months, and annually thereafter (n=5), confirmed graft patency in all patients. No patient died during the median postoperative follow-up time period of 26.5 months (range 18–49 months). All patients reported a lasting relief from the symptoms of CMI and had a median increase in body weight of 2 kg (range 2–18 kg).

Discussion

This study is the first to report a series of laparoscopic mesenteric revascularization procedures for the treatment of CMI. To the best of our knowledge, laparoscopic bypass to splenic artery has not been mentioned earlier in the literature. Javerliat et al reported in 2004 a case of a laparoscopic bypass to SMA during a planned laparoscopic aortobifemoral bypass for the treatment of aortoiliac occlusive disease. In 2006 Bakoyiannis et al reported a case of the bypass from infrarenal aorta to common hepatic artery in a patient undergoing endovascular stent-graft repair of a thoracoabdominal aortic aneurysm. In both these case reports the laparoscopic approach utilized to dissect infrarenal aorta was transabdominal retro-colic. In our study, the sole indication for the treatment was

Table 2 (Continued).

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<th>Case/Year</th>
<th>Follow-up in months</th>
<th>Patient (Y/N)</th>
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<td>36</td>
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<tr>
<td>5/2017</td>
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</tr>
<tr>
<td>6/2018</td>
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<tr>
<td>7/2018</td>
<td>18</td>
<td>Yes</td>
</tr>
<tr>
<td>8/2018</td>
<td>26.5</td>
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Abbreviations: CA, Celiac artery; SMA, Superior mesenteric artery; IMA, Inferior mesenteric artery; PTA, Percutaneous Transluminal Angioplasty; CTA, Computed Tomography Angiography.
mesenteric ischemia, and the results are followed-up systematically. Besides, we used a transabdominal direct approach to the abdominal aorta and the mesenteric vessels. This direct approach does not require dissection for medial mobilization of the splenic flexure, descending, and sigmoid colon. A longer length of SMA and its branches can be free dissected by this direct approach. The trocar positions also allow the operator to stand, if necessary, on the right side of the patient to perform the aortic anastomosis. Through a retrorenal approach, full aortic length, from the diaphragm to the left iliac artery can be achieved laparoscopically. However, the dissection is more extensive, and the peripheral segment of SMA and CA branches remain inaccessible.

With the patient in the supine position, the small intestine and transverse colon may disturb the operation field. However, we managed this problem by using two fan retractors. All our bypasses were in a retrograde fashion, i.e., from the infrarenal aorta or the iliac artery/graft. The results of retrograde and antegrade mesenteric bypass have comparable patency, as mentioned in the guidelines. Although one can transect SMA distal to the occlusion and construct an end-to-end anastomosis, all anastomoses were in an end-to-side fashion to the SMA. In our patients, the atherosclerotic plaque extended through the entire length of Fullen’s zone 1 and 2 and incorporated the origins of the inferior pancreaticoduodenal artery and middle colic artery. The end-to-side anastomosis was better suited for the preservation of these critical branches.

The free dissection of the splenic artery was without any technical difficulty. Elevation of the left liver lobe with Nathanson’s liver retractor provides excellent access to the hepatogastric ligament and the tributaries of the celiac artery. Bakoyiannis et al used a laparoscopic flexible tunneler and placed the graft anterior to the pancreas. With the help of CTA, we carefully planned and could, successfully, place the graft in the retroperitoneum along the aorta in two patients. In one of these patients, we did not stretch the flexible Gore-Tex graft properly and ended up with a long graft besides a kinking close to the aortic anastomosis. This long graft was considered to need an early re-laparoscopy correction to optimize long-term patency.

Laparoscopic aortic clamps, although bulky, can be used on the SMA and splenic artery. However, laparoscopic artery bulldog clamps were more appropriate and provided functional working space for anastomosis. Alternatively, long (30 cm) vascular loops through trocars can be used for clamping of the mesenteric arteries. We had two early graft occlusions and one graft stenosis, which resulted in early redo surgery. In all these three cases, instead of reclamping SMA or splenic artery after flushing of the graft with heparinized NaCl, ring enforced ePTFE was clamped, directly, with the laparoscopic aortic clamp. Thrombendarterectomy of the mesenteric artery and the cross-clamping time of the graft during proximal anastomosis might also have contributed to the development of graft thrombosis. Although the greater omentum

![Figure 4 (A). 3D reconstruction of the laparoscopic retrograde aorto-splenic bypass, with graft kinking (green arrow). Hem-o-loc clips on the excised side graft (yellow arrow). (B and C). Anterior and left lateral view of the revised laparoscopic aorto-splenic bypass.](image-url)
could be used to cover the graft to avoid contact with the intestine, we successfully covered the graft with the retroperitoneum in all the patients in this study. None of our patients has so far developed any graft infection.

Due to graft thrombosis and graft stenosis, we had to modify our technique in later cases. In vitro, a 6 mm ePTFE graft, was anastomosed end-to-side with the main graft (8 mm), close to the site of the distal (mesenteric) anastomosis (Figure 3C). This side canal allowed a safe and effective route for the flushing of the main graft during the operation. If necessary, this side canal can be used for thrombectomy of the main graft. One may also perform completion angiography through this side graft and if required, even stenting of mesenteric arteries. After the bypass completion, Hem-o-loc polymer clips and a large metal clip were applied close to the intergraft anastomosis, and the rest of the 6 mm ePTFE graft was excised and discarded. Furthermore, we avoided cross-clamping of the graft after completion of the distal anastomosis, in the latter cases.

One case of conversion due to venous bleeding and another with the left ureter injury occurred in the patients with severe peritoneal adhesions due to earlier abdominal operations. It is estimated that 10 to 37% of patients with elective abdominal surgery will require repeated abdominal surgery. The risk of such complications in the patients with previous multiple abdominal surgeries is high, even with open surgery. Use of preoperative evaluation tools like Hostile Abdomen Index risk stratification may help to select the right patients for laparoscopic procedures.

One of the significant limitations of our operative technique was the failure to assess the patency of the graft during operation. Only in one case, we used an ultrasound probe (Mira Q Vascular, Medistim) to control the anastomosis and confirm blood flow through the graft. The imaging probe was bulky and not designed for laparoscopic use through a trocar. Retrospectively, we realize that a routinely use of laparoscopic ultrasounds, explicitly manufactured for laparoscopic use, should have been mandatory to confirm graft patency during the operations. Alone, this vital step could have helped us to avoid three major complications in our study, with a limited number of patients included. A completion angiography may be a better alternative, since one may also visualize the periphery of the revascularized artery.

The present early experience with laparoscopic revascularization treatment of chronic mesenteric ischemia suffered from complications related to the technique. This is even though the operating team has a long experience with laparoscopic aortic surgery. Nevertheless, the previous experience did help during the construction of anastomosis. We experienced that when the operative field for the anastomosis construction was once achieved, the laparoscopic anastomosis could be performed within an acceptable time, as reflected in our results (Table 2). The operative time was long during these procedures. This can be explained by the early experience with the new technique, besides time consumption due to adhesiolysis in most of the patients. Long operation time has also been observed during the initial experience with laparoscopic aortic surgery. However, the operation time for such procedures is not significantly longer in the later experience. We can, in the future, expect to observe a similar progression in operation time consumption also with laparoscopic mesenteric revascularization procedures. The number of trocars used is to provide a safe peritoneal adhesiolysis and proper positioning for anastomoses construction on the infrarenal aorta, iliac artery, SMA, and splenic artery. Despite many trocars, the patients with laparoscopy seem to have less postoperative abdominal pain, demonstrated using postoperative epidural analgesia.

The benefits of a minimally invasive procedure like laparoscopic mesenteric revascularization can only be achieved by a better patient selection, meticulous free dissection technique, avoidance of graft cross-clamping, and mandatory use of ultrasound during the operation or a completion angiography in future studies. These advanced laparoscopic procedures should only be performed at centers by vascular surgeons with experience in laparoscopic aortic surgery.

Conclusions

Chronic mesenteric ischemia patients can be treated with laparoscopic mesenteric bypass procedures. Careful patient selection and meticulous operative technique are mandatory for achieving acceptable results.

Data Sharing Statement

This small cohort is a subgroup of patients participating in the study of chronic mesenteric ischemia. The study data will be made available online at the completion of the main study in 2022.

Acknowledgments

We are thankful for all the support from our colleagues within the departments of vascular surgery, anesthesiology, and operation theatre.

Author Contributions

All authors, SSKH, STB, MS, AWM, and JOS, made substantial contribution to conception and design, acquisition of
Disclosure
The authors have nothing to disclose.

References