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# Improvement of the splanchnic blood flow and hepatic vein oxygenation following revascularization in patients with chronic mesenteric ischaemia

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## Abstract

**Objectives:** Chronic mesenteric ischaemia (CMI) is an underdiagnosed but severe condition. Access to functional testing is often limited and the diagnosis is usually based primarily on symptoms and imaging. One of the functional tests available is measurement of the splanchnic blood flow (SBF). The purpose of the present investigation was to evaluate if changes in the splanchnic perfusion after revascularization can be detected by measuring the SBF and hepatic vein oxygenation.

**Materials and Methods:** The SBF was measured in 10 patients before and after revascularization of the mesenteric arteries by either percutaneous transluminal angioplasty ( $n = 9$ ) or open revascularization ( $n = 1$ ). The SBF was measured indirectly using Fick's principle and using the tracer Tc-99m Mebrofenin along with assessment of hepatic blood oxygenation, before and after a standard meal, following catheterization of a hepatic vein and the femoral artery.

**Results:** Nine of 10 patients (90%) achieved a profound increase in SBF after revascularization (mean increase in postprandial response to meal stimulation from  $71 \pm 95$  to  $531 \pm 295$  ml/min,  $p = 0.001$ ), and an increase in postprandial hepatic vein oxygen saturation (from  $52 \pm 14\%$  to  $59 \pm 13\%$ ,  $p = 0.006$ ). The symptoms of the patients diminished accordingly. One patient had no symptom relief, and no increase in postprandial SBF, but an angiographic result with no significant stenosis postrevascularization.

**Conclusions:** Revascularization increased the SBF and hepatic vein oxygen saturation significantly concurrent with symptom relief and according with the angiographic successful result in the vast majority of patients. A satisfying angiographic result post vascular intervention does not rule out CMI.

## KEYWORDS

angiography, atherosclerosis, chronic mesenteric ischaemia, clinical laboratory techniques, percutaneous transluminal angioplasty, splanchnic blood flow

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## 1 | INTRODUCTION

The symptoms of chronic mesenteric ischaemia (CMI) are often equivocal but frequently consist of postprandial abdominal pain, weight loss and diarrhoea. Due to the nonspecific clinical findings CMI may be a challenge to diagnose (Kolkman & Geelkerken, 2017). CMI involve atherosclerotic, constrictive or microvascular lesions, which give rise to decreased mesenteric perfusion due to vessel stenosis (Thomas et al., 1998). However, asymptomatic mesenteric artery stenosis are common in the general population (Bjorck et al., 2017). The abundant collateral circulation between the coeliac artery, the superior mesenteric artery and the inferior mesenteric artery may be an explanation (Acosta, 2010). Earlier it was proposed that CMI is unlikely unless at least two of the three vessel need to have a haemodynamic significant stenosis limiting the splanchnic blood flow (SBF) (Brandt & Boley, 2000). However, CMI can also arise from single-vessel mesenteric artery disease and studies have reported symptom relief in the majority of these patients after intervention (Altintas et al., 2021; L.J.D. van Dijk et al., 2018; Høyer et al., 2022; Mensink et al., 2006). There are only a few methods available for functional testing such as tonometry or visible light spectroscopy based on endoscopy or indirect measurement of the SBF via catheterization of the hepatic vein (Terlouw et al., 2020). The findings in patients with CMI is usually an insufficient SBF increase to meal stimulation along with a drop in hepatic vein oxygenation. Due to limited access to function testing, the diagnosis of CMI are in most vascular centres primarily based on symptoms together with a finding of mesenteric artery stenosis, and ruling out other possible explanations for the symptoms by for example, endoscopy and imaging (Altintas et al., 2021).

The purpose of the present investigation was to evaluate if improvement in the splanchnic perfusion after revascularization of the mesenteric vessels in patients with CMI can be detected by measuring the SBF and hepatic vein oxygenation concomitant with symptom relief.

## 2 | MATERIALS AND METHODS

### 2.1 | Design

Prospective single-blinded comparative trial.

### 2.2 | Subjects

Patients undergoing revascularization of the mesenteric arteries at the Department of Vascular Surgery, Rigshospitalet, Denmark following diagnosis of CMI by measurement of the SBF at the Department of Clinical Physiology, Viborg Regional Hospital were invited to participate in the trial. The eligibility criteria were patients >18 years with mental capacity for complying with study procedure, and willing to have measurement of SBF performed following

revascularization. A total of 10 patients were included (2008–2017). The patients were reinvestigated at least 5 weeks after revascularization. The median time between baseline and postinterventional SBF measurement of was 84 days (range 35–335 days). Exclusion criteria were patients with previous revascularization of the mesenteric vessels or patients not able to ingest the test meal. The study was approved by the Danish Health and Medicines Authority and all patients provided signed informed consent.

### 2.3 | Experimental procedure

The method for measuring the SBF has been described in detail earlier (Zacho & Abrahamsen, 2008). In brief, all investigations were performed in the morning following an overnight fast. Local analgesia was applied in the groin region and a 4 F sheath was inserted in the femoral artery and a 7 F sheath was inserted in the femoral vein. Through the venous sheath a Swan-Ganz catheter (7 F) was positioned in a hepatic vein under fluoroscopic control. The presence of a portosystemic shunt caused by portal hypertension was excluded by measuring the hepatic vein pressure gradient (Xu et al., 2019).

### 2.4 | Hemodynamic measurements and imaging

The total SBF was measured indirectly via Fick's principle by using a primer followed by constant tracerinfusion with Tc-99m labelled Mebrofenin (Mebrofenin<sup>®</sup>; GE Healthcare), as described in previous studies (Zacho & Abrahamsen, 2010). Blood samples were extracted simultaneously from the hepatic vein and femoral artery every 10 min. Following baseline measurements for 1 h, the patients consumed a standard liquid meal of 4000 kJ. After the test meal, the measurement continued for another hour. A normal SBF response to the test meal is an increase of more than 250 ml/min or 30% compared to baseline flow (Zacho, et al., 2013). Finally, a 4 F pigtail catheter was placed in the aorta to allow aorto-iliac subtraction angiography with anterior and lateral horizontal projections with a pig-tail catheter positioned appropriately. On average, 12 ml Iomeron (Iomeron<sup>®</sup> 200 mG iodine/ml; Bracco) was used for each the projection. After completion of the trial all angiographies were reread by a trained vascular radiologist blinded to the clinical data and blinded to the outcome of the SBF measurements. A significant mesenteric artery stenosis was defined as having a vessel stenosis of more than 70% of the vessel diameter (Terlouw et al., 2020).

### 2.5 | Revascularization

Percutaneous transluminal angioplasty (PTA) with stenting was performed according to the institutional standards of the Department of Vascular Surgery, Rigshospitalet, Denmark as described recently

(Altintas et al., 2021). In connection with PTA, a stent was placed in all treated arteries. In 1 patient open surgery with transposition of the superior mesenteric artery with preimplantation into the aorta was necessary.

## 2.6 | Statistical analysis

The data are presented as the mean  $\pm$  standard deviation. The differences in hemodynamic variables were analysed using a paired *t*-test in the case of quantitative variables with approximate normal distribution. A *p*-value below 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS software version 20.0 (SPSS Inc.).

## 3 | RESULTS

### 3.1 | Patients and data sampling

The demographic data before revascularization is presented in Table 1 for the 10 patients which included 4 female patients (40%). All patients had postprandial abdominal pain and weight loss. Eight of the patients (80%) had diarrhoea. Four of the patient (40%) has significant three-vessel disease, 3 (30%) had two-vessel disease and 3 (30%) had one-vessel disease according to the angiography. In 8 of the 10 patients PTA with stenting was performed on a single

**TABLE 1** Demographic characteristics

N	10
Female	4 (40%)
Age	66 $\pm$ 13
Height (cm)	170 $\pm$ 8
Weight (kg)	64 $\pm$ 17
BMI (kg/m <sup>2</sup> )	22 $\pm$ 5
Weight loss (kg)	17 $\pm$ 9
Postprandial abdominal pain	10 (100%)
Meal induced nausea	4 (40%)
Chronic diarrhoea	8 (80%)
Smokers	4 (40%)
Hypercholesterolaemia	4 (40%)
Arterial hypertension	5 (50%)
Diabetes	2 (20%)
Ischaemic heart disease	2 (20%)
Claudication	4 (40%)
Cerebral ischaemia	2 (20%)

Abbreviation: BMI, body mass index.

mesenteric artery. One patient underwent surgical transposition of the superior mesenteric artery into the aorta, and 1 patient had PTA with stenting of both the coeliac artery and the superior mesenteric artery (Table 2). At follow-up, 9 of the 10 patients (90%) had an increase in postprandial SBF after revascularization, a concomitant relief of abdominal pain and no longer a significant stenosis on the targeted vessels for revascularization (Table 2). As several significant stenoses were not intervened upon in cases with multivessel disease, 3 patients (30%) had two-vessel disease and 4 patients had (40%) one-vessel disease after the revascularization. No complications were registered in relation to the revascularization procedures or the SBF measurements.

The results of SBF measurements and hepatic vein oxygen saturation before and after revascularization are shown in Table 2. The individual haemodynamic parameters of the 10 patients are listed in Table 3. Nine patients (90%) had an enhancement in postprandial SBF excluding CMI according to the flow criteria. At same time the abdominal pain was abolished. One patient had persistent postprandial abdominal pain and a lack of increase in postprandial SBF, despite a visual radiographic disappearance of the stenosis in the superior mesenteric artery after PTA (patient number 7).

The SBF and hepatic oxygen saturation as a function of time before and after a standard meal both before and after intervention are demonstrated in the Figures 1 and 2, respectively.

The changes in SBF as well as the lowest postprandial hepatic vein oxygen saturation before and after intervention are shown in Figure 3.

## 4 | DISCUSSION

Ten patients with abdominal pain and weight loss who met the criteria of CMI according to measurements of SBF were revascularised. The vascular intervention increased the SBF and hepatic vein oxygen saturation significantly concurrent with symptom relief and according with the angiographic successful result in the vast majority of patients. The demand for increased oxygen consumption postprandially can be met by either increased SBF, increased oxygen extraction, that is, decrease in hepatic vein oxygen saturation, or a combination of increased SBF and oxygen extraction. The normal physiological response to meal stimulation is an increase in venous blood oxygenation in the hepatic vein due to an abundant splanchnic hyperaemia surpassing the need for oxygen (Zacho et al., 2013). In patients with CMI on the other hand, a gradual decrease in hepatic vein oxygenation is typically seen postprandially (Høyer et al., 2022). In the present study, the majority of the patients had an increase in the postprandial oxygenation after revascularization. In 2 patients, the enhanced SBF did not satisfy the need for extra oxygen in the postprandial state and a slight decrease in hepatic oxygen saturation was seen. Although the postprandial changes in hepatic vein oxygen saturation is a plausible indicator of splanchnic malperfusion, there has not been established clear diagnostic cut-offs for diagnosis of

**TABLE 2** Angiography, SBF and hepatic vein oxygen saturation pre and postintervention

		Angiography % stenosis		Intervention	Postprandial increase in SBF (ml/min)		Postprandial increase in HV <sub>sat</sub> (%)		Symptom relief
		Pre	Post		Pre	Post	Pre	Post	
Patient 1	CA	100%	nc	PTA of IMA	79	469	-4%	-4%	Yes
	SMA	100%	nc						
	IMA	70%-99%	0%-10%						
Patient 2	CA	7%-99%	11%-49%	PTA of CA	106	1000	-2%	11%	Yes
	SMA	0%-10%	nc						
	IMA	0%-10%	nc						
Patient 3	CA	70%-99%	0%-10%	PTA of CA and SMA	-15	865	-2%	-1%	Yes
	SMA	70%-99%	0%-10%						
	IMA	100%	nc						
Patient 4	CA	100%	nc	PTA of SMA	102	712	-12%	0%	Yes
	SMA	70%-99%	0%-10%						
	IMA	0%-10%	nc						
Patient 5	CA	100%	nc	PTA of SMA	-16	274	-16%	-12%	Yes
	SMA	70%-99%	0%-10%						
	IMA	50%-69%	nc						
Patient 6	CA	100%	nc	PTA of SMA	74	350	-3%	3%	Yes
	SMA	100%	0%-10%						
	IMA	100%	nc						
Patient 7	CA	50%-69%	nc	PTA of SMA	56	49	-1%	-2%	No
	SMA	70%-99%	0%-10%						
	IMA	0%-10%	nc						
Patient 8	CA	100%	nc	Transposition of SMA	169	665	-8%	1%	Yes
	SMA	100%	0%-10%						
	IMA	100%	nc						
Patient 9	CA	70%-99%	nc	PTA of SMA	-90	629	-6%	-5%	Yes
	SMA	70%-99%	0%-10%						
	IMA	0%-10%	nc						
Patient 10	CA	11%-49%	nc	PTA of SMA	239	300	0%	-1%	Yes
	SMA	70%-99%	50%-69%						
	IMA	11%-49%	nc						

Abbreviations: CA, coeliac artery; HV<sub>sat</sub>, hepatic vein oxygen saturation, pre- and postrevascularization; IMA, inferior mesenteric artery; nc, no change; PTA, percutaneous transluminal angioplasty; SBF, splanchnic blood flow; SMA, superior mesenteric artery.

CMI. The present results are in agreement with an older study from 1977 including 6 patients who had open surgery to achieve revascularization (Hansen et al., 1977).

In 1 patient with unchanged symptoms postintervention with an acceptable visual result on arteriography, the SBF still did not increase and the hepatic vein oxygen saturation remained very low, indicating persistent splanchnic ischaemia. Non-occlusive mesenteric

ischaemia (NOMI) is suggested to consist of a combination of clinical symptoms of CMI, absence of significant mesenteric artery stenosis and preferably a positive functional test (Harki et al., 2017; Terlouw et al., 2020). The present patient could be a NOMI patient since both clinical symptoms and SBF were unaffected after PTA, although the patient did have a borderline coeliac artery stenosis not intervened upon.

Discrepancies between clinical improvement and angiographic results after vascular intervention are well known due to a high prevalence of asymptomatic mesenteric artery stenosis (L.J.D. van Dijk et al., 2018). In a recent study, a total of 178 CMI patients were subjected to endovascular treatment of the mesenteric arteries (Altintas et al., 2021). Sixty-seven percent of the patients had a complete relief of symptoms, and 12% had partial clinical improvement after 6 months postintervention. The diagnosis of CMI in that study was based on a combination of clinical symptoms (99.4% suffering from abdominal pain), and the presence of significant mesenteric artery stenosis. Due to the limited availability of functional testing, the diagnose of CMI is

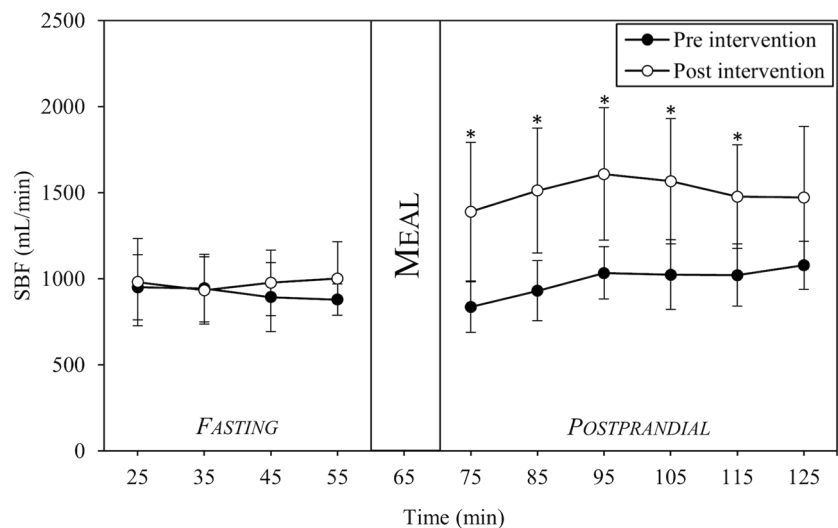
usually based primarily on these criteria's. Functional testing may improve the diagnose of CMI as described in guidelines (Bjorck et al., 2017; Terlouw et al., 2020). Several proposals for such tests have been forwarded (Mensink et al., 2008; van Noord et al., 2013; Sana et al., 2015). None, however, with widespread clinical use, due to limited access. Noninvasive methods such as MRI and CT based calcium scoring offer a noninvasive approach, and are also being investigated although their diagnostic potential in CMI remain to be clarified (Hall Barrientos et al., 2021; Terlouw et al., 2021). In contrast to CMI, there is a vast availability of advanced methods for the diagnosis of ischaemic heart disease. It has been well established that insufficient coronary blood flow requiring intervention to improve the prognosis, does not only present itself with classic angina, but also as with vague symptoms such as for example, fatigue or dyspnoea (Neumann et al., 2019). Similarly, there has also been described a broad symptomatology in CMI. The insufficient blood flow can induce symptoms of general bowel dysfunction, not dominated of pain, such as abdominal discomfort, nausea, vomiting, diarrhoea or constipation (L.J. van Dijk et al., 2019; Kolkman & Geelkerken, 2017). Further development of diagnostic modalities for CMI will likely reveal a currently undetected large proportion of patients with atypical CMI symptoms that could benefit from mesenteric artery revascularization to restore bowel function. PTA of the mesenteric arteries in patients falsely diagnosed with CMI should also be avoided, as the procedure is not without risk of complications (Altintas et al., 2021).

The advantage of the present method, as a functional test measuring SBF, despite its cumbersome setup, is that it offers a method that has been demonstrated in the present study and in former studies, to be able to detect flow changes in regard to revascularization (Møller & Madsen, 2002). The disadvantage is its cumbersome work up and a lack of a large scale clinical trials to verify the diagnostic accuracy to predict the outcome of vascular intervention.

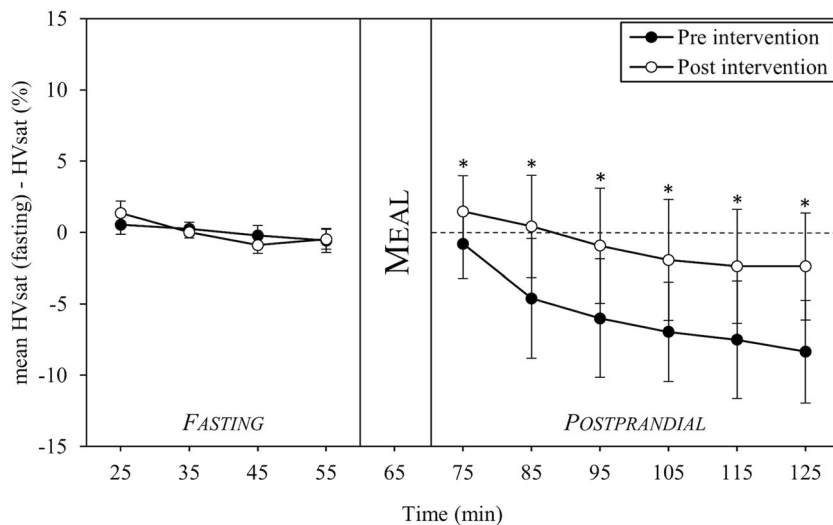
**TABLE 3** Haemodynamic parameters

	Preintervention	Postintervention	p Value
N	10	10	
SBF fasting [ml/min]	916 ± 229	972 ± 339	0.425
SBF postprandial [ml/min]	987 ± 226	1504 ± 567	0.004
SBF increase [ml/min]	71 ± 95	531 ± 295	0.001
SBF increase [%]	9 ± 10	54 ± 30	0.001
HVsat fasting [%]	58 ± 11	60 ± 9	0.266
HVsat postprandial [%]	52 ± 14	59 ± 13	0.006
HVsat increase [%]	-5 ± 5	-1 ± 6	0.023
VO <sub>2</sub> fasting [ml/min]	49 ± 13	48 ± 11	0.507
VO <sub>2</sub> postprandial [ml/min]	62 ± 14	74 ± 19	0.028
VO <sub>2</sub> increase [%]	28 ± 23	56 ± 25	0.014

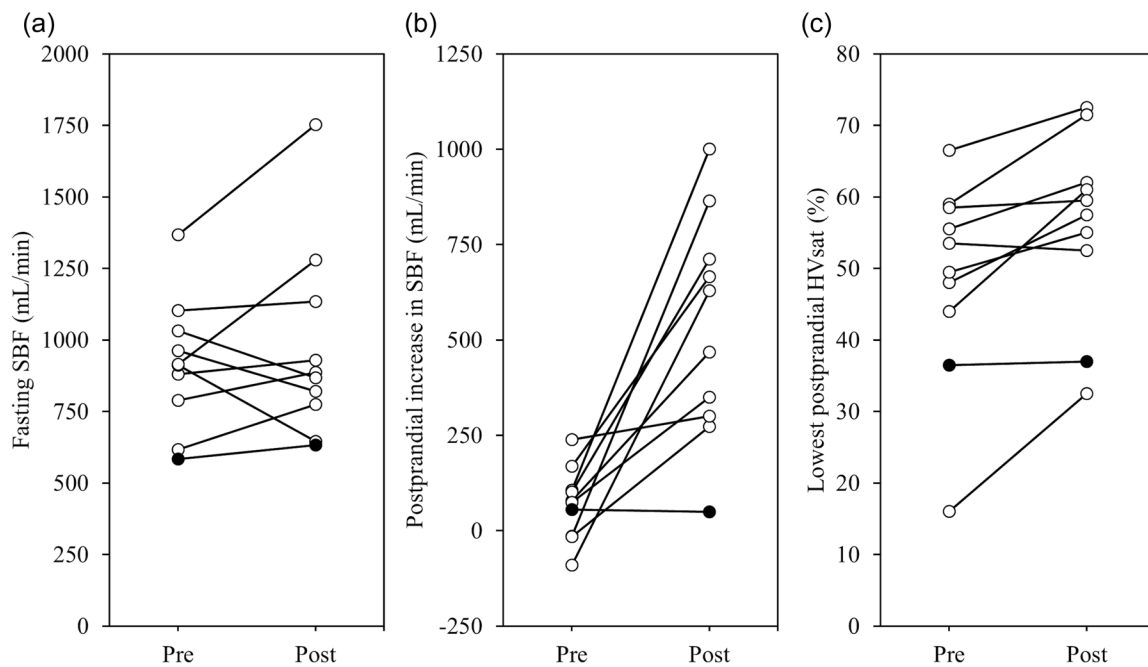
Abbreviations: HVsat, hepatic vein oxygen saturation; SBF, splanchnic blood flow; VO<sub>2</sub>, oxygen consumption.



**FIGURE 1** Total splanchnic blood flow (SBF) before and after revascularization with 95% confidence intervals. \* $p < 0.05$ .



**FIGURE 2** Change in hepatic vein oxygen saturation compared to mean fasting values with 95% confidence intervals ( $n = 10$ ).  $*p < 0.05$ .



**FIGURE 3** Changes in fasting SBF (a), postprandial increase in SBF (b) and lowest hepatic vein saturation (c) pre and postrevascularization on a patient basis ( $n = 10$ ). The patient with no symptom relief is indicated with a full dot. SBF, splanchnic blood flow.

## 5 | STUDY LIMITATIONS

Not all patients diagnosed with CMI based on SBF measurement that had revascularization performed in the inclusion period were invited to participate in the trial, due to failure to invite the patients. We found no significant difference in major haemodynamic variables when comparing the included patients at baseline to other patient diagnosed with CMI at our Department in the same period (data not shown) (Høyer et al., 2022). However, the patients enrolled in the present trial had a higher mean weight,

height and female ratio, which could influence the generalizability of our study.

## 6 | CONCLUSION

Revascularization increased the SBF and hepatic vein oxygen saturation significantly concurrent with symptom relief and according with the angiographic successful result in the vast majority of patients.

As a functional test for the diagnosis of CMI, measurement of the SBF was able to detect the hemodynamic effects of revascularization. A satisfying angiographic result post vascular intervention does not rule out CMI.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data will be available upon reasonable request.

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