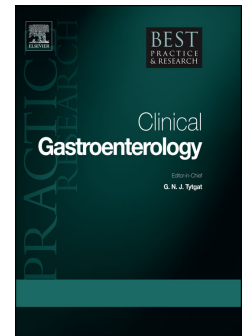# Accepted Manuscript

Functional testing in the diagnosis of chronic mesenteric ischemia

Desirée van Noord, MD PhD, Jeroen J. Kolkman, MD PhD

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4 **Functional testing in the diagnosis of chronic mesenteric ischemia**

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6 Desirée van Noord MD PhD[1,2] (corresponding author), Jeroen J. Kolkman MD PhD[3,4]

7 [1]Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands, department of

8 Gastroenterology and Hepatology

9 [2]Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands, department of Gastroenterology and

10 Hepatology

11 [3]Medisch Spectrum Twente, Enschede, The Netherlands, department of Gastroenterology and

12 Hepatology

13 [4]Universitair Medisch Centrum Groningen, Groningen, The Netherlands, department of

14 Gastroenterology and Hepatology

15

16 d.leemreis@franciscus.nl, tel 0031-10-461680, fax 0031-10-4612692

17 j.kolkman@mst.nl

18

1

2 **Abstract**

3 Chronic mesenteric ischemia (CMI) results from insufficient oxygen delivery or utilization to meet

4 metabolic demand. Two main mechanisms may lead to mesenteric ischemia: occlusion in the arteries

5 or veins of the gastrointestinal tract, or reduced blood flow from shock states or increased intra-

6 abdominal pressure, so-called non-occlusive mesenteric ischemia. Severe stenoses in the three main

7 mesenteric vessels as demonstrated with CT-angiography or MR-angiography are sufficient to proof

8 mesenteric ischemia, for example in patients who present with weight loss, postprandial pain and

9 diarrhea. Still in many clinical situations mesenteric ischemia is only one of many possible

10 explanations. Especially in patients with a single vessel stenosis in the celiac artery or superior

11 mesenteric artery with postprandial pain, mesenteric ischemia remains a diagnosis of probability or

12 assumption without functional proof of actual ischemia. This review is aimed to provide an overview

13 of all past, present and future ways to functionally proof CMI.

14

15 **Key words**

16 Chronic mesenteric ischemia, chronic gastrointestinal ischemia, chronic splanchnic ischemia,

17 functional test, functional testing, tonometry, visible light spectroscopy

1   **Introduction**

2   Chronic mesenteric ischemia (CMI) results from insufficient oxygen delivery or utilization to meet

3   metabolic demand. Two main mechanisms may lead to mesenteric ischemia: occlusion in the arteries

4   or veins of the gastrointestinal tract, or reduced blood flow from shock states or increased intra-

5   abdominal pressure, so-called non-occlusive mesenteric ischemia (NOMI). Demonstration of arterial

6   or venous stenoses is now easily achieved with diagnostics like computed tomographic angiography

7   (CTA) or magnetic resonance angiography (MRA). The vessel abnormalities are sufficient to proof

8   mesenteric ischemia, for example in patients with severe stenoses or occlusions in the three main

9   mesenteric vessels who present with weight loss, postprandial pain and diarrhea. Still in many clinical

10 situations mesenteric ischemia is only one of many possible explanations, and one of the more

11 improbable at that. The most challenging patient may be the patient with a single vessel stenosis in

12 the celiac artery (CA) or superior mesenteric artery (SMA) with postprandial pain. Without functional

13 proof of actual ischemia mesenteric ischemia remains a diagnosis of probability or assumption. The

14 same holds true for NOMI where vessel anatomy is essentially normal and without actual proof of

15 ischemia the diagnosis cannot be made with certainty until end-organ damage is proven by

16 endoscopy showing colonic ischemia or during surgery showing necrotic bowel. This review is aimed

17 to provide an overview of all past, present and future ways to functionally proof ischemic bowel.

18 **The mesenteric circulation in relation to ischemic function tests**

19 The macro- and microvascular properties of GI perfusion, and the response to meals largely dictate

20 the areas and timing to use functional tests.

21 The macrovascular distribution of gastrointestinal perfusion is characterized by three main arteries

22 and numerous collaterals. The (CA) is the artery of the foregut and supplies the stomach and

23 duodenal bulb and descending duodenum. The SMA supplies the distal duodenum, small bowel and

24 right colon. The inferior mesenteric artery (IMA) supplies the second part of colon. The normal

25 diameters and grade of stenosis of these vessels are highly relevant when judging the risk of

3

1 ischaemia. The CA and SMA both have diameter of 6 and 7 mm, whereas the IMA normally measures

2 1 mm. Consequently, an IMA occlusion would reduce the total mesenteric vessel surface by only 4%,

3 whereas a 70% stenosis of CA and SMA would reduce this by 87% (1).

4 The venous system involves the inferior mesenteric vein (IMV) and superior mesenteric vein (SMV).

5 Both combine with the splenic vein (SV) to form the portal vein (PV). The liver thus has a dual

6 vascularization from PV and common hepatic arty. This renders the liver resistant to ischemia, as

7 recently demonstrated in large cohort of CMI patients (2). Because the portal vein receives blood

8 from both the CA and SMA, measurement of blood flow properties of the PV could be used to study

9 insufficient blood flow in either the CA or SMA. For application of functional testing the anatomical

10 distribution dictates that with a normal upper endoscopy only the area perfused by the CA can be

11 inspected. For assessment of the area perfused by the SMA inspection of the more distal duodenum,

12 small bowel or right colon region would be mandatory. This is challenging, because it is widely

13 assumed the SMA is the most important of the mesenteric arteries.

14 The microvascular perfusion is characterized by larger arteries on the serosal side with large

15 networks of vessels in the outer layers (submucosal, muscular and serosal layers) and a central

16 arteriole with surrounding venules. The mucosal layer has a high metabolic demand and receives

17 app. 80% of the bowel wall blood flow (3, 4). Consequently, the mucosal layer is the first part of the

18 bowel wall affected by reduced perfusion and ischemia leading to early damage in severe ischemia

19 (5, 6). Due to the typical countercurrent organization of the villus the most superficial layers are

20 especially sensitive to ischemic damage. In contrast, ischemic damage to the muscular and serosal

21 layers is a late event in severe ischemia. Consequently, functional test for early ischemia should be

22 focused on the mucosal layer, be it by measuring PO_2 and PCO_2 directly, or by measuring early

23 ischemia-specific proteins and waste products.

24 The gastrointestinal blood flow response to meals or generalized hypoperfusion is relatively well

25 studied. Following meals, the basal, fasting gastrointestinal blood flow increases from app. 1000

4

1 ml/min. to up to 2000 ml/min. The CA blood flow increases and peaks already during the meal and

2 returns to baseline within 20 minutes after the meal, whereas the SMA blood flow increases only

3 after the meal, peaks 30-45 minutes postprandially and returns to baseline within 2-3 hours (7, 8). To

4 complicate simple measurement of blood flow it was demonstrated that the increase in blood flow

5 was due to both increased blood flow velocity and increased vessel diameter as well (8). The duration

6 of the increased SMA blood flow, and the time-to-peak depends on meal composition. Meals with

7 high fat content lead to later and higher peak blood flow and longer duration of increased blood flow

8 (8, 9). The consequences of this pattern of these meal-induced flow patterns are that 1) the time-

9 window for functional tests using test meals would ideally include the meal and first 1-2 hours

10 postprandially to cover both the CA and SMA perfusion problems, and 2) that the composition of test

11 meals should be taken into account.

12 The mesenteric blood flow on the other hand decreases whenever the systemic perfusion pressure

13 lowers, even before actual shock develops (10). The mesenteric circulation is the first vascular bed to

14 develop vasoconstriction in shock states (11). This so-called non-occlusive mesenteric ischemia

15 (NOMI) may develop with various low flow and shock states including sepsis, hypovolemia,

16 anaphylaxis, and even strenuous exercise. In the first reported mesenteric ischemia function test, the

17 gastric exercise tonometry, we used exercise to trigger redistribution of blood flow from the GI tract

18 to the exercising muscles to induce ischemia in patients with mesenteric stenoses (12).

19 Effects of tissue ischemia. The first effect of reduced gastrointestinal perfusion is an increased

20 arteriolar-venous oxygen extraction rate. If this does not suffice to maintain aerobic metabolism then

21 the tissue switches to anaerobic metabolism with decreased oxygen content in the tissues and at the

22 same time the tissue CO_2 and acidity increases. Next the mitochondrial failure leads to damage to

23 tight junctions, and failing cell membrane pumps. Later, cell swelling and leakage of cell contents in

24 the surrounding tissues and blood stream follow. In later stages re-entry of oxygen following

25 restoration of blood flow can cause reperfusion effects characterized by development of free oxygen

1   radicals and outflow of ischemic products into the systemic circulation. This sequence of events

2   serves as background when assessing the various function tests and their clinical potential, for

3   example as markers for early ischemia or late ischemia.

4   <u>Functional tests for mesenteric ischemia</u> can be divided into techniques aimed at direct evidence for

5   mucosal ischemia, blood-flow related parameters, and those that measure ischemia-related

6   products. Evidence for mucosal ischemia can be detected by measurement of: 1) reduced mucosal

7   oxygen content, 2) increased mucosal lactate, 3) increased mucosal PCO_2, 4) evaluation of mucosal

8   biopsies. The main blood-flow parameters that have been used, or are currently under investigation,

9   were aimed at showing both fasting and postprandial blood flow. They include: 1) measurement of

10   mesenteric blood flow, 2) measurement of portal vein blood flow.

11   Measurement of ischemia-derived proteins or waste-products will be briefly discussed, as it is

12   covered extensively in this issue by Dierickx et al.

13   **The clinical challenge**

14   Proving CMI is a diagnostic challenge in clinical practice. Currently there is no single test with high

15   sensitivity and specificity to diagnose or exclude this condition. Chronic abdominal pain is a common

16   symptom in the general population as are vascular stenoses of the gastrointestinal arteries (13, 14).

17   Occlusive gastrointestinal arterial disease often remains asymptomatic in most cases probably due to

18   the presence of abundant collateral circulation. Only patients with significant arterial stenosis in

19   combination with insufficient collateral circulation may develop clinical signs of gastrointestinal

20   ischemia. This was recently demonstrated in patients with single-vessel stenosis where the presence

21   of large collaterals, visible on non-selective angiography, ischemia was less common than in those

22   without these large collaterals (15). The same group showed that patients with single-vessel stenosis

23   showed increased flow in the non-affected vessel, indicating a compensatory effect via collateral

24   pathways (16).

1 The diagnostic approach in patients referred for evaluation of possible CMI focuses on identification

2 of gastrointestinal arterial stenosis and demonstration of mucosal ischemia. Currently, diagnostic

3 approaches include assessment of medical history, clinical symptoms and physical examination,

4 imaging of the gastrointestinal arteries by duplex ultrasound, digital subtraction angiography (DSA),

5 CTA or MRA and assessment of gastrointestinal mucosal perfusion by means of tonometry or Visible

6 Light Spectroscopy (VLS).

7 Functional testing is not widely available and wider use is often hampered by its cumbersome and

8 invasive nature. Until now, TM and VLS are only used in a limited number of dedicated centers with a

9 CMI program, which means that the majority of CGI patients is still assessed without functional

10 testing. However, development of mucosal perfusion assessment techniques would have additional

11 diagnostic value in identifying and grading the severity of gastrointestinal ischemia.

12 **Gastrointestinal tonometry**

13 <u>Physiological background</u>

14 That tissue PCO_2 is an accurate indicator for ischemia has been shown repeatedly in both animal tests

15 and human studies (17). The first mention of this technique was published in 1926 which established

16 that in dogs, the pCO_2 in the stomach cavity was equal to that in arterial blood. With hypoventilation

17 PCO_2 in both arterial blood and the stomach went up, while hyperventilation reduced both values.

18 That was lost as soon as the afferent blood flow was interrupted. Now, luminal PCO_2 rose while the

19 arterial PCO_2 remained stable (18). In 1959 Boda published the first study in patients and confirmed

20 both the narrow relation between gastric and arterial PCO_2, as well as increased gastric PCO_2 levels in

21 patients who developed shock or signs of ischemia (19). In the late 1980's a catheter based

22 measurement device was developed, the tonometer, to allow for simple and clean ex vivo

23 measurement of gastric, small and large bowel PCO_2 (20) It was filled with saline, left in the balloon

24 for 20-40 minutes, then the saline was aspirated and PCO_2 was measured with a blood gas analyzer.

25 Later, the catheter was attached to a specialized capnograph, the Tonocap, that allowed for

7

1   automated measurement with 10-minute cycles (21). Most literature on tonometry focused on NOMI

2   patients in the intensive care or perioperative theatre. It was found that tonometry was a reliable

3   indicator of – ischemic – stress ulcerations (22), colonic ischemia following aortic surgery (23, 24),

4   complications and mortality in ICU patients (25-27), and complications in acute pancreatitis patients

5   (28). However, its popularity waned mainly because the technique is relatively complicated – need

6   for acid suppression and complex influence of meals on PCO_2 – and because PCO_2-guided treatment

7   studies were unconvincing. The latter has been challenged recently in meta-analysis suggesting a

8   significant effect of tonometry-based treatment (29). Still, the technique has virtually disappeared

9   from the intensive care and perioperative care theatres.

10   Our groups (Enschede and Rotterdam) have mainly focused on occlusive mesenteric ischemia. In this

11   paragraph we will discuss our 20-year experience in over 1500 patients suspected of occlusive

12   mesenteric ischemia. The principle of tonometry is based on measurement of increased PCO_2 levels

13   during ischemia. This excess CO_2 stems from buffering of acids, like lactate, in the ischemic tissues by

14   interstitial bicarbonate. With normal oxygenation the cells metabolize sugars as main energy source

15   in the citric acid cycle under formation of H_2O and CO_2. This CO_2 is the removed by the blood flow

16   and exhaled in the lungs. With ischemia this CO_2 production increases in relation to the severity of

17   ischemia (30). In numerous studies the strict relation between ischemia and increased PCO_2 has been

18   demonstrated. Simply stated: ischemia = increased tissue PCO_2. In the gastrointestinal tract this

19   excess PCO_2 will accumulate first in the mucosa but diffuse quickly into the lumen where it can be

20   easily measured using a tonometer. Because mesenteric ischemia is often patchy, tonometry is able

21   to detect the overall excess CO_2 production, with little influence of exact location of the tonometer

22   catheter (figure 1). Our initial work focused on measurement technique and test prerequisites, and

23   validation in healthy volunteers (31).

24   Exercise tonometry

1   Initial studies with tonometry used an exercise test to elicit mesenteric ischemia. The underlying

2   mechanism is a steal phenomenon from the mesenteric circulation to the exercising muscles (12)

3   with reductions in mesenteric and hepatic blood flow up to 25-50% (32). Normal values for this

4   gastric exercise tonometry were obtained from a healthy volunteers study. No increase in gastric-

5   arterial difference over the normal upper threshold of 0.8 kPa was seen during exercise provided that

6   lactate levels were below 8 mmol/l. With lactate levels above 8 mmol/l, mesenteric ischemia was

7   seen in 5/11 subjects (33). The exercise tonometry consists of a 10-minute exercise on a bicycle,

8   aimed at submaximal exercise (70% of maximal). The exercise level is determined by rapid lactate

9   measurements from arterialized blood and is aimed at a lactate level between 4-8 mmol/l at 10-

10   minutes exercise. Using this validated gastric exercise test we could establish a 78% sensitivity and

11   92% specificity in 102 patients with chronic abdominal pain suspected for mesenteric ischemia (34).

12   Because some patients had SMA stenosis only, we then started to use small bowel tonometry as

13   well. The tonometer catheter is placed beyond either in the distal duodenum or jejunum to reach the

14   'SMA perfusion area'. Using the same exercise protocol, we established a normal upper limit of

15   jejunal-arterial PCO_2 difference of 1.4 kPa (35). We used this same test in patients with celiac

16   compression and found the gastric exercise test to be accurate in selecting patients who later

17   benefitted from treatment by crural release (36). Of 43 referred patients with celiac compression, 30

18   had abnormal tonometry of whom 29 were operated. After a median follow-up of three years 83%

19   were free of abdominal pain. The main draw-backs of exercise tonometry is first the need to exercise

20   up to submaximal levels and some patients cannot exercise, or not enough to reach that level.

21   Secondly, although many patients with mesenteric ischemia complain of post-exercise abdominal

22   pain, this complaint did not differentiate between ischemic and non-ischemic subjects with

23   mesenteric stenoses (37). Post-prandial pain on the other hand, is a key complaint in the vast

24   majority of mesenteric ischemia patients (37, 38). We therefore focused our attention on

25   development of a reliable and reproducible tonometry test using meals as ischemic trigger.

26   24- hour Tonometry

1 There are several methodological issues when performing postprandial tonometry. First, acid

2 suppression must be maximal, because persistent acid production leads to increased PCO_2 from

3 buffering by bicarbonate (39, 40). There are three potential bicarbonate sources: the gastric mucosal

4 layer, small bowel content or the ingested food itself. We therefore use high-dose PPI treatment of

5 Omeprazole 80 mg bolus followed by 8 mg per hour. Because it was shown that PCO_2 increase after

6 meals could be related to acids in food as well (40), we tested different test meals in vitro to

7 minimalize these effects. The ideal candidate was Nutridrink ®, a standard liquid nutrition (39). We

8 then used the Nutridrink as a standard meal and established normal values in a 24-hour tonometry

9 test in healthy subjects. The normal baseline of gastric PCO_2 and small bowel PCO_2 levels (41) as well

10 as the response to meals were assessed. The cut-off value for baseline PCO_2 in stomach and small

11 bowel was < 8.0 kPa. The cut-off values for the maximum PCO_2 from 0-120 minutes after meals were

12 for the stomach: 11.3 after Nutridrink, 11,4 after dinner and 12.1 kPa after breakfast. For the small

13 bowel these values were 10.6, 13.6 and 12.0 kPa (41). An abnormal test was defined as (1) pathologic

14 responses after three or more (standard) meals, or (2) a combination of one or two pathologic

15 responses after (standard) meals combined with a median PCO_2 > 8.0 kPa, measured in between

16 meals. Using these cut-off values a sensitivity of 76% and specificity of 94% was calculated. In a larger

17 study Sana et al. confirmed the value of 24-hr tonometry and showed an overall accuracy of 87%

18 (sensitivity 92%, specificity 77%). When this function test was incorporated in the decision with a

19 greater impact than the medical history or radiological findings (42). This study re-emphasized the

20 importance of a consensus diagnosis using a multidisciplinary approach with a diagnostic accuracy

21 >90% on follow-up, when all elements (anamnesis, radiology and tonometry) were included in

22 decision making.

23 In patients with end-stage CMI two patterns can be observed. Typically, the baseline PCO_2 is grossly

24 elevated, with long and high PCO_2 peaks after meals, indicating imminent or ongoing mesenteric

25 infarction. In patients with acute ischemia for longer duration a very low PCO_2 pattern with hardly

26 any variation was observed. The latter can be seen in non-ischemic subjects, but was observed in

10

1   several patients with ongoing, and yet undetected, bowel infarction. In the latter years, we have not

2   seen this pattern as patients with persistent pain, or pain unassociated with meals are now treated

3   immediately and do not undergo tonometry anymore (figure 2).

4   <u>Tonometry after intervention</u>

5   Only one study investigated the effects of treatment on tonometry. In the study on CACS patients,

6   Mensink et al. showed improved tonometry in all patients who responded to treatment. In contrast,

7   in those without improvement of pain after treatment 50% was unchanged, 25% improved and 25%

8   worsened (36).

9   <u>Procedure</u>

10   The tonometer, a balloon-tipped catheter can be placed via the nose in stomach and small bowel,

11   using a guide wire placed endoscopically, and checked by fluoroscopy or with fluoroscopy alone. A

12   second tonometer is placed in the stomach and the placement is checked by fluoroscopy. The

13   catheter is then attached to a specialized capnograph, the Tonocap, that measures the PCO_2 every 10

14   minutes. The patient should be fasting for 6 hours, and use of intravenous high-dose PPI is advised to

15   prevent false-positive PCO_2 peaks from buffering of gastric acid (39, 43). The Tonocap is now

16   connected to a PC with software that captures the data directly. After measurement the data are

17   exported from this PC to MMS software (Medical Measurement Systems, Enschede, the Netherlands)

18   and analyzed using this software program that was developed for manometry and pH-impedance

19   studies.

20   <u>Limitations of tonometry</u>

21   Although the data for tonometry as measure for mesenteric ischemia are rather convincing, the

22   technique never was really accepted in the medical community. There are several limitations that

23   hampered its wider use. First, in the first years the technique involved measurement of manually

24   infused and aspirated saline by blood gas analyzer, and was notoriously cumbersome, error-prone,

1 and laborious (31). The switch to automated air tonometry was a clear improvement (21). Second,

2 tonometry was mainly used for critical care patients, but failed to impact the outcome significantly.

3 Third, the technique is still challenging, with need for strict testing conditions (acid suppression,

4 meals, timing, analysis). Fourth, even with these strict conditions the current device is far from fail

5 safe, and slight kinking of the catheter, or occasional leakage in the balloon results in failed

6 measurement and need for repetition. Fifth, the need for two, small and soft, catheters trans-nasally

7 is burdensome for patients, as is the setup with a large PC and two Tonocaps next to the bed, limiting

8 the freedom of movement for 24 hours. Finally, the current producer has stopped making and

9 maintaining the Tonocaps, limiting its future to the very near future. A new 'balloon-less' technique

10 has been described by the late Professor Boda (44, 45). We have done some ex vivo studies using this

11 technique and found that it was able to measure multiple compartments with short response times

12 (unpublished data) and are currently developing further validation and pilot studies. Still, further

13 studies are needed to evaluate its actual diagnostic accuracy and clinical applicability**.**

14 **Visible light spectroscopy**

15 <u>Physiological background</u>

16 Measurement of mucosal oxygen saturation dates back to the early 1950's, and was used for skin

17 measurement mainly. Measurement of gastrointestinal mucosal oxygen saturation became possible

18 with microfiber technique combining a light source and external spectrometer (46). This technique is

19 used in the reflectance spectrophotometer (RS) that can be used endoscopically, and is known as

20 visible light spectroscopy (VLS). VLS is a relatively new technique that enables non-invasively

21 measurements of mucosal capillary hemoglobin oxygen saturations during upper endoscopy. Unlike

22 near-infrared spectroscopy (NIRS) or pulse oximetry (SpO_2%), that are mostly used for tissue

23 measurement, VLS is based on locally absorbed, shallow-penetrating visible light for measurement of

24 microvascular hemoglobin oxygen saturation, and was developed as a catheter based measurement

25 device (47). The technique uses white light delivered by a fiber optic probe to directly measure intra-

1 mucosal hemoglobin saturation, relying on the marked difference in absorption spectra of

2 oxygenated and deoxygenated hemoglobin. It was indeed shown that gastrointestinal mucosal

3 ischemia by hypotension, smoking, or injection of vasoconstricting substances could be detected by

4 reflectance spectroscopy (48). Using RS Kamada et al. found decreased oxygenated hemoglobin in

5 patients with stress ulcers (48), around the same time that Fiddian Green published a similar

6 relationship using tonometry in stress ulcer patients (22). Both studies thus noticed the importance

7 of gastric hypoperfusion in the development of stress ulcers. The relation between gastric mucosal

8 perfusion and mucosal oxygen saturation was later confirmed in ICU-model during cardiac bypass

9 surgery (49).

10 The data on human mesenteric ischemia using VLS is limited. It is expected that gastrointestinal

11 arterial stenosis would decrease the delivery of oxygen to the gastrointestinal mucosa resulting in

12 lower mucosal hemoglobin oxygen saturations. Indeed, a pilot study showed promising results: VLS

13 was able to demonstrate mesenteric ischemia in three patients (50). The authors developed normal

14 values using healthy volunteers and laid a foundation to further develop upon. The major drawback

15 of their paper is that the three patients with abnormal VLS all had end-stage mesenteric ischemia, all

16 with subtotal stenosed or occluded CA and SMA and end-organ damage (gastric ulcers in two and

17 bloody diarrhea in the third), as pointed out in commentary following the paper (51). However,

18 following this pilot study, VLS did detect mucosal hypoxemia in patients clinically suspected for CMI

19 in a large cohort, showing excellent correlation with the established ischemia work-up using

20 tonometry (52).

21 <u>Procedure</u>

22 VLS is performed during upper endoscopy under conscious sedation. The peripheral saturation level

23 has to be above 94%. After irrigation of the target area to remove any bile remnants, the fiberoptic

24 catheter-based visible light spectroscopy oximeter (T-Stat 303 Microvascular Oximeter, Spectros,

25 California, USA) can be passed through the accessory channel of the endoscope. After administration

1   of Butylscopolamin to prevent luminal spasms, point measurements of the oxygen saturation are

2   performed at three locations: antrum of the stomach, duodenal bulb and descending duodenum. The

3   probe is positioned 1 to 5 mm above the mucosa. Once a stable reading is obtained with less than 5%

4   variation in panel read-out , the actual measurement can be started. Then three repeated readings of

5   each location will be taken and averaged. This average per location is regarded as most accurate

6   reflection of mucosal oxygen saturation. The oxygen saturation measurements are regarded positive

7   for ischemia below the following cut-off values: 63% in antrum and/or 62% in duodenal bulb and/or

8   58% in descending duodenum (Figure 3).

9   <u>Diagnostic value</u>

10 VLS is a validated diagnostic method to correctly detect CMI with a sensitivity of 90% and a specificity

11 of 60% (52). Because missing a mesenteric ischemia patient was considered more harmfull than

12 having false-positives the cut-off values were chosen with high sensitivity and low specificity. The

13 rationale being that undiagnosed and untreated patients with ischemia have a higher morbidity and

14 mortality rate. Harki et al. (53) confirmed the diagnostic value of VLS in distinguishing patients with

15 CMI from patients without CMI and healthy subjects. Patients with CMI have significantly lower

16 mucosal oxygenation saturation measurements using VLS compared to patients without CMI and

17 healthy controls. Sana et al. investigated the response of patients with occlusive CMI to treatment

18 after evaluation by radiologic imaging of the vasculature and functional testing using VLS (54). A

19 corpus mucosal saturation level <56% (OR, 4.84) was one of the strongest predictors of a positive

20 response to treatment.

21 <u>VLS after intervention</u>

22 After successful treatment, improved repeated VLS measurements can be observed, 80% of patients

23 with relief of symptoms showed improvement of even normalization of VLS measurements (52). In

24 patients with persistent symptoms no change in mucosal perfusion was observed.

1 <u>Limitations of VLS</u>

2 VLS has some limitations and unsolved issues. First, VLS is a relatively new test method with few

3 studies to support its value. All published data from the Rotterdam group are based on a trainee data

4 set and additionally confirmed in a validation cohort. Still, there is only one large single center cohort

5 and the data are not yet reproduced by other research groups.

6 Second, current specificity is rather low, and could lead to treatment of too many non-ischemic

7 patients. Third, the intra- and interobserver variability of VLS measurements has never been

8 investigated. This may be of importance because small changes in the position of the probe can

9 cause small variations in the oxygen saturation. Moreover, the mean of mucosal saturation

10 measurements in patients with CGI showed great variation and the range of measurements is large

11 (52). Therefore, it is sometimes quite hard to classify a measurement as positive or negative for

12 mucosal ischemia when the obtained average value is around the cut-off value.

13 Fourth, mucosal ischemia might be patchy and could be missed because VLS is limited to repeated

14 point measurements. A very large number of repeated point measurements might in theory increase

15 the diagnostic yield of VLS, this remains to be established in future research.

16 Furthermore, the hypothesis rises that mucosal ischemia only occurs postprandially, in response to

17 an increased metabolic demand or exercise related, indicating a time-dependent relation. Currently,

18 VLS measurements are performed in a fasting state due to the nature of the test as performed during

19 upper endoscopy. In theory, patients with CGI with less impaired gastrointestinal blood flow could

20 show normal mucosal saturation measurements in this fasting condition and could therefore be

21 missed or underestimated. VLS measurements after luminal feeding stimulation may overcome these

22 false negative results, thereby enhancing the specificity of the test. Currently, the diagnostic accuracy

23 of postprandial VLS measurements is investigated, the results of this study will follow during the next

24 year.

25 **Total splanchnic blood flow**

15

1 In Scandinavian countries invasive measurement of mesenteric and hepatic blood flow has been used

2 as functional test for several decades. This so-called total splanchnic blood flow (SBF) can be

3 determined by catheterization of the liver vein and subsequent blood sampling after infusion of

4 indocyanin green or radio-active markers and measured by Fick's principle. Hansen reported in 1977

5 that an increase in SBF after test meal of less than 250 ml/min in SBF indicated CMI (55). In that first

6 paper the six patients with <250 ml/min postprandial SBF increase all had severe 2- and 3-vessel CMI.

7 The blood flow increase in single-vessel CMI patients did not differ from healthy controls. They also

8 observed a wide variation in basal SBF (from 700-1500 ml/min) and postprandial increase (from 410-

9 880 ml/min). In a carefully conducted study Zacho et al. confirmed the wide variation in SBF in

10 healthy volunteers, and could not relate them to age, body weight or sex (56). In a study in 46

11 patients the same group found an abnormal increase after meals, but again only in patients with

12 multi-vessel disease (57). We therefore think that this technique has no place as functional test in

13 suspected single-vessel CMI.

14

15 **Future, new function tests**

16 <u>Endomicroscopy of the microcirculation</u>

17 Recently, studies in patients with acute gastrointestinal ischemia demonstrated a correlation

18 between intestinal ischemia and sublingual microcirculatory alterations (58). There is increasing data

19 and interest in assessing microcirculation changes, especially in critical care patients. The current

20 most applicable technique for critical patients is a hand-held microscope that can easily investigate

21 the sublingual mucosal capillaries (59). With this technique a tissue endomicroscopy is targeted at

22 the mucosa after removal of all fluids (saliva, bowel content) and avoidance of pressure on the

23 mucosa. It is recommended to measure five different areas for 20 seconds with steady image. The

24 filmed fragments are then analyzed for patterns of microvascular flow and particularly the presence

25 of stopped or intermittent flow. Various parameters have been described in literature, including

1 vessel diameter, vessel length, capillary perfusion patterns (no flow, intermittent flow, sluggish flow

2 or continuous flow), and vessel density (58, 60).

3 It is unclear whether measuring sublingual perfusion will be of value in occlusive mesenteric

4 ischemia. There is data that suggests that sublingual perfusion is closely related to gastrointestinal

5 perfusion. Animal studies in shock using tonometry found significant relations between sublingual

6 and gastric perfusion (61, 62). Patients with CGI may suffer of systemic microcirculation

7 disturbances, therefore a correlation with a decrease in sublingual oxygen saturation, as captured by

8 the Cytocam-incidental dark field illumination handheld microscope(63), can theoretically be possible

9 in patients with CGI with decreased mucosal oxygen measurements indicating impaired intestinal

10 perfusion and is currently investigated. We could identify two studies that looked at gastrointestinal

11 microcirculatory patterns in human patients. Kara et al. studied 22 septic patients with confocal

12 microscopy of both sublingual and intestinal mucosa. The latter could be obtained because all 22 had

13 either an ileostomy or colostomy. It was observed that during shock and resuscitation of

14 postoperative septic patients, the response of sublingual and intestinal microcirculation differed,

15 where the former followed generalized perfusion failure and restoration. Finally, a distorted

16 perfusion pattern in small bowel villi was associated with adverse outcome.

17 Schmidt et al. studied 10 septic patients using an endoscope-based technique. The imaging probe

18 was introduced through the working channel of any standard endoscope. The probe is attached to a

19 laser scanning unit, and an acquisition and image analysis device (60). The patients were injected

20 with 1 ml fluorescein 10% i.v. 10 minutes before measurement. They observed a reduction in number

21 of perfused vessels as well as their diameter in septic patients compared to healthy controls. Further

22 developments, including image stabilization (64) might make the technique clinical feasible. Still,

23 studies in occlusive mesenteric ischemia are lacking. A pilot study is currently initiated by our groups.

24 *Mitochondrial PO$_2$ measurements*

1 Another approach is to measure oxygen at the site where it is utilized, the mitochondria. Mik et al.

2 introduced the protoporphyrin IX-triplet state lifetime technique for measuring PO_2 in mitochondria

3 (mitoPO$_2$) (65). The technique resulted in the development of the COMET monitor, a clinical monitor

4 for assessment of Cellular Oxygen METabolism, which allows cutaneous mitoPO$_2$ measurements to

5 be made in humans (66) .This non-invasive technique is not yet tested in the stomach and small

6 intestine. If it is possible to measure mitochondrial oxygen tension in the gastrointestinal tract, for

7 example during endoscopy, mitoPO$_2$ measurements could be used in the work-up of CGI. Whether it

8 will be an improvement over VLS remains to be determined. A pilot study is currently initiated by our

9 groups.

10 Volatile organic compounds (VOC's)

11 An interesting development in the diagnostic arsenal is measurement of exhaled VOC's. Pathological

12 conditions often cause metabolic changes in the body resulting in measurable changes in the blood.

13 At the lung surface, there is an intensive exchange of organic compounds between the blood and the

14 air in the lungs. They are referred to as volatile organic compounds (VOC's). Using exhaled air as

15 potential diagnostic indicator is an emerging activity in detection of malignancies, infections and

16 inflammatory bowel disease (67-70). There are two animal studies to VOC detection of the changes

17 in metabolic activity following ischemia. The first used an occlusive model (SMA occlusion) and

18 detected various VOC's during ischemia (71). A second study studied the effects of hypovolemic

19 shock in VOC patterns in rats and detected different molecules in early ischemia, reperfusion and

20 during recovery (72). A pilot study to VOC detection for mesenteric ischemia is currently initiated by

21 our groups.

22 Mesenteric and hepatic blood flow

23 Another approach to functionally test the bowel's perfusion would be to measure blood flow under

24 fasting and postprandial conditions. The normal fasting bowel receives an average blood flow of 1000

1 ml/min. After meals this blood flow can double. Theoretically, it would be interesting to see whether

2 blunted postprandial increase, or lower basal blood flow could be used as indicator for CMI.

3 *Magnetic resonance imaging*

4 Less invasive alternatives to measure GI blood flow response to meals would be to measure PV blood

5 flow using MRI. MRI can be used to non-invasively measure both the SMA, SMV and PV blood flow.

6 The PV is the common outflow vein from both CA and SMA. Therefore, insufficient mesenteric

7 perfusion should be detectable by MRI. The variation in basal blood flow varies widely (73). After

8 meals the PV and SMV flow increases. The 250% increase in SMV flow seems the main determinant

9 of the 70% increase in PV flow after meals (74). The latter increase was later confirmed in a study in

10 healthy subjects, where the increase in PV after a meal was mean 800 ml (66% of baseline) with 95%

11 CI of 570 - 1030 ml/min (75). In patients with CMI the mesenteric blood flow is suspected to increase

12 less postprandially due to the hemodynamically significant stenosis of the mesenteric vessels.

13 Currently the feasibility to assess the hemodynamics of the mesenteric arteries and portal vein using

14 MR flow measurements is investigated by the Rotterdam group and seems a promising technique.

15

16 **Practice points**

17 • The diagnostic approach in patients referred for evaluation of possible chronic mesenteric

18 ischemia focuses on identification of gastrointestinal arterial stenosis by CT-angiography or

19 MR-angiography and demonstration of mucosal ischemia.

20 • Assessment of gastrointestinal mucosal perfusion adequacy is performed by means of a

21 functional test: Tonometry or Visible Light Spectroscopy.

22 • Exercise tonometry and 24-hour tonometry are established techniques that measure

23 increased PCO_2 levels during ischemia, as induced by exercise or a meal, by a balloon-tipped

24 catheter placed via the nose in stomach and small bowel.

1   •   Visible Light Spectroscopy is a relatively new technique that enables non-invasively

2   measurements of mucosal capillary hemoglobin oxygen saturations during upper endoscopy.

3 **Research agenda**

4   •   Balloon-less tonometry

5   •   VLS measurement after luminal feeding stimulation

6   •   Intra- and interobserver variability of VLS measurement

7   •   Endomicroscopy of microcirculation

8   •   Mitochondrial PO_2 measurement

9   •   Volatile organic compounds detection

10   •   Hemodynamics of the mesenteric arteries and portal vein using MR flow measurements

11 **Summary**

12 Functional ischemia tests are crucial for patients with single-vessel and non-occlusive mesenteric

13 ischemia. The two functional tests tonometry and visible light spectroscopy have important

14 limitations including availability, accuracy and complexity. New tests that are currently under

15 development include balloon-less tonometry, endomicroscopy of microcirculation, mitochondrial

16 PO_2 measurement and VOC detection.

17

18 **Conflicts of interest statement**

19 None.

20

21

22

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Table 1

Exercise tonometry

Preparation

PPI intravenous (80 mg bolus, 8 mg/hr, > 2 hr before test)

Exercise

Duration 10 minutes, aimed at 70-80% submaximal at least three minutes

Measurements

Heart rate

ECG continuous with ST segment detection (avoid coronary events)

Gastric and jejunal PCO_2 every 10 minutes

Arterialized blood gas baseline and peak exercise

Arterialized lactate baseline, at 5-7-9 minutes (monitor exercise level, aim at 3-8 mmol/l at peak exercise)

Interpretation

Lactate 3-8 mmol, and

　　　Gastric-arterial PCO_2 difference > 0.8 kPa → ischemia

　　　Jejununal-arterial PCO_2 difference > 1.4 kPa →ischemia

Lactate levels < 3 mmol/l: insufficient exercise level with normal PCO_2 gaps (risk: false-negative)

Lactate levels > 8 mmol/l: maximal exercise, chance of physiological ischemia (risk: false-positive)

Table 2

24-hr tonometry

Preparation

PPI intravenous (80 mg bolus, 8 mg/hr, > 2 hr before test, continued throughout test)

Meals

At least 2 liquid compound meals 400 ml (Nutridrink, Nutricia, the Netherlands), normal dinner,

normal breakfast (2 slices of bread, tea or coffee). No acidific or CO_2 containing beverages.

Measurements

Baseline PCO_2 (lowest stable measurement of PCO_2 for at least 60 minutes)

PCO_2 peaks after meals (window: start of meal – 2 hrs after end of meal)

PCO_2 peaks (>11 kPa) not associated with meals

Pain episodes

Interpretation

Threshold values (upper levels of normal) PCO_2 (41)

Gastric: baseline < 8.0 kPa

                postprandial: breakfast: 12.1 kPa, dinner: 11.4 kPa, Nutridrink: 11.3 KPa

                associated with pain: 11.0 kPa

Jejunum: baseline < 8.0 kPa

                breakfast: 12.0 kPa, dinner: 12.0 kPa, Nutridrink: 10.6 KPa

                associated with pain: 11.0 kPa

Abnormal test when

-3 or more peaks,postprandial peaks or peaks associated with pain, above threshold

-baseline PCO_2 above threshold, at least one postprandial peak or peak associated with pain above

threshold.

Legends to the Figures

Figure 1

Principle of PCO_2 tonometry. In mucosal ischemia a patchy distribution is characteristic with normal flow (A) reduced flow (B) and no flow (C) areas in close approximation. Because the PCO_2 in normal perfused mucosa equals blood values, and low flow areas have moderate increased PCO_2 (B), and no flow areas have very high PCO_2 values, the overall measured PCO_2 is an integral of these value. In other words: even early ischemia can be measured, but with worsening ischemia, the PCO_2 increases.

Figure 2

Analysis of 24-hr tonometry.

A. 24 hour read-out with the stomach PCO_2 in the top and the jejunal PCO_2 in the bottom panel. The baseline values during day- and night time are indicated by the dotted lines.

B. Detail of the stomach and jejunal PCO_2 response with meals (twice Nutridrink and one dinner). The PCO_2 within a 2-hour period of meals is analysed. The response is abnormal if the maximum PCO_2 exceeds the upper limit of normal (11 kPa with Nutridrink).

C. The typical PCO_2 pattern is end-stage ischemia. A flat, hardly changing PCO_2 curve can be seen, indicative of ischemic cell death.
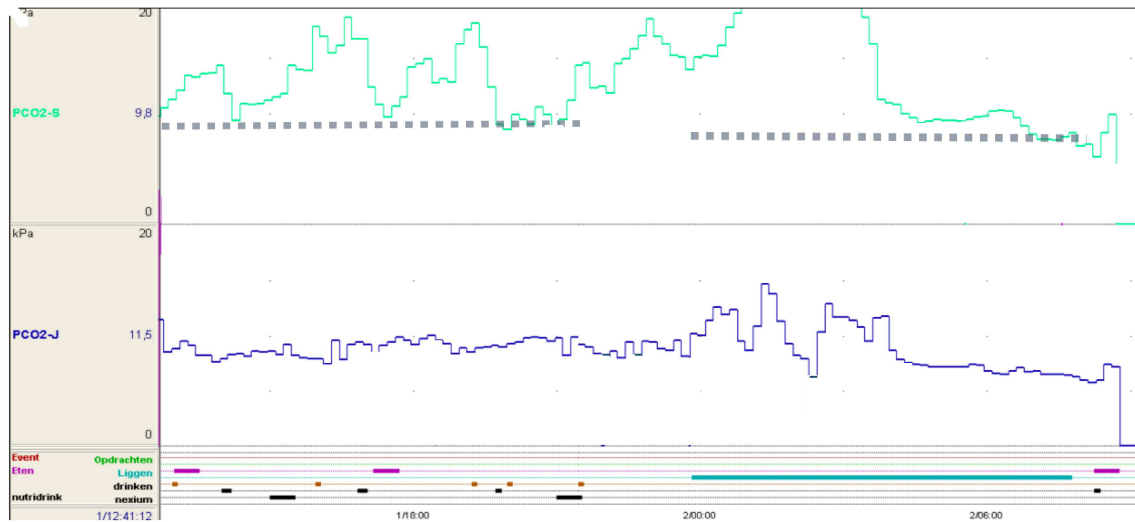
Figure 3

VLS measurements using a fiberoptic catheter-based visible light spectroscopy oximeter. The catheter is passed through the accessory channel of the endoscope and positioned approximately 1 to 5 mm above the mucosa.
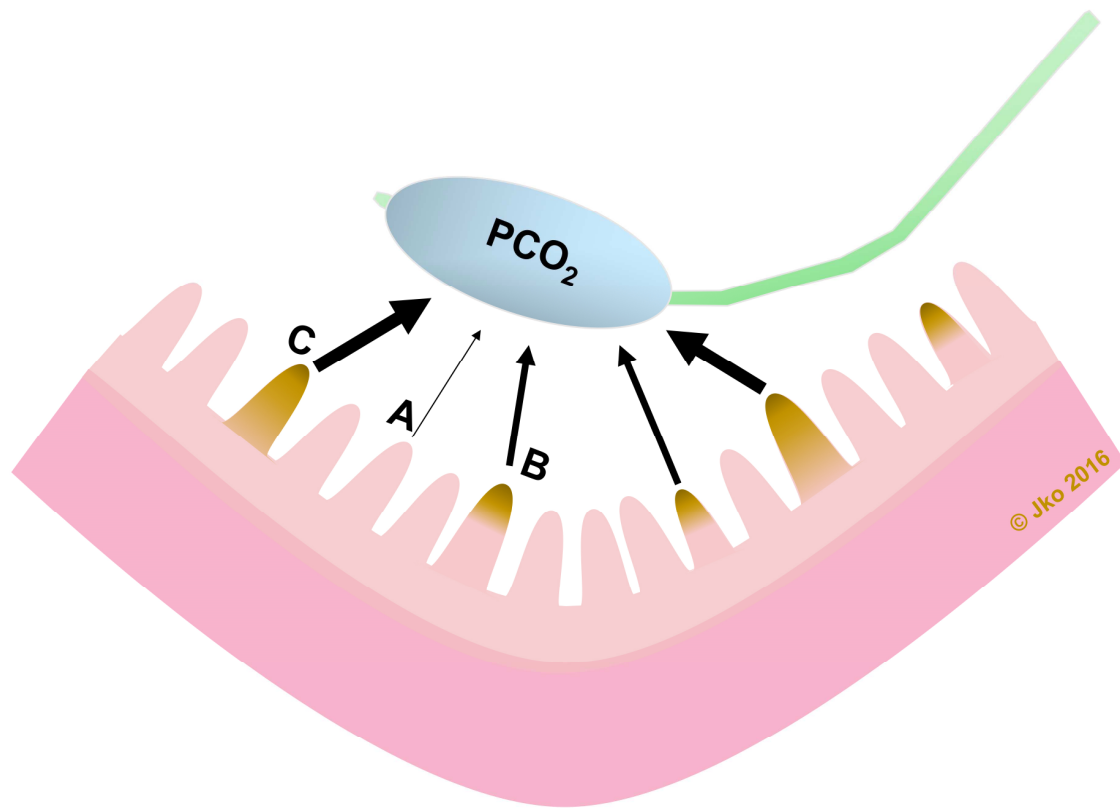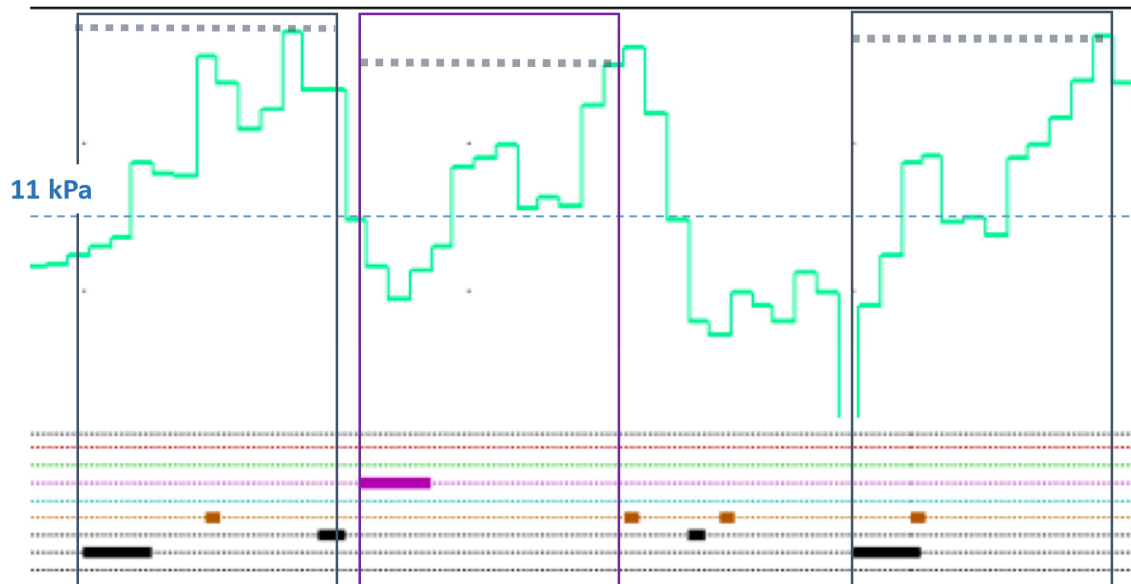
A. 24-hr tonometry: baseline

B. Analysis of meal-related peaks

11 kPa

C. Flat curve; severe ischemia