**Reviewer Response**

We sincerely appreciate the thorough review and constructive criticism provided by the editorial team and referees, which have helped to improve the manuscript by incorporating several edits and clarifications. Most notably, we have compiled 3 additional tables (2 in the Appendix) containing detailed clinical information on the patients as requested. This task took us a considerable amount of time because the clinician on our team had recently moved to another institution. We also needed to work through regulatory issues (the IRB associated with this clinician ran out with his departure) and we added a second clinician to help with carefully reviewing the medical history and records of the patients. We used the additional parameters and more clearly defined criteria to recategorize patients as MCI+ or MCI-. That lead to 2 changes from the original classifications and all statistical test were redone accordingly. We are grateful to the reviewers to prompt us for the additional follow-ups and the editorial team to provide us sufficient time to follow through. We feel that the newly added clinical information and edits make for a much stronger and more transparent manuscript. Please find our point-by-point response below.

**Referee 1:**

**Comments to the Author:**

*In a retrospective study the authors attempted to assess mesenteric hemodynamics in patients with suspected chronic mesenteric ischemia using 4D flow MRI with 1.5T or 3.0T scanner. The topic is interesting and has a clinical and radiological relevance.*

*In particular, considering great limitations related to the retrospective nature of this study (lack of the possibility to standardize data according to different 1.5T and 3.0T scanner, and to measure differences in vessels diameter before and after meal), I think this manuscript is well organized and structured. Mesenteric blood flow is not altered by different scanners used (1.5T or 3.0T), so the results seem to be realistic. Unfortunately, it was not possible to measure inferior mesenteric artery not always included. However the authors take all the flow measures distant from the beginnings of interested vessels and use to evaluate the flow in the aorta pre and post interested vessels to check the flow preservation, so that reduce the need to add inferior mesenteric artery flow value.*

**R1.1:**

**Comment:**

*Please specify how the authors decide to quantify mean blood flow, why did you evaluate blood flow in all cardiac cycle phases and do not prefer to evaluate blood flow separately in max systolic and max diastolic phase? I think that a separated evaluation of blood flow in max systolic and max diastolic phase can allow to distinguish if the reduced post-meal blood flow is due to a minor stenosis (reduction in caliber and speed flow increase in systolic phase).*

**Response:**

Note that the following page and line numbers for each response are referring to the “track-changes” blinded manuscript.

The reviewer makes a good point in stating that targeted systolic and diastolic analysis can potentially provide additional information on stenosis severity. We had targeted the mean volumetric flow rates as the primary clinical metric because it reflects the overall amount of blood flow going into the mesenteric vessels, which is the underlying physiological concern in mesenteric ischemia. Secondly, this metric is more established as it has been used in several studies of similar scope (Burkart, Johnson et al. 1993, Burkart, Johnson et al. 1993, Li, Whitney et al. 1994, Burkart, Johnson et al. 1995, Li, Hopkins et al. 1995, Dalman, Li et al. 1996). We actually had performed an analysis of diastolic and systolic flow as suggested, but found criteria derived from mean flow more powerful. For all these reasons, and to preserve manuscript length and focus, the authors feel it is best to not add the analysis of both maximum systolic and diastolic blood flows. Please note that some information regarding stenoses severity has been provided in the Appendix Tables 1-2.

**R1.2:**

**Comment:**

*Another consideration should be done, all blood flow were evaluated in a single cardiac cycle and were not evaluated in unit of time. For example, an increase of cardiac frequency, also with a reduced mean blood flow, can determine an increase of blood supply in time unit.*

**Response:**

The referee is correct in stating that increases in cardiac frequency would lead to increases in the volume of blood flowing through a vessel per unit time, which would not be portrayed if analyzing flow per cardiac cycle. This is indeed crucial, as heart rate invariably increases after meal consumption. However, our analyses were evaluated in unit time. Data exported from the customized flow analysis tool after manual segmentation provided total flow measurements in units of L/cycle. These values were then converted to ‘time units’ by multiplying total flow (L/cycle) by the HR (cycle/min) and multiplying by a factor of 1000 (mL/L) to achieve a ‘time-averaged’ flow rate in units of mL/min. This compensates for influences of heart rate on volumetric flow rates. To clarify this, we have adjusted the wording in the Methods section (P10:L188-190).

**R1.3:**

**Comment:**

*Quite good level of written English: there are some mistakes in the main text. I suggest a more careful rereading.*

**Response:**

Thank you for the comment. Several mistakes have been corrected at the following locations within the manuscript: P3:L38, P6:L123, P16:L275, P17:L297, P24:L452, and P25:L485.

**R1.4:**

**Comment:**

*Reference: match with author's guidelines.*

**Response:**

For this work, the authors utilized the downloadable EndNote style file provided on the Abdominal Radiology Submission Guidelines webpage. The authors have verified that the reference formatting is consistent with the stated guidelines.

**R1.5:**

**Comment:**

*Please add some references:*

*- Page 3, line 51, Terlouw LG, Moelker A, Abrahamsen J, et al. European guidelines on chronic mesenteric ischaemia - joint United European Gastroenterology, European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Gastrointestinal and Abdominal Radiology, Netherlands Association of Hepatogastroenterologists, Hellenic Society of Gastroenterology, Cardiovascular and Interventional Radiological Society of Europe, and Dutch Mesenteric Ischemia Study group clinical guidelines on the diagnosis and treatment of patients with chronic mesenteric ischaemia. United European Gastroenterol J. 2020;8(4):371-395. doi:10.1177/2050640620916681*

*- Page 3, line 54, Mazzei MA, Guerrini S, Cioffi Squitieri N, Genovese EA, Mazzei FG, Volterrani L. La diagnosi di ischemia/infarto intestinale nell'era della TC multistrato [Diagnosis of acute mesenteric ischemia/infarction in the era of multislice CT]. Recenti Prog Med. 2012;103(11):435-437. doi:10.1701/1166.12884*

*- Page 3, line 54, Mazzei MA, Guerrini S, Cioffi Squitieri N, et al. Reperfusion in non-occlusive mesenteric ischaemia (NOMI): effectiveness of CT in an emergency setting. Br J Radiol. 2016;89(1061):20150956. doi:10.1259/bjr.20150956*

*- Page 4, line 80, Mazzei MA, Guerrini S, Cioffi Squitieri N, et al. Magnetic resonance imaging: is there a role in clinical management for acute ischemic colitis?. World J Gastroenterol. 2013;19(8):1256-1263. doi:10.3748/wjg.v19.i8.1256*

**Response:**

Thank you for the suggestion for additional citations. The first reference suggested (Terlouw, Moelker et al. 2020) provides a comprehensive overview of current evidence and multidisciplinary expert agreement on diagnosis and treatment of chronic mesenteric ischemia. This reference emphasizes the difficulty of diagnosing chronic mesenteric ischemia and contains information quite relevant to this study; this reference has been added to P3:L53. Also note that this reference was suggested by Referee 2 (see R2.1).

The second and fourth references related to work from Mazzei, MA were added to P3:L59-60 regarding the clinical effectiveness of CT and MRI in mesenteric ischemia diagnoses.

The third suggested reference, also by Mazzei, is published in Italian and was not added to this manuscript.

**Referee 2:**

**Comments to the Author:**

*Mesenteric flow measurements could become a valuable functional test to identify CMI patients. Especially, since a food stimulus can be given to increase oxygen demand, which is not possible in current functional tests, such as visible light spectroscopy. 4d flow measurements are probably the way to go, because the duration of the MRI is far shorter than 2d or 3d flow measurements. Though promising and highly relevant, the current study has some major methodological issues limiting the clinical value and interpretability of the study.*

**R2.1:**

**Comment:**

*Background (page 3, line 50) - A high index of clinical suspicion is quite vague, perhaps the authors could consider elaborating on when the index of clinical suspicion is high. A set of criteria for patients with suspected CMI that is commonly reported in literature is a typical history (e.g. postprandial abdominal pain, fear of eating, weight loss, etc.), presence of mesenteric artery stenosis on abdominal imaging, and exclusion of alternative diagnoses. The recent multidisciplinary* *European CMI guidelines might offer guidance as well.*

**Response:**

Note that the following page and line numbers for each response are referring to the “track-changes” blinded manuscript.

We agree and added text to that affect (P3:L50-53) using the aforementioned set of criteria stated by the referee: typical presenting symptoms of CMI, presence of mesenteric artery stenoses from imaging findings, and exclusion of other alternative pathologies. We would also like to add that coexistence of risk factors for atherosclerosis, such as smoking, hypertension, hypercholesterolemia, etc., is an important consideration in these patients. The European CMI guidelines paper (Terlouw, Moelker et al. 2020) offer a comprehensive overview of characteristic symptoms of CMI, associated risk factors, and potential diagnostic tests for exclusion and will be cited at P3:L53.

**R2.2:**

**Comment:**

*Methods (page 5, line 36) - When was CMI suspected in a patient? Was imaging of the mesenteric arteries used to raise clinical suspicion or just symptoms?*

**Response:**

Thank you for this good question. Both symptoms and imaging findings were used to raise suspicion. However, in many cases, suspicion was *initially* raised from presenting symptoms. We defined characteristic CMI symptoms to include: postprandial abdominal pain, weight loss, adapted eating patterns, diarrhea, and/or nausea; however, absence of one did not exclude the possibility of CMI. Upon performing diagnostic testing to exclude other potential diagnoses and to assess vascular involvement, imaging findings either further raised suspicion or excluded CMI. There were several patients in which angiographic imaging findings alone lead to the initial suspicion of CMI. A statement to that effect was added to the Methods section (P5:L102-104). Details on whether a subject’s suspicion was raised from symptoms, imaging, or both, are provided in the new Tables 1-2 (Appendix).

**R2.3:**

**Comment:**

*Methods (page 5, line 48) - CMI patients were subcategorized based on imaging and clinical findings. Relief or sustained improvement of symptoms after mesenteric artery revascularization is considered the gold standard definition in CMI literature. Did all CMI+ patients undergo mesenteric artery revascularization and did they experience symptom improvement? This should be reported in the result section when another definition than the gold standard definition is used.*

**Response:**

Our subcategorization was also based on the results of follow-ups after revascularization. This is clarified at P6:L110-112. Revascularization resolved symptoms in several of the CMI+ subjects. However, there were subjects in which imaging findings supported the notion of 2 or more moderate to severe stenoses but who did not undergo revascularization. This is now stated in the Results section (P11-12:L227-231) and information regarding the specific procedure and clinical follow-ups are provided in Tables 1-2.

After revisiting clinical notes and follow-up exams with additional scrutiny and using better defined criteria (see R2.1), we recategorized two subjects that were incorrectly categorized into CMI- and CMI+ groups (these are subjects No. 6 in Table 1 and Subject No. 13 in Table 2, respectively).

**R2.4:**

**Comment:**

*Methods (page 5, line 56) - Please clarify the used definitions of stenosis severity in order to improve readability. Perhaps stating that a stenosis severity of ≥50% was considered significant would be clearer.*

**Response:**

Thank you for pointing this out. Our current wording was based on diction from the article (Carlos, Stanley et al. 2001). Referencing the terminology specific to this publication requires the reader to reference this article. Stating the stenoses severity in more generic terms would increase readability and has thus been rephrased in P6:L109.

**R2.5:**

**Comment:**

*Methods (page 7, line 137) - Retrospective cardiac and respiration gating has been performed during reconstruction. According to the discussion respiratory gating on expiration was used. Has the same respiratory phase been used for PC angiograms? A reason to opt for expiratory phase angiography is the influence of the position of the diaphragm on the severity of CA compression by the median arcuate ligament (Osiecki M, Chirurgia Polska 2003, 5, 4, 229-234).*

**Response:**

That is correct. Here, respiratory gating signals from bellows are used to separate inspiration from expiration. We used a 50% acceptance window for data acquired during expiration as this is the more quiescent and reproducible position in the respiratory cycle. We also agree that this position will exacerbate compression of the median arcuate ligament. Data acquired during inspiration are essentially discarded. The PC angiogram and the flow data are all reconstructed from the identical remaining data representing expiration. The Methods section has been revised at P7-8:L150-151 to state this more clearly.

**R2.6:**

**Comment:**

*Methods (page 9, line 161) - At what level is the 2D cut-plane of the infrarenal aorta taken? Above or below the origin of the IMA? And if above IMA, as suggested by figure 2, what is the rationale for not including the IMA? The % contribution of the IMA to the mesenteric circulation is believed to be low in healthy subjects. Yet, asymptomatic patients (thus not meeting the used definition of CMI in this study) with an occluded CA and SMA have been described. A hypertrophic IMA is able to provide sufficient collateral flow in these patients to protect them against mesenteric ischemia. Not including the IMA should be reported as a limitation.*

**Response:**

The 2D cut-plane was placed approximately 2-4 cm below the renal bifurcations, which is above the origin of the IMA. In order to properly measure both the SCAo and IRAo, the scan had to be prescribed such that the IMA was often out of the field of view, or in several subjects (Figure 5b), was visualized at the very edge of the field of view. Because this was visualized in so few patients, statistical analysis of IMA flow rates between cohorts would likely be underpowered. Secondly, analysis of vessels so close to the edge of field of view can be prone to measurement error due to gradient non-linearities that exist in large field of view scans such as PCVIPR. This was the rationale for not including the IMA in our analysis. It is correct that a hypertrophic IMA is able to provide sufficient collateral flow in cases were stenoses exist in CA and SMA. However, this limitation has already been noted in the Discussion section (P24-25:L460-465) and the authors believe that no further clarification is needed.

**R2.7:**

**Comment:**

*Results - It would be interesting to know more about presenting symptoms, comorbidities and cardiovascular risk factors of the patients suspected of having CMI.*

**Response:**

Thank you for bringing this to our attention. We had left these details out for space reductions in the initial submission and because they have not been reported in similar studies in the past. However, we agree with the reviewer that these factors are useful information for the reader and demonstrate the heterogeneity in the subjects and illustrate the difficulty in performing a proper diagnosis. We conducted a thorough review of the clinical records and obtained symptoms, comorbidities, and cardiovascular risk factors for each subject and summarized them in Table 3. This has been added to the Results section (P12:L241). Furthermore, specific presenting symptoms for individual subjects can now be found in the additional Tables 1-2 (Appendix).

**R2.8:**

**Comment:**

*Results (table 1) - It is interesting and unexpected to observe a significantly lower preprandial SCAo flow in CMI+ patients compared to both CMI- and control patients. Do the authors have a possible explanation? For example, were patients with cardiac forward failure/decreased left ventricular ejection fraction included in the CMI+ group?*

**Response:**

As stated in 2.3, we recategorized two subjects into CMI- and CMI+ groups (these are subjects No. 6 in Table 1 and Subject No. 13 in Table 2, respectively). Upon reperforming statistical analysis, lower preprandial SCAo flow in CMI+ was no longer statistically significant. This is mostly due to the MALS patient (No. 6 CMI+) having relatively high preprandial SCAo flow, shifting the group mean towards the controls.

While not significant, one study suggests that a considerable demographic of CMI+ patients may have concomitant hypertension, coronary artery disease, and peripheral artery disease (Barret, Martineau et al. 2015). This may be causing decreased cardiac output, resulting in decreased volumetric flow rates and flow responses in the SCAo in some CMI+ patients. However, this hypothesis is not be addressed in the manuscript due to the non-significant SCAo results.

**R2.9:**

**Comment:**

*Results - A detailed overview of number, location and severity of the observed mesenteric artery stenoses seems indispensable in a study concerning flow volumes. Could the authors provide such an overview and display any differences in stenosis location and severity in the CMI- vs. CMI+ group? This study could be biased by large numbers of patients with single vessel disease in the CMI- group, while all CMI+ patients have multi vessel disease.*

**Response:**

Clinical notes were obtained for each patient, both in the CMI- and CMI+ group. For some patients, the exact severity (in terms of percent luminal narrowing) was not provided. Therefore, the location and number of stenoses are fully described in Tables 1-2 but the degree of stenosis is not.

**R2.10:**

**Comment:**

*Discussion (page 23, line 22) - Sixty percent of the control group was male, while only 33% of the CMI+ group was male.* *Significantly higher flow volumes have been reported in mesenteric arteries of healthy males compared to healthy females (*[*https://doi.org/10.1016/j.mri.2018.06.021*](https://doi.org/10.1016/j.mri.2018.06.021)*). The differences in male:female ratio between the groups of the current study could have induced bias, this should be mentioned as a limitation.*

**Response:**

This is indeed a noteworthy observation that we failed to make; gender differences are quite important. The Discussion section has been modified to address this limitation (P24:L443-445).

**R2.11:**

**Comment:**

*Discussion (page 23, line 22) - Several studies have reported on the timing of the peak mesenteric flow after a meal. The cited references by Someya et al. is among these studies, the study by Jäger et al. is another example (doi: 10.1067/mva.1986.avs0030462). The vast majority of studies report a maximal mesenteric arterial flow at 30-40 minutes after a meal. Maximal mesenteric flow is likely to be missed when starting the flow measurement at 20 minutes after a meal and ceasing measurements at 30 minutes after a meal. This should be mentioned as a possible limitation, since maximal flow (thus maximal vasodilatory capacity of the mesenteric circulation) would be most interesting when using flow measurements to identify CMI patients. A scan time of 20 minutes (T= 20 until T=40) would seem more appropriate, especially when considering the timing of the maximal mesenteric flow varies between individuals. Did the authors examine differences in flow volume between for example the first 2 minutes and last 2 minutes of the flow measurements? These data would be interesting to see.*

**Response:**

The discussion of optimal timing to capture a maximum flow response is interesting and has various angles. The quoted study by Someya, et al. retrospectively analyzed various Doppler ultrasound papers studying the temporal characteristics of postprandial SMA blood flow and summarizes the results very nicely in Table 1 of their paper (Someya, Endo et al. 2008). Peak SMA blood flow values were reported for each study. Analysis of this tables demonstrates a mean value of 29.2 minutes for peak SMA blood flow responses with a variance of 14.3 minutes. It is important to note that the increased variance is likely due to differences in meal content (high fat/high carbohydrate), type (solid/liquid), volume, energy content, duration of meal, etc. These factors can have a stark impact on mesenteric blood flow characteristics. While the study that the reviewer has cited demonstrated maximal SMA blood flows between 45 minutes, the meal challenge was much different than our study, consisting of chocolate pudding (solid meal, 1000 kcal, carbs=50%, proteins=15%, lipids=35%).

A study similar to ours was performed by (Sieber, Beglinger et al. 1991) in which Ensure was ingested and blood flow was measured with US in intervals of 15 minutes. The time to maximal blood flow was 30 minutes. Additionally, a 2D PC study by (Li, Whitney et al. 1994) using Ensure showed maximal blood flow in the SMA 30 minutes after a meal. Lastly, a study by (Burkart, Johnson et al. 1995) using Ensure Plus showed maximal SMV at 20 minutes post-meal. Thus, by obtaining blood flow measurements between 20-31 minutes, near maximal blood flow measurements are likely achieved during this time. Furthermore, while maximal flow may be missed in some individuals, acquiring data near this window would likely still provide elevated blood flow rates.

We did not examine the difference between initial and final stages of this acquisition window. However, this would be a very interesting analysis. Sampling over the 11-minute scan window provided us with enough raw data to generate images with large volumetric coverage and with 3-directional velocity encoding. Breaking the reconstruction up into early and late stages of the acquisition would result in severe undersampling and would undermine data integrity required to produce reliable velocity (flow) measurements. However, in future studies, advanced reconstructions with additional constraints could be used to reduce acquisition windows, allowing for flow analysis at various stages in the digestion phase and identify optimal timing. This is fully discussed in the Future Directions portion of the Discussion section (P25:L465-477), in which it is highlighted that acquiring multiple 4D flow scans across different points in the digestion phase may provide further insight into the temporal nature of blood flow patterns in various vessels. It is also clarified in the Discussion that finite acquisition times may not reflect hemodynamic changes that may occur *within* the data acquisition window (P24:L445-447).

**R2.12:**

**Comment:**

*Discussion (page 23, line 22) - The method used to classify patients as CMI+ or CMI- should be mentioned as a limitation. When using the current definition the CMI+ group could contain patients without symptom improvement after revascularization and thus no CMI, but an alternative diagnosis.* *Classifying all patients with single vessel disease as CMI- could result in misclassification and undertreatment of patients with CMI due to single vessel disease. CMI is indeed less likely in patients with single vessel disease, but CMI does occur in these patients.*

**Response:**

This is indeed a limitation of this study. We did investigate follow-up status of patients after revascularization in both patient groups. However, there were several CMI+ subjects who did not undergo revascularization but demonstrated 2-3 vessels with moderate to severe stenoses. The reviewer is correct in stating that these patients could be miscategorized if they were to now undergo revascularization with no symptom improvement, suggesting an alternative diagnosis. On the other hand, there could be patients in the CMI- group with single vessel disease who did not undergo revascularization but could see improvement post-operatively (as in MALS). Though, as the reviewer states, single vessel disease CMI is less likely (~30% of patients according the study conducted by (Barret, Martineau et al. 2015)). With the lack of a gold-standard imaging metric, categorization becomes quite difficult. The Discussion section was adjusted to be completely transparent about this limitation. In the original manuscript, this limitation was stated in the Methods section (P6:L112-114) but the authors felt that this was better suited in the Discussion section (P23-24:L436-443).

**R2.13:**

**Comment:**

*Discussion (page 23, line 22) - A study performing 4d mesenteric artery flow measurements in asymptomatic patients with a mesenteric artery stenosis and healthy controls, observed differences in both flow velocity and flow volume between healthy volunteers and asymptomatic patients (even when severity of the stenosis was <50%) (*[*https://doi.org/10.1016/j.mri.2018.06.021*](https://doi.org/10.1016/j.mri.2018.06.021)*).*

**Response:**

Thank you for pointing out this study. The citation has been added to the Introduction (P5:L86).

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