**Reviewer Response**

We sincerely appreciate the work of the editorial team and referees in guiding the submission process and improving the manuscript quality. 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:**

Analysis of peak systolic and minimum diastolic volumetric flow rates was performed on all patients and were statistically compared between groups. A brief segment was added to the methods section and results were reported on a vessel-by-vessel basis in the *Flow Analysis* section of the Results. The reviewer is correct in stating that this can allow one to distinguish between stenosis severity. However, mean volumetric flow rates will remain the primary clinical metric because (1) we provide a tabulated overview of stenoses location/severity for each patient and (2) because this metric is often what is used clinically and has been used in 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).

**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 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:L177-181).

**R1.3:**

**Comment:**

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

**Response:**

Several grammatical errors have been corrected and minor edits have been made to increase clarity. These corrections are located at the following locations within the manuscript: A1:L15, P3:L38, P3:L39, P4:L78, P6:L116, P16:L257, P16:L276, P21:L351, P23:L396, P24:L423, P24:L424-425, P24:L426, and P25:L460.

**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. No changes regarding this comment were deemed necessary.

**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:**

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 P3L51.

The second, third, and fourth references related to work from Mazzei, MA will be added to P3:L54 and P3:L56 regarding the clinical effectiveness of CT and MRI in CMI diagnoses.

**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, line50) - A high index of clinical suspicion is quite vague, perhaps the authors could consider to elaborate 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:**

**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:**

**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:**

**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:**

Our current wording was based on diction from the article (Carlos, Stanley et al. 2001). Referencing the terminology specific to this publication his does require the reader to reference this article. Stating the stenoses severity in more generic terms would increase readability and has thus been rephrased in P5:L103-104.

**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:**

During 4D flow image reconstruction, the retrospective respiratory gating algorithm kept any data acquired in ≤50% of respiratory cycle (expiration) and discarded any data acquired on inspiration (>50%). After the gating procedure was performed, volumetric complex-valued datasets were then generated which were then used to produce both velocity information as well as PC angiograms. Because the PC angiograms are generated from reconstructed data (specifically complex difference data), the angiograms were subsequently represented in the expiration phase. The methods section has been revised in P7:L142 to state this point 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 would likely 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 (P28:L418-424) 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:**

**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:**

In this analysis, we showed significantly lower postprandial SCAo flow rates in CMI+ patients compared to both CMI- and control patients. Explanations for this result were not provided in the Discussion section.

It is possible that downstream stenosis and potential arteriosclerosis is leading to increased vascular resistance in some CMI+ patients. 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), lending plausibility to this theory. This may be causing decreased cardiac output, explaining the observed decreased volumetric flow rates and flow responses in the SCAo in this patient group. A brief comment was added in the discussion section (P22:L387-390)

**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:**

A table will

**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 an excellent observation and an oversight by the authors. This Discussion section has been modified to address this limitation in P23:L413-415.

**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:**

Someya, et al. retrospectively analyzed multiple 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 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 compared to 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 also occurred 30 minutes after a meal. Lastly, a study by (Burkart, Johnson et al. 1995) using Ensure Plus showed maximal SMV blood flow occurred at 20 minutes. Thus, by obtaining blood flow measurements between 20-31 minutes, maximal blood flow measurements are likely achieved during this time. Furthermore, while maximal may be missed in some individuals, acquiring data near this window would likely still provide elevated blood flow rates (near maximal values) as seen by the SMA flow-time curves in the studies cited by Someya, et al.

The authors did not examine the difference between initial and final stages of this acquisition window. Sampling over the 11-minute scan window provided us with sufficient data to reconstruct the large 3D volume with velocity encoding in 3-directions. 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, constrained reconstructions could be used to accelerate acquisition times, allowing for flow analysis at various stages in the digestion phase. This is fully discussed in the Future Directions portion of the discussion section (P24-25:L440-452), 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. An additional comment, however, a limitation will be noted in that the finite measurement time of the acquisition may not reflect hemodynamic changes that may occur during acquisition (P23-24:L417-419).

**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 likely the largest limitation of this study. However, gold standard imaging techniques and follow up reports were not obtained for these individuals. It is correct in stating that misclassification could occur in individuals with single vessel disease and are CMI+. As the reviewer stated, this classification is less likely (~30% of patients according the study done by (Barret, Martineau et al. 2015)). The Discussion section was adjusted to be completely transparent about this limitation. In the original manuscript, this limitation was stated in the Methods section (P5-6:L105-107) but the authors felt that this was better suited in the Discussion section (P23:L412-414).

**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 providing this reference. A citation was added in the introduction (P5:L84).

References Cited

Barret, M., C. Martineau, G. Rahmi, O. Pellerin, M. Sapoval, J. M. Alsac, J. N. Fabiani, G. Malamut, E. Samaha and C. Cellier (2015). "Chronic Mesenteric Ischemia: A Rare Cause of Chronic Abdominal Pain." Am J Med **128**(12): 1363.e1361-1368.

Burkart, D. J., C. D. Johnson and R. L. Ehman (1993). "Correlation of arterial and venous blood flow in the mesenteric system based on MR findings. 1993 ARRS Executive Council Award." AJR Am J Roentgenol **161**(6): 1279-1282.

Burkart, D. J., C. D. Johnson, M. J. Morton, R. L. Wolf and R. L. Ehman (1993). "Volumetric flow rates in the portal venous system: measurement with cine phase-contrast MR imaging." AJR Am J Roentgenol **160**(5): 1113-1118.

Burkart, D. J., C. D. Johnson, C. C. Reading and R. L. Ehman (1995). "MR measurements of mesenteric venous flow: prospective evaluation in healthy volunteers and patients with suspected chronic mesenteric ischemia." Radiology **194**(3): 801-806.

Carlos, R. C., J. C. Stanley, D. Stafford-Johnson and M. R. Prince (2001). "Interobserver variability in the evaluation of chronic mesenteric ischemia with gadolinium-enhanced MR angiography." Acad Radiol **8**(9): 879-887.

Dalman, R. L., K. C. Li, W. K. Moon, I. Chen and C. K. Zarins (1996). "Diminished postprandial hyperemia in patients with aortic and mesenteric arterial occlusive disease. Quantification by magnetic resonance flow imaging." Circulation **94**(9 Suppl): Ii206-210.

Li, K. C., K. L. Hopkins, R. L. Dalman and C. K. Song (1995). "Simultaneous measurement of flow in the superior mesenteric vein and artery with cine phase-contrast MR imaging: value in diagnosis of chronic mesenteric ischemia. Work in progress." Radiology **194**(2): 327-330.

Li, K. C., W. S. Whitney, C. H. McDonnell, J. O. Fredrickson, N. J. Pelc, R. L. Dalman and R. B. Jeffrey, Jr. (1994). "Chronic mesenteric ischemia: evaluation with phase-contrast cine MR imaging." Radiology **190**(1): 175-179.

Sieber, C., C. Beglinger, K. Jaeger, P. Hildebrand and G. A. Stalder (1991). "Regulation of postprandial mesenteric blood flow in humans: evidence for a cholinergic nervous reflex." Gut **32**(4): 361-366.

Someya, N., M. Y. Endo, Y. Fukuba and N. Hayashi (2008). "Blood flow responses in celiac and superior mesenteric arteries in the initial phase of digestion." Am J Physiol Regul Integr Comp Physiol **294**(6): R1790-1796.

Terlouw, L. G., A. Moelker, J. Abrahamsen, S. Acosta, O. J. Bakker, I. Baumgartner, L. Boyer, O. Corcos, L. J. van Dijk, M. Duran, R. H. Geelkerken, G. Illuminati, R. W. Jackson, J. M. Kärkkäinen, J. J. Kolkman, L. Lönn, M. A. Mazzei, A. Nuzzo, F. Pecoraro, J. Raupach, H. J. Verhagen, C. J. Zech, D. van Noord and M. J. Bruno (2020). "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 gastroenterology journal **8**(4): 371-395.

**Table A.1: Clinical Details of CMI+ Patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Patient ID | Presenting Symptoms | Risk Factors /Comorbidities | Imaging | Stenosis Location/Severity | Revascularization? | Symptom relief? |
| Subject 1 |  |  |  |  |  |  |
| Subject 2 |  |  |  |  |  |  |
| Subject 3 |  |  |  |  |  |  |
| Subject 4 |  |  |  |  |  |  |
| Subject 5 |  |  |  |  |  |  |
| Subject 6 |  |  |  |  |  |  |

**Table A.2: Clinical Details of CMI- Patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Patient ID | Presenting Symptoms | Risk Factors /Comorbidities | Imaging | Stenosis Location/Severity | Revascularization? | Symptom relief? |
| Subject 1 |  |  |  |  |  |  |
| Subject 2 |  |  |  |  |  |  |
| Subject 3 |  |  |  |  |  |  |
| Subject 4 |  |  |  |  |  |  |
| Subject 5 |  |  |  |  |  |  |
| Subject 6 |  |  |  |  |  |  |
| Subject 7 |  |  |  |  |  |  |
| Subject 8 |  |  |  |  |  |  |
| Subject 9 |  |  |  |  |  |  |
| Subject 10 |  |  |  |  |  |  |
| Subject 11 |  |  |  |  |  |  |
| Subject 12 |  |  |  |  |  |  |
| Subject 13 |  |  |  |  |  |  |