**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:**

**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. Furthermore, this is indeed crucial, as heart rate invariably increases after meal consumption. However, our analyses were indeed evaluated in unit time. Data was exported from the customized flow analysis tool after manual segmentation, providing 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 at the following locations within the manuscript: P3:L38, P6:L115, P17:L299, P18:L303, P23:L410, …

**R1.4:**

**Comment:**

*Reference: match with author's guidelines.*

**Response:**

For this work, the authors utilized the 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:**

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 has been added to P3L51.

The second reference (Mazzei, Guerrini et al. 2012) will be added to P3:L54.

The third (Mazzei, Guerrini et al. 2016) and fourth (Mazzei, Guerrini et al. 2013) references will not be cited in this work. While acute mesenteric ischemia and NOMI are indeed closely related to chronic mesenteric ischemia, they are physiologically and clinically distinct pathologies.

**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), however this does require the reader to reference this article. Stating the stenoses severity in more generic terms would increase readability. This is 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. Thus, all PC angiograms were 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 either on the edge of the imaging volume (as seen in several subjects) or was completely out of the field of view. This was the rationale for not including the IMA in our analysis. It is correct to say that a hypertrophic IMA is able to provide sufficient collateral flow in cases were stenoses exist in CA and SMA. 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. However, it is possible that t

**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:**

**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:**

**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:**

**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:**

**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:**

References Cited

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.

Mazzei, M. A., S. Guerrini, N. Cioffi Squitieri, E. A. Genovese, F. G. Mazzei and L. Volterrani (2012). "[Diagnosis of acute mesenteric ischemia/infarction in the era of multislice CT]." Recenti Prog Med **103**(11): 435-437.

Mazzei, M. A., S. Guerrini, N. Cioffi Squitieri, G. Imbriaco, R. Chieca, S. Civitelli, V. Savelli, F. G. Mazzei and L. Volterrani (2013). "Magnetic resonance imaging: is there a role in clinical management for acute ischemic colitis?" World journal of gastroenterology **19**(8): 1256-1263.

Mazzei, M. A., S. Guerrini, N. Cioffi Squitieri, C. Vindigni, G. Imbriaco, F. Gentili, D. Berritto, F. G. Mazzei, R. Grassi and L. Volterrani (2016). "Reperfusion in non-occlusive mesenteric ischaemia (NOMI): effectiveness of CT in an emergency setting." The British journal of radiology **89**(1061): 20150956-20150956.

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.