Manuscript number JMRI-20-0466 entitled "Non-invasive Assessment of Mesenteric Hemodynamics in Patients with Suspected Chronic Mesenteric Ischemia using 4D flow MRI," which you submitted to the Journal of Magnetic Resonance Imaging, has completed the review process. The purpose of this letter is to inform you that the reviewer rankings of this paper are inadequate to justify publication in JMRI. Comments from the reviewer(s) are provided at the bottom of this letter.

There were three main reasons for the lower priority for publication

1.- Modest clinical utility

2.- Verification bias

3.- Described as a retrospective study, but the health control group must have been accrued prospectively. I do not see how they could undergo the exact same protocol without ethics approval.

Mark E. Schweitzer, MD

**Reviewer 1**

The article “Non-invasive Assessment of Mesenteric Hemodynamics in Patients with Suspected Chronic Mesenteric Ischemia using 4D flow MRI” is describing 4D radially undersampled MRI flow measurements in patients with suspected CMI before and after intake of a standardized meal to assess the degree of flow change in the mesenteric arteries. Flow measurements of 11 min duration were acquired to determine the blood flow in the major abdominal arteries of the celiac trunk before and after food intake. Measurements were performed in 19 potential CMI patients, of which 6 were diagnosed as CMI-positive, and in 20 control subjects. In CMI+ patients no change in mesenteric blood flow was observed after food intake, whereas a significant flow increase could be seen in the healthy controls in the abdominal aorta as well as in the SMA.

In general, the topic is of clinical interest as it addresses the important clinical question of a differential diagnosis of CMI in a quantitative way. I have the following general comments to this manuscript:

1. The authors perform the flow measurements (mostly) in the presence of an intravascular contrast agent to shorten T1 of blood. They do this to increase the magnitude of the signal in the blood stream which reduces the phase noise, and, thus, increases the precision of the flow measurements. It is known that gadofosveset trisodium (the contrast agent used here) shortens T1 to about 170 ms (at 1.5T) even 30 minutes after injection (cf. <https://doi.org/10.1007/s10334-008-0134-2>). Thus, the optimal flip angle for the TR = 7.5 ms used here is on the order of 17°-20°, and not 14° as was used in the study. Is this choice of the flip angle motivated by SAR limits?

2. “Subsequently, subjects ingested 474 mL of Ensure Plus…” (page 7, line 34f): I do not understand this concept of giving the same amount of food to every subject, while later flow values are normalized to the body weight. I would have expected that the amount of food is also adjusted to the body weight. Please comment.

3. Mean flow rates are a good in quantifying blood flow to the small intestine. The authors mention that CMI is potentially caused by stenotic changes of the supplying arteries – in many other cases such as renal artery stenosis changes of the mean flow are only a good indicator for stenotic changes when the vessel lumen is reduced by more than 70%. Smaller stenotic changes, however, can be found by analyzing the changes in the flow curves which is often done with Doppler US. This information is also available here – I would really like to see exemplary flow-time curves (rather than streamlines) as they might contain additional information (e.g., the absence of an early systolic peak in mildly stenosed vessels).

4. The authors mention that it is difficult to diagnose CMI (“the proper diagnosis of CMI is difficult and requires a high index of clinical suspicion with currently no well-established diagnostic criteria”, page 4, line 36f), and they acknowledge as a limitation of the study that “classifying patients as ischemic versus non-ischemic based on MRA stenoses measurements and clinical findings may be prone to error due to the lack of a widely-accepted gold standard imaging method” (page 17, line 20ff), but they never present any other clinical criteria for a CMI diagnosis. In essence, I wonder whether the CMI diagnosis based “2 or more primary vessel occlusions of grade 2 or higher” and “clinical findings strongly suggested CMI” (page 6, line 53) is sufficient.

> page 9, line 46ff: In the description of the consistency measurements it should be mentioned that the volume flow Q is given by the velocity v times the cross-sectional area A. This mass conservation is actually known as Kirchhoffs law (#1).

> page 9, line 32f: “Percent changes in blood flow were calculated by subtracting average postprandial flow rates from average preprandial flow rates and dividing by the average preprandial flow rate.” This is the definition of a percent change and can be deleted.

**Reviewer 2**

Assessment of the functional mucosal perfusion of the mesenteric is crucial in the workup of patients suspected of one vessel chronic mesenteric ischemia as is underlined in the two European guidelines (Bjorck EJVES 2017 and Terlouw UEG 2020). Consequently, I read with much interest the present paper including 19 patients suspected of CMI of which 6 with confirmed CMI and 20 controls. The authors quantitatively compared mesenteric hemodynamics before and after a standardized meal with 4D flow MRI technique and they clearly demonstrated the potential of 4D flow MRI studies to help disentangle the complex flow patterns observed in the mesenteric vessels.

I have a few remarks and questions to further increase the potential value of this pilot study.

Introduction

1. \*Page 4 line 20-21; At present also the existence of 1 vessel CMI is recognized nowadays, see Bjorck 2017 and Terlouw 2020. Please rephrase “Thus, it is commonly recognized that at least 2 of the 3 main mesenteric arteries must be occluded to result in symptomatic CMI” in line with the present guidelines.

2. Page 4 line 41-45; The guidelines advised Doppler-Ultrasound as first screening tool

3. Page 5 line 34; What do you mean with “compared to those who were symptomatic but did not have CMI”. Patients with symptoms and stenosis but no ischemia or patients with symptoms without stenosis with or without ischemia or patients with stenosis without symptoms and ischemia? Please rephrase.

Methods

4. \*Page 6 line 35; I assume that the scan were prospectively gathered and retrospectively analysed?

5. \*Page 6 line 37; Is it possible to report the BMI including the range?

6. Page 6 line 53; The diagnosis of CMI is notoriously challenging in 1-vessel disease. The a priory chance in two vessel disease with symptoms fitting to CMI is doable. So the present study, although very valuable, is only a “proof of principle”

7. \*\*Page 8 line 17-18; “normal respiration “during scanning allowed? That means that you missed the CA compression only during deep expiration (the real MALS).

8. \* Page 7 line 8-9; Were the controls completely free of mesenteric artery stenosis?

9. \*Page 7 line 32-40; Did the patients reported symptoms according to CMI 20 minutes after the test meal?

10. \*\*Page 9 line 6-10; All cut-planes were placed at least 3 diameters away from either a confluence or bifurcation to avoid regions of highly disturbed flow due to entrance effects.”” That means that the CA was at least 6 cm long and the SMA also between the origin and the first side branch. Please explain, because in my view the anatomy you described is very rare/ not present in human.

Results

11. \*\*Page 12; I missed the infrarenal aortic measurements of the different cohorts in the result section

12. Page 13; line 5-6; “There were also no significant differences in postprandial SMV flow between any of the groups.” That is remarkable because the inflow increases in the CM(-) cohort and does not increase in the CMI(+) cohort and in the next paragraph you demonstrated a differences in portal vein flow increase between the cohorts.

Discussion

13. \*\* Page 16 line 15-17 “Furthermore, postprandial blood flow responses (percent changes in blood flow) in the SMA, SMV, and PV” Is this in line with your results (SMV?), see also remark 12

14. Page 16 line 31-33: In this study, patients were imaged 20 minutes after ingestion of a meal, allowing postprandial CA flow rates to return to near baseline levels, explaining the negligible observed increases in CA flow rates”. Most patients with multivessel CMI experienced postprandial pain for at least one hour after a normal meal. Is your test meal the explanation for your observation? Is reactive SMA outflow vasoconstriction the explanation? Geelkerken RH, et al. Ultrasound Med Biol. 1998 Nov;24(9):1351-6.

15. \* Page 16 line 48-50; “We theorize that, due to blood flow restriction in the CA, flow that would have otherwise entered the CA is being directed to the SMA, resulting in higher preprandial flow values and thus diminished SMA flow responses.” I agree that compensatory increase in the SMA in patients with one vessel AC CMI is reported (van Petersen AS, et al. J Vasc Surg. 2017 May;65(5):1366-1374 and J Vasc Surg. 2014 Jul;60(1):111-9) but is this also the case in multivessel CMI? Does that mean that multivessel in the present study means CA and IMA stenosis with an normal SMA? How do you explain a significant increase in flow in a severely stenoses SMA?

16. Page 17 line 34-35 and page 19 line 6-10; The proof of the pudding is a RCT based on the outcome of the MRI test focussing on the clinically most demanding diagnosis of 1 vessel CMI.

17. The portal vein is the exclusive drain of the bowel, cumulating the flow through the three mesenteric arteries and all the collatarals (also extraordinary mesenteric collaterals via the hypogastrcis, the phrenics, the intercostals.) Is PV flow measurements not the way to go?

Tables

18. \*\*Table 1 and 2 merged into 1 large table is helpful in interpreting the results

19. \*\*Please add the individual P values if significant.