

## Peer Review File

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### Reviewer A

**Comment:** In this paper, 76 patients undergoing either on-pump CABG or off-pump CABG for stable CAD and preserved LVEF got a CMR before and shortly after surgery. T1 mapping was performed, and further correlated with the interval evolution in cardiac biomarkers. The results suggested that despite an increase in postprocedural cardiac biomarkers (especially in off-pump compared to on-pump CABG, as expected), the T1 mapping did not change after surgery.

T1 mapping is certainly a hot topic in cardiovascular imaging and these findings are relevant to physicians and surgeons in cardiac sciences. The authors are to be congratulated for their novel project.

**Reply:** Thank you very much for your valuable time and contributions to this manuscript. They improved the quality of our paper. Answers are provided after each question and changes in the text are stated after each answer.

- Major comment:

**Comment 1:** How were patients assigned to on-pump versus off-pump CABG? Was it a surgeon preference, predefined in the trial protocol or an institutional protocol? I think this information would be pertinent to add in the methods section.

**Reply 1:** Thank you for your important suggestion. The present study is a post-hoc analysis of the MASS V trial, and patients were enrolled in the main trial if they had symptomatic multivessel CAD and a formal indication to CABG. Patients were prospectively enrolled, and assigned to on-pump or off-pump CABG at the discretion of the principal investigator and after the evaluation of the cardiac surgeon, both based on the best strategy to perform a complete anatomical revascularization.

**Changes in the text:** In lines 142-144, in the Methods section, we included the following paragraph:

“After enrollment, patients were assigned to on-pump or off-pump CABG at the discretion of the principal investigator, based on the best strategy to perform a complete anatomical revascularization, and after the evaluation of the cardiac surgeon.”

**Comment 2:** Lines 346 and 350: There is mention of "myocardial infarction". Please be more specific. Do you mean procedural myocardial infarction (in which case it should be defined in

the Methods section) or do you mean a history of recent myocardial infarction as in your exclusion criteria?

**Reply 2:** Thank you for your suggestion. In both lines, we meant procedural myocardial infarction. Patients who had new late gadolinium enhancement or high T2 hypersignal on CMR were excluded in the present analysis. This is mentioned in lines 140-142, in the "Methods" section.

**Changes in the text:** As requested by this reviewer, we have modified lines 346 and 350, as shown below.

Lines 346-348: "Therefore, the general results of the present study confirm that in the absence of procedural myocardial infarction or edema, myocardial structure and function are not compromised after revascularization surgeries."

Lines 350-352: "In the absence of procedural documented myocardial infarction, T1 mapping did not identify myocardial tissue damage after surgical revascularization with or without cardiopulmonary bypass, despite the excessive release of cardiac biomarkers."

- Minor comments:

**Comment 3:** Line 132: Ideally, sentence should not start with a number; change if possible.

**Reply 3:** Change was done as requested.

**Change in the text:** "From 136 patients who underwent CABG, 69 underwent ONCAB, and 67 with similar arterial and ventricular conditions underwent OPCAB."

**Comment 4:** Line 227: "syntax" should be written in caps letters, "SYNTAX".

**Reply 4:** Perfect. Change was done.

**Change in the text:** The baseline characteristics of the two groups were similar, except for the SYNTAX score and mean number of grafts, which were significantly higher in the ONCAB group ( $P=.002$  and  $P<.001$ , respectively).

**Comment 5:** Line 230: change "anterior descending artery" to "left anterior descending artery"

**Reply:** Done.

**Change in the text:** "Triple-vessel disease was present in 54 patients (71%), and 74 patients (97.4%) had significant involvement of the left anterior descending artery."

**Reviewer B**

**Comment:** AR Dallazen and coworkers have investigated cardiac damage related to on-pump and off-pump coronary artery bypass grafting (CABG) using native T1 mapping with magnetic resonance imaging (MRI), cardiac troponin-I (cTnI), and creatine kinase (CK-MB). 76 patients from the MASS V trial were included in this post-hoc study, of which n=44 patients were operated off-pump and n=32 patients were operated using cardiopulmonary bypass. The included patients were selected as not to have late gadolinium enhancement, cardiac edema, or new ECG changes. The authors report that the native T1 changes were non-significant and indicated preserved myocardial integrity in both groups, whereas CK-MB and cTnI release was larger in the on-pump group. There were no significant correlations between peak CK-MB release and MRI parameters or left ventricular ejection fraction. The authors conclude that in the absence of myocardial infarction or edema, myocardial structure and function are not compromised during off- or on-pump revascularization.

**Reply:** Thank you for your time, and all your comments and suggestions that greatly improved the quality of the manuscript. Answers are provided after each question.

The manuscript is easy to follow. I have some questions, comments, and suggestions for improvements:

**Comment 1:** The authors have given an aim in the introduction. What was their hypothesis? In this study, the patients seem to be very carefully selected. CABG patients are usually a rather heterogenous group. The aim of the paper would be clarified if the rationale for patient selection is explained better. Furthermore, could the selection process have any consequences for the results of the study?

**Reply 1:** Thank you for these important comments. Based on the significant release of cardiac biomarkers, even after the exclusion of patients with LGE and edema, our hypothesis was that the release of these biomarkers would be associated with cardiac damage, and that this would be captured by T1 mapping on CMR. Based on this hypothesis, we have selected from the main MASS V trial, patients who have not evolved with new LGE and edema. Although we agree with this reviewer that the population that is submitted to CABG can be heterogenous, our population was quite homogeneous because of restricted inclusion and exclusion criteria. This population homogeneity may be observed in Table 1. Interestingly, the results from the present work still found a significant release of biomarkers after CABG, but no changes in T1 mapping. Confirming these results, the other parameters of CMR also confirmed the stability of myocardial function after revascularization surgeries. To make our hypothesis clear in the manuscript, we have added a sentence in the Introduction section.

**Changes in the text:** We have added the following statement, in line 114, in the “Introduction”

section.

“Based on this background, we have hypothesized that CABG would impose cardiac injury, captured by the release of cardiac biomarkers and changes in T1 mapping on CMR.”

**Comment 2:** Is it possible that the results could have been different using an MRI scanner giving images with higher resolution? In other words, was the employed method sensitive enough to match the biomarkers?

**Reply 2:** Thank you for this important question. Although it is possible that new advances in CMR may bring new information on this theme, the careful methodology of this work, and the assessment of cardiac tissue characteristics before and soon after the revascularization interventions strengthens the results of the present study. Moreover, the stability of many other cardiac parameters, such as ejection fraction, and left and right end ventricular diastolic volumes reinforce the findings of the stability of myocardial function by T1 mapping. Interestingly, ejection fraction and these indexed volumes numerically improved after on-pump and off-pump interventions.

**Comment 3:** The authors report serial measurements of cTnI and CK-MB up to 72 hrs after CAB. For cTnI they have not explicitly explained that peak values were used. There should also be a clearly stated justification for making comparisons between patients with CK-MB peak values above and below 10 times the upper reference limit.

**Reply 3:** Thank you for these important questions. Both CK-MB and troponin were analyzed using their peak values. This information will be explicitly explained. Because 10 times the upper reference limit is the biomarker criteria for considering procedural myocardial damage related to CABG, we have used this cut-off to differentiate groups of patients with meaningful releases and to test whether in such patients T1 mapping and other CMR parameters would be different. CK-MB was preferred over troponin because CK-MB had higher accuracy to detect procedural myocardial infarction in the analysis of ROC curves in the main MASS V trial. Notably, even in the patients who had peak CK-MB levels higher than 10 times the upper reference limit, T1 mapping and all the other CMR parameters were still similar compared to the group with lower release of biomarkers.

**Change in the text:**

In line 208, we have added the following statement: “Both CK-MB and troponin peak values were used to assess the association between biomarkers release and T1 mapping parameters.”

In line 209, we have added the following statement: “This cut-off was chosen because this is the biomarker criteria for considering procedural myocardial infarction related to CABG

according to the 3<sup>rd</sup> Universal Definition of Myocardial Infarction (22). We have chosen CK-MB rather than troponin because in the MASS V trial CK-MB had better accuracy to detect procedural myocardial infarction.”

**Comment 4:** I miss some more information regarding the surgery, for example use of cardioplegia, anticoagulation protocols, temperature, etc.

**Reply 4:** Thank you for this important observation. Of note, CABG technique was standardized in the MASS V trial. Because the main trial aimed to study procedural MI, we have carefully selected a group of cardiac surgeons with an excellent expertise in both on-pump and off-pump procedures. They used the same antegrade blood cardioplegic solution, standardized normothermic temperature, and institutional anticoagulation protocol. In off-pump CABG, surgery was also performed in a standardized fashion, using the Octopus stabilizer. This information was updated in the text.

**Change in the text:** In lines 146 to 150, we have updated the following sentence: “CABG was performed electively, with or without the use of CPB, by the same team of cardiac surgeons with extensive experience in both ONCAB and OPCAB. Standardized surgical techniques were used, with the same surgical access site, the same aortic and coronary clamping location, antegrade blood cardioplegic solution, normothermic temperature, and anticoagulation protocol. An Octopus stabilizer was used for all OPCAB patients, with the same technique.”

**Comment 5:** Units of measurements should be given with all relevant data in the Results section, as well as for CK-MB in Table 3.

**Reply 5:** Thank for the comment. We have added all the units of measurements in the Results section and for CK-MB in Table 3, as requested.

**Comment 6:** In the Methods section, the authors should indicate how long before and after surgery MRI was performed. Would one expect changes in the MRI findings by time postoperatively, so that the time aspect could bias the results?

**Reply 6:** Thank you for these important questions. In this study, MRI was performed 2 days before the intervention and 6 days after surgery. This information was added to the text. Regarding whether timing could bias the results, this was deeply discussed when the main trial was planned. We have decided to perform both preoperative and postoperative CMR close to surgery to minimize other factors rather than surgery that could potentially interfere with CMR findings. Performing CMR before 6 days would impose challenges regarding

thoracic discomfort to the patients.

**Changes in the text:** In lines 153-155, the following statement was updated: “All patients underwent CMR in a 1.5 Tesla magnetic resonance scanner (Philips Achieva®) 2 days before and 6 days after the surgical interventions during the hospitalization period.”

**Comment 7:** All abbreviations should be defined, including standard ones like CABG. ROI should be written out in full instead of using the abbreviation (line 164, Supplemental Figure 1). Instead of HT for hematocrit, the standard abbreviation HCT should be used. When an abbreviation has been defined, it should be used in the rest of the text (e.g. URL). If the authors feel that they need to use the full term again later, the abbreviation should rather be dropped. The abbreviations OPCAB and ONCAB should be explained in the footnote to Figure 1.

**Reply 7:** As requested, all abbreviations were defined and explained.

**Comment 8:** In Table 1, the phrase “Cross-clamp time” should be used instead of “Anoxia time”.

**Reply 8:** Done.

**Comment 9:** There seems to be something wrong with the second confidence interval given on line 263.

**Reply 9:** Thank you for the correction. The right confidence interval is (0.69-3.4). This was corrected in the text.

**Comment 10:** Supplemental Figure 1 would be easier to understand if the two panels are given a heading, i.e. T1 and ECV. The text above the figure should be modified to read “... construction of the native T1 map (left panel) and ECV map (right panel), with segmentation....”

**Reply 10:** Changes were done, as requested. Thank you.

**Comment 11:** The p-values in tables and figures that are given as “p=0.5” should be changed to p=0.50 to agree with the format of the other p-values. If Supplemental Table 1 is showing biomarker changes, this should be stated in the heading.

**Reply 11:** Thank you for these suggestions. Changes were done, as requested.

**Reviewer C**

The presented results of the study, which aimed to determine whether the release of biomarkers is associated with heart damage by assessing the microstructure of the myocardium on T1 mapping after on-pump CABG (ONCAB) and off-pump CABG (OPCAB), indicate the lack of a clear correlation between the structural tissue damage after surgical revascularization with or without cardiopulmonary bypass and T1 mapping in the absence of documented myocardial infarction despite the excessive release of cardiac biomarkers.

The results were presented concisely, and clearly for the reader and per the applicable rules for writing experimental papers. The tables and figures are legible. In addition, the photos made with the MOLLI technique add to the attractiveness of the work. The language of the manuscript is correct, requiring minor corrections. The results of statistical calculations are presented correctly. After minor language corrections, the work can be published.

**Reply:** Thank you very much for your valuable time and thoroughly understanding of this work. Language has been revised throughout the text.