Author’s response to reviews

Title: Abnormal elevation of myocardial necrosis biomarkers after coronary artery bypass grafting without established myocardial infarction assessed by cardiac magnetic resonance

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Author’s response to reviews:

TO EDITOR:

I am really grateful for your careful analysis of the manuscript. The criticisms are entirely appropriate, and I believe that the manuscript has been greatly improved by addressing these concerns. Specific responses are stated in this letter and changes to the text of the manuscript are highlighted in red.
Reviewer #1:

This study aimed to assess the diagnostic performance of TNI and CK-MB in the setting of ONCAB, by means of LE-CMR. The manuscript is easy to read, however, some criticisms are needed:

Reply: Thanks for the comments. I will incorporate all the criticisms and suggestions and, when requested, add to the text.

Minor:

Question: I would suggest adding more details about the ECG pre and post.

Reply: Thanks for the suggestion. I think these data clarify, definitively, one of the diagnostic tools used in the study. I'll add them to the text, and highlight them in red.

All 54 patients who were free of late enhancement on the CMR after the procedure and who were selected for this study underwent ECG at entry and sequentially. None of the patients had a new bundle-branch block, ischemic ST-segment, new pathologic Q wave conduction disorder, or new Q wave after the procedure.

Question: Would also add more information regarding the renal status pre and post that is a major factor determining the TNI levels.

Reply: Good comment: As you mentioned, renal function plays an important role in the excretion of troponin. Because of this, abnormal renal function was an exclusion criterion.

Even so, we took care “to monitor” renal function post procedure. Thus, no patient had a loss of renal function after the intervention. These data will be added to the text and highlighted in red.

All patients had preserved glomerular filtration rate on admission. Sequential measures of renal function indicated that no loss of this function occurred.

Major:

Question: I would also suggest to "fine tune" the conclusions: both TNI and CK-MB had a poor performance in predicting a CMR detectable MI, not an MI. In other words, this manuscript assumes that CK-MB and TNI showed something that did not exist because the CMR did not confirm it: this is wrong. CK-MB and TnI, particularly the TnI, showed that an MI did happen; however, the CMR could not show it. Thus, I would not be so clear-cut in stating that we need
different cutoffs or something. The results of this manuscript support the idea that a CMR detectable "post ONCAB" MI is poorly correlated with the levels of CK and TnI.

The statement that the CMR could be included in the assessment of post ONCAB MI is strongly misleading.

Reply: Thanks for the comment. In fact, the basis of the study was to identify the occurrence of AMI with different tools. Thus, ECG, enzymes, and CMR were used. As you mentioned, CK-MB and TnI, particularly the TnI, showed that an MI did happen.

These observed data support the fact that the ultrasensitive properties of troponin allow identification of the presence of MI even in the absence of any event. Measures of troponin performed at our hospital on the occasion of the BARI-2D trial revealed the presence of troponin above the 99th percentile at baseline.

In addition, high troponin measurements are often obtained in marathon athletes, at rest and also after a marathon. Thus, it is reasonable to expect an excessive increase in this biomarker after surgical trauma even without myocardial injury.

Regarding a new cutoff, for diagnosis of post-procedure AMI, we have to consider that measures were found to be above 170 times the cutoff without the corresponding change in CMR and ECG, a condition not observed in CK-MB measurements. I believe that the "ultra sensitivity" of troponin plays a role in the destabilization of this diagnostic correlation.

Reply: This technological resource allows the analysis of myocardial tissue in a spectral way. Assuming that all tissues exhibit a characteristic range of normal T1 relaxation times (longitudinal or spin-lattice) that are based on the composite of their cellular and interstitial components, all subjects can undergo T1 mapping.

A region of interest in the study is the myocardium, ensuring that the region does not include blood or epicardial fat. The resulting pixel by pixel color T1 maps are displayed using a customized table (0-2000 ms) where normal myocardium is purple and increasing T1 ranges from yellow to orange.

T1 mapping reflects myocardial disease involving the myocyte and the interstitium.

Therefore, any interstitial or cellular alteration that results in edema can be detected by T1 mapping, thus providing a useful tool for diagnosis of "fine" alterations in myocardial tissue.

Question: The concept of "diffuse" myocardial damage should be mentioned and discussed, as it is a clear limitation of the CMR analysis.
Reply: Thanks for the suggestion. A trial is underway at our hospital to analyze the "fine" structural changes in myocardium through T1 mapping after surgery with and without extracorporeal circulation. This study will allow identifying possible "diffuse" myocardial damage attributed to the extracorporeal circuit.

I appreciate the suggestion and will include this concept in the discussion. This suggestion will be added to the text and highlighted in red.

Therefore, a possible deleterious effect of extracorporeal circulation may contribute to the occurrence of discrete and "diffuse" myocardial damage. This damage can compromise subcellular structures that are difficult to identify evidencing a clear limitation of CMR analysis.

Once again, I am very grateful for your careful analysis of the manuscript. The criticisms are entirely appropriate, and I believe that these have improved the manuscript.

Reviewer #2:

This manuscript documents the increase in cardiac markers following coronary artery bypass surgery. Presented data are limited to patients without evidence of myocardial necrosis on MRI.

The patient group is well characterized with pre- and post-operative MRI scans and multiple perioperative sample points for cardiac markers.

The central message is that in patients with no evidence on cMRI of myocardial necrosis, cardiac troponin release routinely occurs > 10* 99th percentile. Elevations of CKMB above this threshold were less common.

Reply: Thank you for the comments. I will incorporate all the suggestions and, when requested, add to the text. Modifications in the manuscript are highlighted in red after each answer.

Major comments:

Question: This finding is relevant with respect to the guideline definition of CABG-related MI, and other groups have reported similar data.

The manuscript would be strengthened greatly by including analysis and discussion of the 15 patients who developed myocardial necrosis on cMRI. It is possible the data from these patients was presented elsewhere as part of the MASS-V study.
Reply: Good point. The patients who developed myocardial necrosis depicted on cMRI were presented as part of the main study. In fact, and reinforcing these findings, the group of patients with MI on cMRI had much higher elevations of both troponin and CK-MB than patients with no evidence of MI on cMRI. However, the major question addressed in the present paper was the elevation of these biomarkers even in the absence of any evidence of MI on cMRI. And this happened especially with troponin, using the cutoff values indicated by guideline definitions.

Question: cMRI is not practical or cost-effective for routine clinical use and diagnosis of perioperative MI. Are there patterns of cardiac troponin I elevation, e.g., change from 6h to 24h that better predict LGE/development of MI?

Reply: Good question. We do agree that cMRI is not cost-effective for routine clinical use for the diagnosis of perioperative MI. However, it could be an option in specific situations of unclear diagnosis after other diagnostic methods. Regarding biomarker elevation, ROC curves were constructed in the main paper in order to find the best cutoff values that could predict an MI. In the on-pump CABG group, the best cutoff value for CK-MB was 37.5 ng/mL, which is 8.5 times the 99th percentile, and for troponin, it was 6.50 ng/mL, which is 162.5 times the 99th percentile.

Question: What was the CPB/cross clamp time and pathology in patients who had myocardial necrosis depicted on cMRI compared to those who did not?

Reply: Good question. CPB/cross clamp time was similar between both groups. The CPB/cross clamp time was 55 ± 11 for patients with no late enhancement and 54 ± 12 for patients with late enhancement on CMR. However, because the central issue of this paper was to assess only the group of patients with no evidence of MI on CMR, this was not pointed out in this manuscript.

Question: Did the ECG help discriminate patients with and without LGE?

Reply: Excellent question. Reviewer #1 also asked this question.

No, ECG did not help to discriminate between patients with and without LGE. This information was also pointed out in the main manuscript. The analysis of results showed that patients who developed new "Q" waves had late enhancement on CMR. Data on ECG results will be added to the text and highlighted in red.

All of the 54 patients who were free of late enhancement in the CMR after the procedure and who were selected for this study underwent ECG at entry and sequentially. None of them had a
new bundle-branch block, ischemic ST-segment, new pathologic Q wave conduction disorder, or new Q wave after the procedure.

Minor comments:

Question: The authors should comment on the ability to perform cMRI in every patient on day 6. Very often post-operative complications prevent scanning until later—with problems with breath-hold etc.

Reply: Thank you for this comment. Indeed, some patients had some difficulties in undergoing cMRI after cardiac procedures, but most difficulties were resolved with analgesic medications and low-dose anxiolytic agents.

Question: There is a discussion section on LGE, which seems out of place given that those patients were not presented in this manuscript.

Reply: Thank you. Section 5.1 “Late Enhancement” has been removed from the text.

Question: The manuscript needs some grammatical improvement.

Reply: The manuscript has been sent again to an English language expert and some grammatical improvements have been made in the final version. These improvements are highlighted in red in the “Final Version with corrections in red”.

Once again, I am very grateful for the reviewers’ careful analyses of the manuscript. The criticisms are entirely appropriate, and I believe that they have improved the manuscript.