Author’s response to reviews

Title: Cardioprotective Effect of Remote Ischemic Preconditioning with Postconditioning on Donor Hearts in Patients Undergoing Heart Transplantation: a single-center, double-blind, randomized controlled trial

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Author’s response to reviews:

POINT-BY-POINT RESPONSE

Dear Mr Fuat, Mr S. Michael Roberts and Mr Demetrio Pittarello:

Thank you very much for your helpful comments and suggestions. With your guidance, we have made significant improvements throughout the entire manuscript.

Response to the reviewers’ comments:

A. Response to the comments of Reviewer #1

I have several concerns with this submission.
Comment 1: First and foremost, significant improvements in the written English are needed throughout the entire manuscript. The impact of many sentences are lost due to inaccuracies in the translation. A significant review of the translation and rewrite would strengthen this manuscript tremendously.

Response: Thank you for your comment. Written English and inaccurate translation are indeed what we have to deal with. We have made significant improvements in English with the aid of American Journal Experts (AJE).

Comment 2: Second, I'm not sure the conclusions the authors drew can be entirely contributed to the intervention. Volatile anesthetics have been shown to afford similar preconditioning effects. The authors mention that sevoflurane was used "as needed" during line placement. Likewise, the use of propofol may attenuate preconditioning effects. The use of volatile anesthetics should have been standardized as a part of the study protocol; ideally avoiding their use entirely. Since this was not done, the use of sevoflurane should be listed in Table 2.

Response: Thank you for your comment. First, we have reanalysed the data of sevoflurane usage, adding the pertinent data to Table 2. After the reanalysis, there was no significant difference in the use of sevoflurane in two groups. Second, the size of the sample, in which anesthesia maintained with sevoflurane, was very small (only 4 patients in the control group and 3 patients in the RIPC+ RIPostC group). Third, we have added new references (References section, 23-25) and relevant discussion in the revised manuscript (Discussion section, line 7-11 and 17-21, page 11).

Comment 3: I'd also like to see the intraoperative use of inotropes in this table. Presumably all transplant patients received inotropes post bypass, but it would be interesting to see if there is a statistically significant difference in dose or number of inotropes required. If the intervention had a significant effect on myocardial protection, the intervention group may have a lower inotrope requirement.

Response: Thank you for your comment. We have added the vasoactive inotropic score (VIS) data to Table 2, Figure 2 and the manuscript (Methods section, line 3-5, page 7). VIS is a score reflecting the amount of inotropic drugs support. We found that the intervention group had a lower VIS score(8.8±6.1 vs. 9.3±6.1). But there was no statistically significant difference between the two groups (P=0.60). A possible explanation for this might be the lack of appropriate samples because the VIS score was not the primary endpoint. Furthermore, many factors affected the use of inotropic drugs during the operation, while the protective effect of RIPC combined with RIPostC could not significantly impact the VIS score. We also added relevant discussion in the revised manuscript (Discussion section, line 11-19, page 12).

Comment 4: Third, there is no p-value listed in Table 1 and there are clearly statistically significant differences between the groups. Most notably the preoperative use of inotropes was significantly higher in the control group. One could argue that this could increase myocardial
work, oxygen consumption, and potentially myocardial damage (despite the fact that troponin was measured in the transplanted heart 6 hours post op). I would include p-values in this table and address any significant differences that are found.

Response: Thank you for your comment. We apologize for the vague explanation and we have added the p-values to Table 1. The number of patients using inotropic drugs preoperatively was significantly larger in the control group [46(76.7%) vs. 23(38.3%); P<0.001]. Indeed, if the patients are treated with inotropic drugs, the concentration of Ca2+ in the heart muscle cells and myocardial energy expenditure will be increased, and the myocardial cell death will be accelerated. All patients enrolled were screened and randomly grouped. Furthermore, we reviewed the cases of our study, only low-dose(3~5μg/kg/min) dopamine or dobutamine infused by microinfusion pump was administered when patients required inotropic drugs before surgery in our center. Moreover, dopamine and dobutamine exhibited short half-life and rapid metabolism. Thus, the difference of the number of patients using inotropic drugs had little impact on the serum cTnI levels in patients 6 h after aortic declamping (the primary endpoint). We also added relevant discussion in the revised manuscript (Discussion section, line 1-10, page 12).

B. Response to the comments of Reviewer #2

The present study is the first demonstration of the effectiveness of RIPC combined with RIPostC in patients undergoing orthotropic heart transplantation. It is an original study that for the first time has been involved in heart transplants with a considerable number of patients. The results presented are in line with the data provided by the literature also of the most recent trials and therefore confirm the hypotheses up to now. The cardiac troponin I difference is in line with what has been supported so far. I think it is an important contribution for those who are interested in preconditioning also because it highlights the possible mechanism of preconditioning linked to the presence of humoral factors responsible for the mechanism. Moreover the analysis of secondary outcomes seems to me very accurate.

Thank you very much for your appreciation. Great efforts were made to complete the research, which we believe will contribute to the patients’ well-being and to the further study in this field. Thus, we sincerely hope that this paper will be approved and published. On behalf of our research group, I would like to extend heartfelt gratitude for your approval.

Comment 1:.As regards table 1, I consider it useful to insert the value of statistical significance (p value).

Response: Thank you for your comment. We apologize for the loophole and we have added the p-values to Table 1.

Comment 2: Finally I think it is necessary to update the bibliography with more recent articles about preconditioning.
Response: Thank you for your comment. We have updated the bibliography, adding recent articles about propofol, volatile anesthetics and RIPC to the revised manuscript (References section, 23-25).

We tried our best to improve and revise the manuscript, hoping that our work can be recognized and published. On behalf of our research group, I would like to extend our sincere thanks for your kind suggestions on our research and publication.