

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-1101>

Reviewer A

The article offers a valuable overview of myocardial protection during cardiothoracic surgery, with a specific focus on anesthetic agents. The article is well written. The article is well-written with clear language and a formal style suitable for a scientific review.

I have some suggestions:

1. Anesthetic Agents: The article provides a comprehensive review of different anesthetic agents, particularly volatile anesthetics, propofol, and opioids, discussing their potential benefits and mechanisms of action in myocardial protection. The authors should mention the role of regional anesthesia in myocardial protection and the role of local anesthetic adjuncts in this matter.

Thank you very much for your comments, we appreciate them. **All changes have been tracked, also in bold.**

Reply 1: We added a section on Anesthetic adjuncts, such as local anesthetics and Dexmedetomidine, along with the role of regional anesthesia. We also added to our conclusion stating our thoughts on these adjuncts.

Changes in text: The section below 'Other Anesthetic Adjuncts' is new, Page 10, Line 6-23. Page 11, Line 1-23. In the conclusion, the new part is Page 12, Line 16-23. Page 13, Lines 1-6.

2. The authors could clarify their strategy and methods to preserve myocardial function. This strategy is not clear enough for the reader. They could describe their concept for myocardial protection in the clinical practice.

Reply 2: We added to our conclusion stating what we do from an Anesthetic perspective at our home institute for myocardial protection.

Changes in text: New text in conclusion, Page 13, Lines 2-6.

3. The authors might refer to the current state of research in the field of myocardial protection and highlights areas where further investigation is needed.

Reply 3: We added a paragraph to our conclusion stating where we believe the field is heading towards.

Changes In Text: New text is in conclusion, Page 13, Lines 7-15.

Reviewer B

It is well structured. Firstly, I found "cardioplegia is not an anesthetic-induced protective

method. You should revise to focus on only anesthetic-induced methods or change the title. Because anesthesiologists usually cannot select the kind of cardioplegia and how to use it. For the same reason, RIPC is not suitable for this review.

The readers of this review expect the contents such as the effects of the drug they use intraoperatively. I guess much more citations of the drugs that anesthesiologists can control are necessary to review. It would be better to lengthen, on focus on the former half of this manuscript.

Thank you very much for your comments, we appreciate them. **All changes have been tracked, also in bold.**

Reply: We have removed the entire section on cardioplegia and RIPC as per reviewers comments. We added a section on Anesthetic adjuncts, such as local anesthetics and Dexmedetomidine, along with the role of regional anesthesia. We also added to our conclusion stating our thoughts on these adjuncts.

Changes In Text: The section below ‘Other Anesthetic Adjuncts’ is new, Page 10, Line 6-23. Page 11, Line 1-23. In the conclusion, the new part is Page 12, Line 16-23. Page 13, Lines 1-6.

Reviewer C

The authors have presented a narrative review on anesthetic therapies for myocardial protection during cardiac surgery. I recognize the authors have spent significant time and effort on this paper. However, I have several concerns and will try to identify areas for improvement seen below.

1) The introduction is general; it non-specifically mixes concepts such as ischemic pre and post-conditioning (minimal clinical experience or utility) and cardioplegic cardiac arrest during cardiac surgery and CPB. Further, there is no exploration of the molecular mechanisms of ischemia-reperfusion and why it's important. There are no comments on the critical inflammatory components of this process and related therapies that have been investigated (steroids, NO, ultrafiltration, C5 antibodies, etc). It might be worthwhile to draft a more concise introduction and project scope.

Thank you very much for your comments, we appreciate them. **All changes have been tracked, also in bold.**

Reply 1: We decided to restructure the manuscript such that now we have removed the entire section on cardioplegia and remote ischemic pre-conditioning section as per prior reviewers comments. We added in other Anesthetic adjuncts such as lidocaine, Dexmedetomidine and role for regional anesthesia. We added in a paragraph in the introduction mentioning some of the mechanisms responsible for myocardial ischemia-reperfusion injury. We mentioned the focus would be on the Anesthetic drugs themselves however in our conclusion we highlighted future research regarding nitric oxide and anti-C5 complement antibodies.

Changes in text: The added text for mechanisms/focus on drugs is on Page 5, Lines 3-8, Lines 13-18. Added text in Anesthetic adjunct section on Page 10, Line 6-23. Page 11, Line 1-23. The NO and anti-C5 complement section is new in the conclusion on Page 13, Lines 10-15.

2) The discussion includes many clinical studies with head-to-head comparisons of various therapies. Including the effect sizes would significantly enhance the quality, rather than stating "lower levels..." or "shorter ICU stay...".

Reply: We added in more objective data for several studies including the p-value and the numerical difference in outcomes.

Changes in Text: Added data to Page 4, Line 6, Lines 9-12, Lines 13-18. Page 9, Lines 8-10.

3) I find the discussion on volatile anesthetics confusing, with some conclusions stating volatile anesthetics are helpful for ischemic conditioning while results from a larger RCT show no clinical impact.

Reply: We rewrote parts of volatile section, acknowledging the limitations but overall we recommended their use.

Changes in Text: Added text to Page 6, Line 6-18. Page 7, Line 17-23. Page 8, Line 1-5.

4) What is the biologic mechanism of inhaled anesthetics and myocardial ischemic conditioning?

Reply: We added in a paragraph stating their biological mechanism, along with referring to Table 1 for a full list of biological pathways.

Changes In Text: Added text Page 7, Lines 21-23. Page 8, Line 1-5.

5) Cardioplegia is the most extensive section in the review. It is not really an anesthetic therapy. The mechanisms and therapeutic necessity have been very well described in the literature to date.

Reply: We removed the entire section on cardioplegia as per prior reviewers comments.

Changes In Text: Previously the entire Cardioplegia section spanned Pages 9-13, including Table 1 outlining the cardioplegia compositions, this has been deleted (easiest to see via tracked changes)

6) There are many conclusions throughout suggestions large RCTs are required; I'm not sure there is clinical equipoise to do so.

Reply: We removed some sentences that state the above. Now in the conclusion of the manuscript, we have one sentence stating the above

Changes In Text: In the conclusion, pre-existing text Page 11, Lines 19-20.

7) Overall, I find the review is quite general and incomplete. I think the discussion would benefit from a more detailed focus on various therapies, their underlying mechanisms and

clinical outcomes.

Reply: We have removed the entire section on cardioplegia and remote ischemic preconditioning as per prior reviewers comments. We added a section on Anesthetic adjuncts, such as local anesthetics and Dexmedetomidine, along with the role of regional anesthesia. We also added to our conclusion stating our thoughts on these adjuncts, the focus of this manuscript now being on the Anesthetic agents.

Changes In Text: The section below 'Other Anesthetic Adjuncts' is new, Page 10, Line 6-23. Page 11, Line 1-23. In the conclusion, the new part is Page 12, Line 16-23. Page 13, Lines 1-6.

Reviewer D

This narrative review offers an expert opinion on myocardial protection during cardiac surgery, ranging from anesthetic agents, cardioplegic solutions to other adjuncts. The manuscript is well written and is a nice piece to read through. I have a few comments:

I am not quite sure if the authors intend to focus on myocardial injury related to induced myocardial ischemia during cardiac surgery vs. some form of myocardial injury related to cardiopulmonary bypass run. I believe the former is much more relevant.

Thank you very much for your comments, we appreciate them. **All changes have been tracked, also in bold.**

Reply: We have removed the entire section on cardioplegia and remote ischemic preconditioning as per prior reviewers comments. We added a section on Anesthetic adjuncts, such as local anesthetics and Dexmedetomidine, along with the role of regional anesthesia. We also added to our conclusion stating our thoughts on these adjuncts, the focus of this manuscript now being on the Anesthetic agents.

Changes In Text: The section below 'Other Anesthetic Adjuncts' is new, Page 10, Line 6-23. Page 11, Line 1-23. In the conclusion, the new part is Page 12, Line 16-23. Page 13, Lines 1-6.

Myocardial protection during induced myocardial ischemia is conducted through combination of multiple modalities, such as delivery of cardioplegic solution, ventricular unloading, and myocardial cooling. It may be a good idea to briefly mention on these non-pharmacologic factors.

Reply: We added a paragraph mentioning these non-pharmacologic factors. We did not go into detail regarding these points, considering we have now restructured the manuscript such that the focus is now on the Anesthetic drugs.

Changes In Text: Added text for non-pharmacologic factors to Page 5, Line 13-18.

Related to above, I believe that cardiac surgeons, including myself, tend to think anesthetic drugs have much smaller role in myocardial protection compared to the above-mentioned factors. Showing evidence/data/studies that demonstrated the influence and importance of the

anesthetics relative to the above-mentioned factors would be informative.

Reply: We believe the additional section on other Anesthesia adjuncts, such as Lidocaine, Dexmedetomidine and regional anesthesia will help give readers a better awareness of the impact of the Anesthetic medication. In addition, we added in more objective data, such as stating the p values and numerical values for outcomes of several of the studies. Finally, we also added a section in the conclusion regarding where we believe future research is needed.

Changes In Text: The section below ‘Other Anesthetic Adjuncts’ is new, Page 10, Line 6-23. Page 11, Line 1-23. New objective data added to Page 4, Line 6, Lines 9-12, Lines 13-18. Page 9, Lines 8-10. In the conclusion, the new part is Page 12, Line 16-23. Page 13, Lines 1-6.

For cardioplegia solutions, studies from 2009-2018 were included whereas for anesthetic agents and other modalities on myocardial protection, studies from 1999-2023 were included. Why were different periods applied?

Reply: We have removed the section on cardioplegia completely, including the prior Table 1 as per prior reviewers comments.

Changes In Text: Previously the entire Cardioplegia section spanned Pages 9-13, including Table 1 outlining the cardioplegia compositions, this has been deleted (easiest to see via tracked changes)

Many of the cardioplegic solutions are mixed with blood as the authors stated, and thus Table 1 may not reflect the final compositions. This could be misleading.

Reply: We have removed Table 1

Changes In Text: The new Table 1 refers to the downstream pathways for the Anesthetic agents

Thank you very much for allowing me to review this manuscript.